

Review

Protein Kinase C at the Crossroad of Mutations, Cancer, Targeted Therapy and Immune Response

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Simple Summary: This review aims to analyze the clinical drawbacks faced by PKC inhibitors and uncovering aspects that might potentially interfere with the clinical outcome of compounds targeting PKC. In-depth analyses of the impact of key PKC mutations, the failures and promises of clinical trials conducted over the years and of the key immunological pathways involving distinctive isoforms in the tumor microenvironment, are critical to improve the drug targeting of PKC. We believe that a more inclusive view of the impact of different PKC variants on both cancer and immune cells should guide future efforts, which must consider current immunotherapy strategies. Also, a comprehensive representation of the pathways and partners involving PKC variants may help provide response biomarkers, which can indicate whether or which PKC isoform can be proficiently targeted, potentially in a feasible combination with immune checkpoint blockade.

Abstract: The frequent PKC dysregulations observed in many tumors have made these enzymes natural targets for anticancer applications. Nevertheless, this considerable interest in the development of PKC modulators has not led to the expected therapeutic benefits, likely due to the complex biological activities regulated by PKC isoenzymes, often playing ambiguous and protective functions, further driven by the occurrence of mutations. The structure, regulation and functions of PKCs have been extensively covered in other publications. Herein, we focused on PKC alterations mostly associated with complete functional loss. We also addressed the modest yet encouraging results obtained targeting PKC in selected malignancies and the more frequent negative clinical outcomes. The reported observations advocate the need for more selective molecules and a better understanding of the involved pathways. Furthermore, we underlined the most relevant immune mechanisms controlled by PKC isoforms potentially impacting the immune checkpoint inhibitor blockade-mediated immune recovery. We believe that a comprehensive examination of the molecular features of the tumor microenvironment might improve clinical outcomes by tailoring PKC modulation. This approach can be further supported by the identification of potential response biomarkers, which may indicate patients who may benefit from the manipulation of distinctive PKC isoforms.

Keywords: PKC; PKC mutations; PKC isoforms; PKC inhibitors; cancer therapy; immune cells; immune checkpoint molecules; immune checkpoint inhibitor blockade



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1. Introduction

The protein kinase C (PKC) family, first discovered in 1977 by Takai et al. [1], includes distinctive phospholipid-dependent enzymes able to phosphorylate the Ser and Thr residues of many substrates involved in either the promotion or suppression of cancer. PKC activation involves a sophisticated mechanism implicating its association with the cell

membrane, followed by its priming and conformational modifications produced by the engagement with additional factors or second messengers. Three distinct groups of PKCs, encoded by nine genes, have been characterized based on specific control mechanisms and the second messenger involved in their activation. Conventional (c)PKCs include the isoforms α , β I, β II, and γ , and require diacylglycerol (DAG), Ca^{2+} and phosphatidylserine (PS) for their activation [2], while novel (n)PKCs, including the δ , ϵ , η and θ isoforms, require only DAG [3]. At variance, atypical (a)PKCs, such as ζ and ι/λ isoforms, are activated neither by DAG or Ca^{2+} [4,5], and are reported to be controlled by sphingosine 1-phosphate [6], phosphatidic acid and PS [7,8]. However, both the structure and mechanism regulating the activity of PKC family members have been extensively described elsewhere and go beyond the scope of this review [9].

Among the mechanisms involved, PKCs can retain an autoinhibited configuration through the binding of a regulatory pseudo-substrate, which prevents the phosphorylation of the actual substrate by the catalytic C-terminal domain [10,11]. The binding of a second messenger, e.g., DG and Ca^{2+} , to their specific PKC subunits induces an open effective conformation, which releases the pseudo-substrate from the active site and provides the phosphorylation of the specific substrate. PKC signaling is strongly impaired by the dephosphorylation of the open form that is carried out by the leucine rich repeat protein phosphatase (PHLPP) and phosphatase 2A (PP2A), both responsible for addressing the kinase to the proteasome-mediated degradation. This event is biased by the binding of Heat Shock Protein 70 that allows the re-phosphorylation of PKC, proving that the balance between the phosphorylated and dephosphorylated forms is crucial for sustaining the kinase signaling within the cell. Of note, the PKC isoforms mainly involved in tumor pathogenesis reveal a compromised mechanism of auto-inhibition related to an impaired regulation by PHLPP [11].

For decades, PKC has been considered an oncoprotein due to its activation by phorbol esters [12], followed by the chronic down-regulation of enzyme levels [13]. Indeed, the finding that PKC isoforms act as cellular receptors for phorbol esters has also provided a possible early explanation of their own T cell stimulating capability [14]. The different isoenzymes can be identified by their distinctive regulatory region, while the catalytic domain, resembling that of other protein kinases (e.g., PKB, also known as AKT), is shared between all the family members, and includes consensus sequences for Ser/Thr residue phosphorylation similar to those observed in PKA. These homologies suggest that several PKC functions may be likely achieved by similar kinases and represent the major obstacle to the development of effective specific inhibitors, leading to off-target effects. Nevertheless, the strong involvement of many PKC isoforms in cancer development and progression has engaged many researchers to target this family of enzymes to uncover novel therapeutic approaches [15]. In this regard, a relevant common feature of tumor cells is the expression of PKC transcriptional variants, leading to either physical alteration or functional loss.

Thus, a comprehensive representation of the pathways and partners involving PKC variants may be beneficial for addressing new therapeutic strategies, to be employed either alone or in combination, and for developing more feasible molecules able to specifically target distinctive PKC isoforms. Not less critical would be a better definition of the networks communicating with PKCs and the interactions with the components of the tumor microenvironment (TME), including immune cells. Indeed, a broader view that considers the impact on the TME features of different PKC variants, either expressed by the tumor or immune cells, would help focus on specific targets and guide future efforts.

2. Levels of PKC and Mutations Sustaining Cancer

The critical role of PKC dysregulation in tumor promotion has been extensively described elsewhere [16]. Based on numerous research studies, it is plausible to reason that this family of kinases can also display a tumor-suppressive role by phosphorylating several downstream substrates, such as K-Ras [17]. Of relevance is the debate on a dual role of PKC as either “good” or “bad” that concerns specific isoenzymes [18], such as PKC ι [19,20],

PKC ϵ [21], PKC δ [22] and PKC ζ [23]. Furthermore, PKC genes are frequently mutated, especially in human cancers, with 20–25% of the mutations detected in melanoma, colorectal cancer and lung squamous cell carcinoma, whereas less than 5% are found in glioblastoma, ovarian and breast cancer [24]. A comprehensive study by Antal et al. on different tumor types has summarized a multitude of mutations (i.e., 554) affecting several members of PKC (i.e., α , β , γ , δ , ϵ , η , θ , ζ , ι) and occurring in both conserved and non-conserved regions [25]. Most of them are associated with a complete functional loss and affect both the regulatory and catalytic protein domains, without distinction, interfering with their own phosphorylation and catalytic potential. The most relevant and experimentally validated mutations, which we are going to discuss, are summarized in Table 1.

Table 1. Mutations affecting PKC isoenzymes, functional loss, or new associated functions.

Isoenzyme	Mutation	Function	Type of Cancer/Pathologies
PKC α	D294G, located in the C2 domain	Kinase functional loss and inhibition of F-actin accumulation, thus interfering with the organization of cytoskeletal filaments at the cell–cell junctions [26]	Highly invasive pituitary and thyroid tumors [27]; adenomas (pituitary, follicular); thyroid carcinomas [28]
PKC α	D463H, affecting only one allele, present in heterozygosity	Affecting the highly conserved Asp residue, fundamental for the kinase activity, and leading to a different distribution and a reduced lifetime of the protein, likely favoring its phosphorylation [29]	Chordoid gliomas [30], affecting the third ventricle [29]
PKC α	M489V, coding SLC44A1-PKC α fusion protein	Gain-of-function is caused by the rearrangement between chromosomes 9 and 17, which generates a constitutive oncogenic and functional kinase [31,32]	Rare mixed neuronal-glia tumors known as PGNTs, difficult to diagnose, (e.g., papillary glioneuronal tumors) [32]; Alzheimer’s disease in mouse model [33]
PKC α , PKC β and PKC δ	Gene fusion	Interaction with membrane-associated proteins, including podoplanin, CD63 and LAMTOR1 [34]	Benign fibrous histiocytoma [34]
PKC β II and PKC β I variants	Spliced isoforms with different C-terminal domain (V5 variants)	Specific maturation processing and distinctive cellular localization [35]; PKC β loss correlates with melanin levels and oxidative stress response; decreased neocortical gene expression	Lung cancer cell lines [36]; melanoma [37]; autistic disorder [38]
PKC β II	P616A and P619A mutations	Abolish its maturation [39], the protein results unphosphorylated	Investigated in COS7 cells [39]
PKC β	A509T mutation in heterozygosity affecting the C2 domain	Functional loss; hemizygous PKC β has lower growth potential than when co-expressing A509T mutation; generation of dominant-negative with greater anchorage-independent cell proliferation [25]	Large intestine identified screening human colorectal cancer cell lines and a NCI-60 cell line panel [40,41];
PKC β	D427N	Constitutively active open conformation able to increase NF- κ B signaling [42]	Hematological malignancy [43]; T-cell leukemia-lymphoma [44] T-cell leukemia/lymphoma [45]; Sézary syndrome [46]

Table 1. Cont.

Isoenzyme	Mutation	Function	Type of Cancer/Pathologies
PKC γ	M501I	Change of the selectivity for the phosphorylation target in favor of a Thr, leading to the preferential recognition of different substrates, thus deviating the canonical kinase networks [47,48]	Lung cancer (dataset: TGCA—Cosmic Cured COSU417 (https://cancer.sanger.ac.uk/cosmic , accessed on 15 July 2023))
PKC δ	Changes in the DFG and APE motifs of the catalytic domain, such as the hinge region or in the Thr residue	Loss-of-function [49] with the inhibition of PKC δ , preventing the cleavage by caspase 3; this differently modulates their downstream targets, such as p53, leading to a decline of its transcription	Gastric cancer [50]; Autoimmune lymphoproliferative syndrome reported in https://www.ncbi.nlm.nih.gov/clinvar/ (accessed on 15 July 2023) with uncertain significance (NM_006254.4(PKCD):c.1501G>A (p.Gly501Arg) and NM_006254.4(PKCD):c.1501G>T (p.Gly501Trp))
PKC ζ	K281W, dominant-negative PKC ζ plasmid	In TRAMP-transfected cells, it reduces proliferation and enhances cell survival [51]; cell-polarizing deficit associated with multi-acinar structures and early luminal cell hyperproliferation [52]	Pancreatic islets and β -cells [53]; breast cancer [52]
PKC ζ	Myristoylated PKC	This modification constitutively activates the kinase, increases cell proliferation and promotes apoptotic cell death [51]	TRAMP cell lines expressing FLAG-PKC ζ -myr [51]
PKC ι	Gene amplification, due to the association of <i>PRKCI</i> gene to the 3q26-29 amplicon, co-amplification with SOX2	Phox and Bem1 (PB1) binding domain of the protein of the 3q amplicon makes PKC ι a therapeutic target [54]	Small-cell lung cancer [55]; pathogenic from https://www.ncbi.nlm.nih.gov/clinvar/ (accessed on 15 July 2023) (GRCh38/hg38 3q26.1-29(chr3:166137209-198125115)x3)
PKC ι	R480C [56], previously mistakenly identified as R471C [57]	Arg471 is involved in the binding of lethal giant larvae 2; change of function: it modifies the recruitments of the corrected target substrates [57]	The most frequent mutation of PKC ι in human cancer [56]

The first characterized mutation is the D294G, located in the C2 domain of the PKC α isoform [26]. This alteration has been reported to cause kinase functional loss and the inhibition of F-actin accumulation, thus interfering with the organization of cytoskeletal filaments at the cell–cell junctions. Another described mutation is the D463H, affecting the highly conserved Asp residue, fundamental for the kinase activity and leading to a different distribution and a reduced lifetime of the protein, likely favoring its phosphorylation. In the rare chordoid glioma, only one allele has been reported to carry this mutation, whereas the wild-type gene encodes a protein that is still able to work [29]. However, it cannot be ruled out that the inactive form encoded by the mutated allele might still interact with different partners, modifying the interactive pathways with consequences impairing the therapeutic approach of this tumor.

Selected alterations that can lead to gain-of-function are more frequently detected in Alzheimer’s disease, as in the case of PKC α M489V mutation [31]. Differently, these variants are rarely detected in cancer settings and include the SLC44A1-PKC α fusion protein, originated by the rearrangement between chromosomes 9 and 17, which generates a constitutive oncogenic and functional PKC α [32]. Other gene fusions with oncogenic

effects have been found in benign fibrous histiocytomas, leading to altered PKC α , PKC β and PKC δ isoforms interacting with membrane-associated proteins, including Podoplanin, CD63 and LAMTOR1 [34].

Numerous investigations agree with a tumor suppressive role for PKC α , which is able to inhibit the proliferation of colorectal cancer cells, and accordingly detected at lower levels in 60% of colorectal cancers [58], while a direct correlation has been reported between low PKC α and the development of intestinal tumors in PKC $\alpha^{-/-}$ mice [59]. PKC α activation has been described to impair the cyclin D1 translation mediated by 4E-BP1, specifically through a PI3K/AKT-independent mechanism, rather regulated by PP2A. Also, in colon cancer, PKC α has been shown to down-regulate the expression of β -catenin by inhibiting the Wnt/ β -catenin pathway and, consequently, the expression of the downstream targets, such as c-Myc [18]. Further evidence of PKC α being a tumor suppressor has been provided in mice, where PKC α knockout contributes to the development of lung cancer, by upregulating K-Ras through a reduced activation of p38 Mitogen-activated protein kinase (MAPK), and a subsequent increase in Transforming Growth Factor (TGF) β 1 [60].

However, this tumor suppressor competence appears to be dependent on the tumor context. Indeed, in other types of tumors, including gastric carcinoma [61], bladder [62], endometrial [63] and breast cancer [64], PKC α is clearly overexpressed, and plays different functional roles related to the distinctive substrates. Targeting PKC α is particularly suitable for the treatment of epithelial cancers, where the PDGFR-PKC α -FRA1 axis is mechanistically involved [65]. In breast cancer cells, the increase in PKC α is associated with the switch to a hormone-independent phenotype [66,67] mediated by Notch-4 [68], also representing an indicator of hormone therapy failure [69,70], and by ErbB2 up-regulation, which determines a constitutive activation of the kinase, promoting cell invasion [71]. An enhanced PKC α has been shown to induce epithelial-to-mesenchymal transition (EMT) and improved cell motility in association with alterations of E-cadherin/ β -catenin expression and increase in MMP-2/MMP-9 [72]. Accordingly, these features are reverted by RNA silencing with siRNA against PKC α [65]. PKC α also displays a role in other crucial changes of cancer cells, as observed in in vitro glioma models [73], where it promotes the cell proliferation and survival in response to anticancer treatments, via activation of the NF- κ B pathway [74]. Of note, the overall PKC α reduction induced by RNA interference rather than the inhibition of its catalytic activity has been implicated in restraining glioma cell growth [75].

Further evidence of the ambiguous involvement of PKC isoforms in cancer is provided by PKC β . The PKC β II variants, together with PKC β I, represent spliced isoforms highly detected in cancer [35], but many aspects of their contribution are still poorly understood. This is due to their diverse functions, partly dependent on the different C-terminal domains conferring specific maturation processing and different cellular localization. In addition, the maintenance of the correct sequence in the C-terminal subunit of the protein is essential to the phosphorylation operated by other kinases, but the P616A and P619A mutations of PKC β II can abolish its maturation.

The overexpression of PKC β II has been associated with the early stages of tumor development [76], found in 18% of primary adenocarcinomas, and reported as a poor survival factor [77]. In transgenic mice, the up-regulation of PKC β II caused the hypertrophy of epithelial colon cells while increasing their sensitivity to the effect of carcinogens [78]. Overexpression of PKC β II has been reported to depend on either the repression of TGF β signaling, high Cyclooxygenase-2 (COX-2) levels [79], K-Ras-mediated MEK/ERK cascade activation [80] or pathways involving other PKCs, like Ras/MEK/PKC ϵ /Rac1 [81].

In addition, during proliferation, cancer cells can deregulate specific genes and accumulate altered PKC variants, either as the consequence of selected mutations or prolonged treatment with anticancer agents. These genetic modifications commonly translate into a loss-of-function, resulting in the generation of inactive enzymes.

The ambiguity of the functional role of PKC in cancer settings is further driven by studies regarding certain mutated isoforms, which seem rather to attribute a protective function to the canonical form [25]. A heterozygous mutation affecting the C2 domain,

associated with functional loss, has also been detected in PKC β . Of note, the induction of an exclusive wild-type PKC β II allele has been associated with a reduced anchoring ability and a decline in cell transformation and infiltration features. Since most detected mutations are heterozygous in cancer cells, the attempt to restore the endogenous PKC β mutated gene (A509T) by using the CRISPR/Cas9 approach has led to an increase in terms of both expression levels and the basal activity of PKC β [25]. The correction of the genetic defects has been associated with reduced cell viability and decreased ability to grow in a suspension medium. Instead, the knockout of the mutated PKC β gene demonstrated that the presence of only one correct allele is sufficient and responsible for greater anchorage-independent cell proliferation compared with the presence of two wild-type alleles. In conclusion, hemizygous PKC β confers lower growth potential than the co-expression of A509T mutation, proposing the former condition as dominant-negative. These findings suggest that the restoration of full PKC β activity in mutated cancer cells could still preserve suppressive effects, debunking its oncogenic role. In synthesis, an oncogenic mutation can be favored when the functional loss of PKC activity occurs.

An extensive analysis of the whole genome and RNA-sequencing technologies have revealed a high rate of PKC β mutagenesis in about 33% of patients with Adult T Cell Leukemia. In particular, a D427N mutation, which translates into a constitutively active PKC open conformation, is able to increase NF- κ B signaling [42].

Other gain-of-function mutations have been reported for PKC γ , albeit many mutations are associated with an inactivated form of the enzyme and affect predominantly conserved motifs [17], while others, mainly occurring in colon and breast cancer have opposite effects [82,83]. In the HCT-116 colon cancer cell line, the knockdown of mutated PKC γ has been reported to decrease cell proliferation [84,85], while aberrant PKC γ expression increases cell migration [86]. In addition, the presence of a mutant form of PKC γ , not properly phosphorylated at Thr514, alters its own de novo synthesis leading to its down-regulation [82]. Of note, the M501I mutation, identified in lung cancer settings [47], has been shown to change the selectivity for the phosphorylation target in favor of a Thr, leading to the recognition of different substrates, thus deviating the kinase towards different networks [48]. From this point of view, considering the pivotal role of phospho-Thr-mediated signaling in cancer, the control of mutant PKC γ isoforms can potentially affect tumor development and metastatization [87].

About PKC δ , a loss-of-function mutation identified in gastric cancer and affecting the catalytic domain has been addressed by an interesting study by Guo et al. [49]. In this setting, the dysfunction is related to changes in the DFG and APE motifs inactivating the catalysis. However, mutations in the hinge region or in the Thr residue have been reported to completely inhibit PKC δ , preventing cleavage by caspase 3. These altered isoforms differently modulate their downstream targets, such as p53, leading to a decline in their transcription. As PKC δ is involved in the cell-to-cell interactions, these mutations hinder the generation of the tight junction complexes, altogether increasing the invasiveness of cancer cells.

Other mutations with a loss-of-function in the PKC δ gene were identified in patients affected by juvenile systemic lupus erythematosus (JSLE) patients [88], that frequently develop B cell lymphomas. The impact of PKC δ defects on its role as an immune response homeostatic regulator will be discussed below.

At the time of writing this review, no further evidence of loss-of-function mutations in PKC δ is available. Most of the studies focus on the extent of expression of this isoform, leading to very conflicting results likely attributable to the differences between the considered cell types. An enrichment in terms of PKC δ has been reported in prostate and breast cancers [89]. In the former, PKC δ promotes invasiveness with the up-regulation of PCPH/ENTPD5 leading to collagen secretion [90]. In a xenograft model of prostate cancer, PKC δ has been shown to sustain tumor growth by increasing HIF-1 α -mediated angiogenesis with the involvement of the NADPH coenzyme and the production of ROS [91]. Breast cancer has been assumed to be a preferential specific context in which PKC can display

an oncogenic role. In particular, high levels of PKC δ promoted tumorigenesis in both the Erb2⁺ and ER⁺ phenotypes, with the latter also correlating with poor survival [92]. In mice, PKC δ up-regulation improves resistance to apoptosis in stress conditions, such as serum deprivation or doxorubicin exposure [93]. However, in breast cancer, the effects of PKC δ are somewhat controversial. Indeed, while in BT-549 cells, the enzyme overexpression reduces the migration ability in MCF-7 cells, the decline in PKC has been reported to favor the cell migratory capacity more than its up-regulation, followed by the secretion of MMP-9. So, the inhibitory effect of PKC δ on cell growth has been reported with different consequences based on the type of cells. PKC δ can drive cell cycle arrest in G1, mediated by the induction of p21cip1 and Rb dephosphorylation [94], although a block in the S phase has also been observed as a consequence of PKC δ overexpression [95]. Several findings underline the PKC δ involvement in apoptosis as a response to chemotherapy [96], and a relocation of the kinase into the nucleus has been observed after exposure to genotoxic drugs [97]. In androgen-dependent prostate carcinoma, apoptosis is rather allosterically activated through either the p38 MAPK/RhoA/ROCK/p21Cip1 [98,99], or the TNF- α /TRAIL/JNK/p38 MAPK caspase 8 networks [100–102]. It is then clear that PKC δ is engaged in so many and complex different processes (e.g., regulation of cell cycle, motility and metastasis diffusion) that it might hardly represent a feasible tumor-associated therapeutic target.

Concerning PKC ϵ , many experimental observations link the pro-oncogenic functions of this isoform to aggressive tumor phenotypes, making PKC ϵ a good target for anticancer applications. In particular, the kinase has been reported as engaged in the Ras-Raf-1 signaling [103,104] and in the autocrine TGF β secretion loop [105]. PKC ϵ is increased in about 75% of patients affected by invasive ductal breast cancer and correlates with the severity of the disease in association with ErbB2⁺/Her2⁺ and ER⁻ and PR⁻ phenotypes [106]. Accordingly, at the cellular level, the PKC ϵ isoform has been shown to inhibit tumor cell apoptosis by blocking the transfer of BAX to the mitochondria [107]. Even greater seems to be the correlation of PKC ϵ with the growth of primary epithelial non-small-cell lung cancer (NSCLC, >90%), in which it is activated in a p21/Cip1-dependent way [108]. Again, PKC ϵ levels are elevated in prostate cancer as compared with benign prostatic epithelia and are associated with higher aggressiveness [109]. Indeed, in human prostate cancer, PKC ϵ participates in survival mechanisms, modulating caspases and Bcl-2 [100,110,111] while modulating invasiveness by activating RhoA and/or RhoC [106,112]. Increased PKC ϵ expression levels and activation have been reported in prostate tumors, where the isoform regulates ERK, AKT and mTOR pathways [18,113,114], the anti-apoptotic TNF- α -dependent NF- κ B signaling and the expression of survival and invasive factors (e.g., COX-2, MMP-9, cyclin D1, VEGF, IL-6), through STAT 3 [115]. Finally, the interaction between PKC and RACK1 has been shown to interfere with integrin β , mediating relevant changes in terms of focal adhesion and cell motility also through ERK [116,117]. Indeed, PKC ϵ has been reported to support the assembly of the adhesion matrix containing actin filaments and β 1-integrins, the latter further linking PKC ϵ to the AKT survival pathway in recurrent prostate cancer cells [114].

PKC ζ and PKC ι (PKC λ) represent atypical PKC, i.e., lacking a C2 domain and endowed with only an unresponsive C1 domain [118–120]. PKC ζ acts predominantly as a suppressor by inducing apoptosis in different tumors [121]. In addition, PKC ζ limits IL-6 secretion through the inhibition of the Ras cascade [122]. Its deletion in PTEN-knockout mice has been reported to promote prostate carcinoma, also in correlation with the c-Myc increase [123]. Only a mutated form of PKC ζ , constitutively activated, has been described in a mouse transgenic model of prostate adenocarcinoma [51]. Since PKC ι works as an oncogene, it is often overexpressed in cancer [124,125], sometimes depending on gene amplification [126,127], due to the association of the *PRKCI* gene to the 3q amplicon [54]. The tumorigenic effects of PKC ι have been described as mediated by the Rac1-PAK-MEK-ERK network [80], but alternative ways are described, including the Rho-GEF-Ect2 pathway, involved in the formation of the PKC ι -Par6 complex [128]. Other links are reported to the NF- κ B signaling [129,130].

In recent years, more attention has been addressed to the PKC ζ isoform. This is significantly overexpressed in pancreatic ductal adenocarcinoma, one of the more lethal tumors, as a marker associated with disease progression and poor prognosis [131,132]. PKC ζ acts on the PI3K/AKT and Wnt/ β -catenin pathways, opposing apoptosis. Of relevance, the RNA interference has shown to reduce proliferation, migration and invasive behaviors of cancer cells, advocating PKC ζ as a feasible target for therapy. Novel investigations indicate that PKC ζ activities, in this context, could depend more on the interaction with other protein partners, rather than on its kinase function. Indeed, a dibasic motif has been identified in some substrates, such as lethal giant larvae 2 and myosin X (but absent in Par3), containing two essential residues: Arg471, involved in the binding of lethal giant larvae 2, and Arg474, involved in the binding of myosin X. A mutation that can frequently occur in this motif was previously misnamed R471C and was recently renamed as R480C [55]. This region of PKC ζ participates in the cell polarization during epithelial morphogenesis; however, the mutation modifies the recruitment of the corrected target substrates, altering the process [56]. Of relevance, the 3q26-29 amplicon including the *PRKCI* gene is reported as pathogenic by <https://www.ncbi.nlm.nih.gov/clinvar/> (accessed on 15 July 2023) (GRCh38/hg38 3q26.1-29(chr3:166137209-198125115)x3) and has been suggested as a marker of small-cell lung cancer (SCLC) [54].

Collectively, these observations suggest that the occurrence of mutations increases the complexity of interactions and biological activities regulated by PKC isoenzymes, thus contributing to restraining the development of selective PKC modulators.

3. The Challenging Task of Targeting PKC for Cancer Therapy

PKC isoenzymes are found at the intersection of multiple signaling pathways in many physiological and pathological conditions. The frequent dysregulation of PKC isoforms observed in many cancers, and the evidence that PKC plays an important role in cell transformation, differentiation, migration, and tumor progression, has generated considerable interest in the development of specific PKC modulators for cancer treatment [10,15,133].

Several strategies have been employed, aiming to discover the selective inhibitors of PKC, mostly competing with ATP to the C3 region within the catalytic domain of the kinase, or binding either to the C4 (substrate competitive PKC inhibitors) or the C1 domain (DAG competitive molecules) in the regulatory region. The PKC isoform-specific antisense oligonucleotides have also been described.

Many PKC modulators are presently at various stages of development in the clinical setting; however, most of these trials have failed to show a significant clinical benefit [10,15,133], which strongly limits the ability to develop cancer treatment strategies by targeting PKC alone. Below is a brief characterization of the main PKC inhibitors employed in both preclinical and clinical settings in different types of tumors.

3.1. Staurosporine

The best-studied ATP competitive PKC inhibitor is staurosporine, a molecule isolated from *Streptomyces staurosporeus* bacterium, with an IC₅₀ value of 2.7 nM [134]. This compound binds to the catalytic domain of all PKC isoforms and exhibits unspecific inhibitory activity against numerous other Ser/Thr as well as tyrosine kinases. Indeed, this lack of selectivity restricts its applicability in clinical studies, nonetheless, several staurosporine analogs, such as 7-hydroxystaurosporine (UCN-01), 4'-N-benzoylstaurosporine (midostaurin), enzastaurin, AEB071 (also known as sotrastaurin), have been developed and used in clinical trials either as single agents or in combined therapeutic approaches in patients with different types of cancer [9].

3.2. UCN-01

UCN-01 is a potent inhibitor of multiple protein kinases, including PKC and cyclin-dependent kinases (CDKs). UCN-01 blocks PKC activity (IC₅₀ 4.1 nM) by binding to its catalytic domain [135] with significantly higher affinity for conventional (c) PKC than for

novel (n) PKC and atypical (a) PKC [136], disturbing the transition from the G1 to S phase, thus preventing cancer cell growth [137].

Preclinical studies have observed a synergistic activity of UCN-01 when combined with several cytotoxic agents [138]. Based on these results, several Phase I studies have been carried out with UCN-01 either as a monotherapy or in combination with cytotoxic chemotherapeutic agents in patients with solid tumors, leukemia and lymphomas [139–141].

UCN-01 can be safely administered as an initial 72 h continuous intravenous infusion, followed by monthly doses given as a 36 h administration, showing good tolerability. In addition, this agent has a very small volume of distribution, low systemic clearance and a prolonged elimination half-life [141]. UCN-01 was tested in Phase I trials in combination with either cisplatin [140] or 5-fluorouracil [139] or topotecan [142] or carboplatin [143], or irinotecan [144,145] in advanced solid tumors. Other phase I studies combining UCN-01 with prednisone in patients with refractory solid tumors and lymphomas [146], and with perifosine in patients with relapsed and refractory acute leukemias and high-risk myelodysplastic syndrome [147] have been carried out, while a combined approach with fludarabine monophosphate has been investigated in patients with chronic lymphocytic leukemia [148]. Also, a Phase II clinical trial with irinotecan has been conducted in patients with metastatic triple negative breast cancer who had previously been treated with anthracyclines and taxanes [145]. Unfortunately, most of these investigations failed to show clinical benefits, which has discouraged further clinical trials with UCN-01.

3.3. Midostaurin

The staurosporine semi-synthetic analogue midostaurin (4'-N-benzoylstaurosporine also known as PKC412; CGP 41251) is an ATP-competitive inhibitor, isolated from *Streptomyces Staurosporeus* with a higher specificity for PKC (PKC α , IC₅₀ 22 nM; PKC β , IC₅₀ 30 nM) compared to its parental compound. Initially developed as a PKC inhibitor analogous to staurosporine, midostaurin inhibits several other protein kinases, although with a lower inhibitory activity on PKC compared with staurosporine. Accordingly, its therapeutic effects are mainly attributed to the inhibition of tyrosine kinases [149]. In promising preclinical studies, midostaurin has shown anti-tumor activity both in vitro and in vivo, and the capacity to reverse P-glycoprotein (Pgp)-mediated multi drug resistance (MDR) [150–153]. Of note, it has also displayed potent anticancer effects against rituximab resistant Burkitt's lymphoma cells by decreasing PKC phosphorylation and enhancing pro-apoptotic activity [154].

The compound was then tested in 56 clinical trials in patients with various tumor types, either as a monotherapy or in combination with other drugs, showing some survival benefit in patients with selected cancers ([155], <https://clinicaltrials.gov/ct2/results?term=midostaurin>, accessed on 13 June 2023). However, although its good tolerability was demonstrated in a Phase I trial, with the most common toxicities including nausea, vomiting, diarrhea and fatigue, in a Phase II study conducted in patients with malignant melanoma, midostaurin failed to demonstrate a statistically significant clinical activity [156].

In patients with AML, FMS-like tyrosine kinase 3 (FLT3) mutations with internal tandem duplication (ITD) are associated with high leukemic burden and poor prognosis [157]. Of relevance, the addition of midostaurin to standard chemotherapy has significantly prolonged median overall and event-free survival in mutant FLT3-positive AML patients in a Phase III study [158]. Nevertheless, the direct inhibition of tyrosine kinase by midostaurin resulted in G1 arrest and apoptosis in FLT3-mutant leukemia cells [149]. Since April 2017, midostaurin has been approved by the Food and Drug Administration (FDA) for the treatment of patients with newly diagnosed FLT3-mutated AML or patients with systemic mastocytosis with associated blood neoplasm or mast cell leukemia. More recently, a high response rate and good tolerability with no evidence of increased toxicity have been shown with the use of the anti-CD33 immunoconjugate gemtuzumab-ozogamicin plus midostaurin added to standard intensive chemotherapeutic regimens in patients with newly diagnosed FLT3-mutated/CD33⁺ AML [159]. However, a larger cohort of patients with longer follow-up is needed to validate these results.

Of note, the oral administration of midostaurin has displayed significant clinical improvements also in patients with advanced systemic mastocytosis in a Phase II study [160].

3.4. Sotrastaurin

Sotrastaurin (AEB071; 3-(1H-indol-3-yl)-4-[2-(4-methylpiperazin-1-yl)quinazolin-4-yl]pyrrole-2,5-dione) is a first-generation oral potent ATP competitive inhibitor, that blocks the catalytic activity of both the classical (α , IC_{50} 0.95 nM; β , IC_{50} 0.64 nM) and novel (δ , ϵ , η , θ , IC_{50} ranging from 0.22 to 3.2 nM) isoforms of PKC [161]. In preclinical studies, it has been shown to considerably reduce the viability of uveal melanoma cells harboring GNAQ/GNA11 mutations by inhibiting PKC isoforms, specifically through the PKC/NF- κ B and PKC/ERK1/2 pathways [162,163]. More than 90% of patients with metastatic uveal melanoma (MUM) have mutations in the GNAQ and GNA11 genes, which encode the alpha subunits of the G-protein-coupled receptor (GPCR) [164]. The phospholipase C/PKC signaling pathway is an important downstream player of the constitutively active G protein alpha subunits (GNAQ or GNA11) [165]. Therefore, PKC inhibitors may be considered as a valuable option for treating MUM. A recent Phase I dose-escalation study, involving patients with MUM treated with sotrastaurin, has exhibited favorable tolerability and moderate clinical activity, although with a low objective response rate (3%) [166].

Sotrastaurin has also been tested in a Phase Ib trial in patients with MUM in combination with the PI3K α inhibitor alpelisib to achieve a sustained suppression of MAPK signaling. Dual therapy was found to be safe, but there was no evidence of clinical efficacy [167].

Darovasertib (LXS196) is a new second generation oral selective PKC inhibitor (PKC α , IC_{50} 1.9 nM; PKC θ , IC_{50} 1.9 nM) (<https://pubchem.ncbi.nlm.nih.gov/docs/compounds>, accessed on 17 July 2023) that demonstrates enhanced pharmacological activity against UM cell lines containing mutant GNAQ or GNA11 [168] when compared to sotrastaurin. Currently, several clinical trials ([https://clinicaltrials.gov/identifier: NCT03947385](https://clinicaltrials.gov/identifier:NCT03947385), accessed on 17 July 2023) are underway to evaluate the safety and anti-tumor activity of darovasertib in patients with solid tumors harboring GNAQ/11 mutations, including MUM, cutaneous malignant melanoma and colorectal cancer.

In a first-in-human Phase I study, darovasertib was well tolerated, with hypotension being the most common dose-limiting toxicity. The compound also proved to encourage clinical activity as a single agent in MUM patients [168].

3.5. Enzastaurin

Enzastaurin (LY317615) is an ATP-competitive, selective inhibitor of PKC β (PKC β , IC_{50} 6 nM; PKC α , IC_{50} 39 nM; PKC γ , IC_{50} 83 nM; PKC ϵ , IC_{50} 10 nM) belonging to the class of acyclic bisindolylmaleimides [169], that also exhibits antiproliferative and proapoptotic effects by targeting AKT and GSK3 β kinases [169].

Enzastaurin has been investigated in various clinical trials for the treatment of different types of cancer. At the time of writing this review, 51 clinical trials with enzastaurin alone or combined with standard treatments, were listed on <https://clinicaltrials.gov> (accessed on 17 July 2023). Although enzastaurin has shown promise in both preclinical studies and distinctive patient populations, demonstrating a favorable toxicity profile in many Phase I studies [170], further research is required to determine its actual efficacy in the clinical setting. In fact, no clear benefit has been observed in several clinical trials evaluating the employment of enzastaurin alone or in combination with other anticancer agents, such as erlotinib or pemetrexed, in patients with advanced NSCLC [171,172], bevacizumab or temozolomide in patients with recurrent malignant gliomas [173,174], docetaxel/prednisone in patients with castration-resistant metastatic prostate cancer [175], and with paclitaxel and carboplatin in patients with advanced ovarian cancer [176]. Unfortunately, the lack of significant clinical improvement after treatment with enzastaurin has also been observed in previously treated patients with multiple myeloma [177], brain metastases [178], epithelial ovarian or primary peritoneal carcinoma [179], refractory mantle cell lymphoma [180], metastatic breast cancer [181] and refractory advanced cutaneous T cell lymphoma [182].

According to the current “precision medicine approach”, a new biomarker in diffuse large B-cell lymphoma (DLBCL), called DGM1 (De novo Genomic Marker 1, a germline polymorphism) located on chromosome 8, has been correlated with response to enzastaurin. These data suggest that adding enzastaurin to the standard-of-care R-CHOP protocol (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, rituximab and prednisone) may improve the outcomes in high-risk DGM1 + DLBCL patients [183].

3.6. Bryostatin

An additional class of PKC modulators with anti-cancer activity are the bryostatins, which are macrocyclic lactones derived from the marine invertebrate bryozoan *Bugula neritina*. Bryostatin-1 (binding affinity for PKC Ki, 1.35 nM, <https://pubchem.ncbi.nlm.nih.gov/compound/>, accessed on 17 July 2023) competes with cancer-promoting PKC ligands such as DAG and phorbol 12-myristate 13-acetate (PMA) to bind to the C1 regulatory domain of PKC-promoting either activation (short-term exposure to the drug) or inhibition (long-term exposure to the drug) of PKC [184]. The ability of PMA to induce a broad range of effects, including maturation/differentiation/apoptosis in hematopoietic cell lines at very low concentrations, has stimulated investigators to administer the phorbol ester to patients with myeloid leukemias. PMA has so far only been used in clinical studies aiming to establishing its dose tolerance [185], with bryostatin-1 being the most widely used compound in clinical trials.

Clinical trials using Bryostatin-1 as monotherapy or combined with other anticancer agents have failed to demonstrate significant clinical benefits in a variety of cancers, including melanoma [186], renal cell carcinoma [187], colorectal cancer [188], non-Hodgkin’s lymphoma (NHL) [189], relapsed multiple myeloma [190], sarcoma, head and neck cancer [191], cervical cancer [192], ovarian cancer [193], pancreatic cancer [194] and NSCLC [195]. Of relevance, the combination of bryostatin-1 and cisplatin has been associated with increased toxicity (mainly severe myalgias) in patients with ovarian cancer pre-treated with platinum [193]. Also, in a clinical study combining bryostatin-1 with paclitaxel in patients with NSCLC, increased myalgia has been reported [195]. On the other hand, a Phase II trial of sequential treatment with paclitaxel and bryostatin-1 in patients with untreated advanced gastric or gastroesophageal junction cancer, displayed a higher response rate than paclitaxel alone [196]. Unfortunately, a subsequent clinical investigation using the same treatment schedule in patients with advanced esophageal cancer was stopped early due to excessive toxicity, despite potential good anti-cancer activity [197]. According to this potential benefit, a Phase II trial, combining bryostatin-1 and vincristine, has demonstrated efficacy in a subset of patients (with an overall response rate of 31%) with aggressive B-cell NHL who had relapsed after autologous stem cell transplantation [198].

3.7. Antisense Oligonucleotides

Another approach to targeting PKC involves the use of antisense oligonucleotides, which can selectively reduce the expression levels of PKC isoforms implicated in cancer cell proliferation, apoptosis and distinctive signaling pathways. The anti-tumor activity of antisense oligonucleotides, as well as their safety and tolerability, have been confirmed in many studies [199,200].

Aprinocarsen (ISIS-3521/LY900003) is a 20-base phosphorothioate antisense oligonucleotide designed to specifically bind to the 3'-untranslated region of human PKC α mRNA [201]. The hybrid complex is then cleaved by RNase H, leading to the inhibition of PKC α expression (IC50 value of 50–100 nM for PKC- α mRNA reduction). Aprinocarsen has been used in Phase II and III clinical trials in patients with recurrent high-grade astrocytoma [202], advanced NSCLC [203], advanced ovarian cancer [204], hormone-refractory prostate cancer [205], breast cancer, [206], colorectal cancer [207] and previously treated low-grade NHL [208]. The drug was well tolerated, with fatigue and thrombocytopenia reported as the most common side effects [200].

However, since most of these trials failed to show an improvement in terms of either survival or other clinical benefits when used alone or in combination with anticancer drugs [202–208], the use of aprinocarsen in clinical trials was discontinued in 2005 [209].

Therefore, it is important to emphasize that the development of new PKC inhibitors with greater isoenzyme specificity and a better understanding of the involved signaling pathways may lead to more effective therapeutic approaches.

Most relevant clinical studies involving the use of PKC inhibitors in cancer settings are summarized in Table 2.

Table 2. Clinical outcomes of most relevant investigations analyzing PKC inhibitors in different cancer settings.

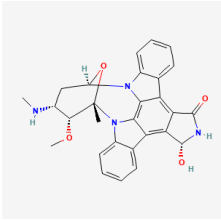
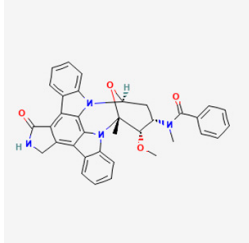
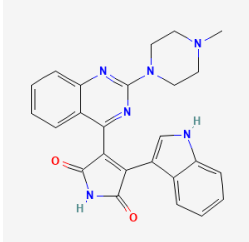
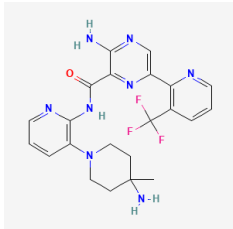
PKC Modulator and Structure/Sequence (https://pubchem.ncbi.nlm.nih.gov/docs/compounds , accessed on 17 July 2023)	Specificity	Inhibition Mechanism	Tumor Type	Phase of Study	Clinical Outcome	Ref.
UGN-01 7-hydroxystaurosporine 	cPKC nPKC	Competitive with ATP binding site	Solid tumors Lymphoma Leukemia	I	Not relevant	[139–145] [141,146] [147,148]
Midostaurin (PKC412) N-benzoylstaurosporine 	cPKC nPKC	Competitive with ATP binding site	Acute myeloid leukemia Melanoma Mutant FLT3-positive Acute Myeloid Leukemia	I, II, II IIA III	Survival benefit Favorable tolerability Not relevant Survival benefit Good tolerability	[155] [156] [158,159]
Sotrastaurin (AEB071) 	PKC α , β , θ , δ	Competitive with ATP binding site	Systemic mastocytosis Metastatic uveal melanoma	II I Ib	Survival benefit No unpredicted toxicities Favorable tolerability	[160] [166] [167]
Darovasertib (LXS196) 	PKC α , PKC θ	Competitive with ATP binding site	Metastatic uveal melanoma	I	Favorable tolerability Promising clinical activity	[168]

Table 2. Cont.

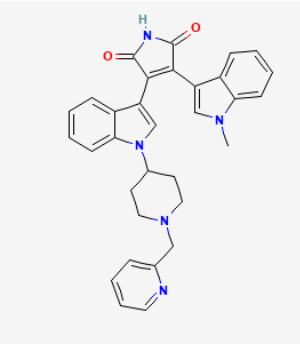
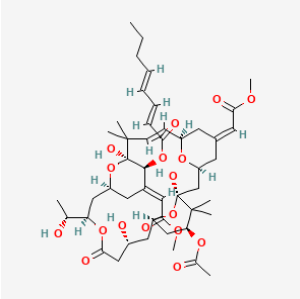
PKC Modulator and Structure/Sequence (https://pubchem.ncbi.nlm.nih.gov/docs/compounds , accessed on 17 July 2023)	Specificity	Inhibition Mechanism	Tumor Type	Phase of Study	Clinical Outcome	Ref.
Enzastaurin (LY317615) 	PKC β	Competitive with ATP binding site	Solid tumors	I	Favorable tolerability	[170]
			NSCLC	II	Not relevant	[171,172]
			Glioma	II	Not relevant	[173,174]
			Prostate cancer	II	Not relevant	[175]
			Ovarian cancer	II	Not relevant	[176]
			Multiple myeloma	II	Not relevant	[177]
			Brain metastasis	II	Not relevant	[178]
			Ovarian, peritoneal cancer	II	Not relevant	[179]
			Mantle cell lymphoma	II	Not relevant	[180]
			Breast cancer	II	Not relevant	[181]
			Cutaneous T cell lymphoma	II	Not relevant	[182]
			B cell lymphoma	III	Clinical benefit when DGM1+	[183]
			Bryostatin 1 	PKC α, ϵ, η	Competitive with phorbol ester binding site	
Melanoma	II	Not relevant				[187]
Renal carcinoma	II	Not relevant				[188]
Colorectal cancer	II	Not relevant				[189]
Non-Hodgkin's lymphoma	II	Not relevant				[190]
Multiple myeloma	II	Not relevant				[191]
Head and neck cancer/sarcoma	II	Not relevant				[192]
Cervical cancer	II	Not relevant				[193]
Ovarian cancer	II	Not relevant				[194]
Pancreatic cancer	II	Not relevant				[195]
NSCLC	II	Not relevant				[196]
Gastric/gastro-esophageal cancer	II	Clinical benefit				[197]
Esophageal cancer	II	Not relevant				[198]
Non-Hodgkin lymphoma	II	Clinical benefit in a subset of patients	[199]			

Table 2. Cont.

PKC Modulator and Structure/Sequence (https://pubchem.ncbi.nlm.nih.gov/docs/compounds , accessed on 17 July 2023)	Specificity	Inhibition Mechanism	Tumor Type	Phase of Study	Clinical Outcome	Ref.
Aprinocarsen (ISIS-3521/LY900003) 5'-GTTCTCGCTGGTGAAGTTTCA-3'	PKC α	Antisense oligonucleotide binding to the 3'-UTR of human PKC- α mRNA	High-grade astrocytoma	II	Not relevant clinical benefit Favorable tolerability	[202]
			NSCLC	III, II	Not relevant clinical benefit Favorable tolerability	[203]
			Ovarian cancer	II	Not relevant clinical benefit Favorable tolerability	[204]
			Prostate cancer	II	Not relevant clinical benefit Favorable tolerability	[205]
			Breast cancer	II	Not relevant clinical benefit Favorable tolerability	[206]
			Colorectal cancer	II	Not relevant clinical benefit Favorable tolerability	[207]
			Non-Hodgkin's Lymphoma	II	Not relevant clinical benefit Favorable tolerability	[208]

4. PKC Isoforms in Anticancer Immune Responses: The Bad and the Good Guys in the Family

4.1. Impact of PKC on T Cell Responses and B Cell Development

By using either knock-down animal models, PKC inhibitors, or PKC-defective T cell lines, many either redundant or unique biological roles have been established for the different PKC isozymes, impacting different pathways required for a proficient T cell response, and extensively reviewed by Pfeifhofer-Obermair et al., back in 2012 [210]. Currently, renewed attention must undeniably be paid to the distinctive PKC isoforms involved in the different aspects of the immune response in light of their potential impact on immune checkpoint blockade (ICB)-induced immune re-invigoration [211].

T cells have been shown to display up to eight distinctive types of PKC members [210], which hinders a detailed categorization of the individual roles.

4.1.1. PKC θ

Among PKC isoforms, PKC θ is critical for the activation of NF- κ B, AP-1 and NFAT transcription factors, a prerequisite for mature T cell stimulation and survival [212]. In particular, PKC θ promotes CARMA1 serine phosphorylation, required for its ability to stimulate NF- κ B [213] through the recruitment of the Bcl10-MALT1 complex, which in turn leads to the degradation of I κ B, resulting in NF- κ B activation and nuclear import [214].

Crucial to an efficient T cell stimulation is the recruitment of PKC θ to a small central area of the immunologic synapse (IS), the supramolecular activation complex (SMAC), where it engages with several proteins which are instrumental for the generation of signaling complexes, including the SRC family tyrosine kinase LCK, which contributes to the phosphorylation of PKC θ mainly at Tyr90 in the regulatory domain [215], the lymphocyte function-associated antigen 1 (LFA-1) [216], and the IL-2-inducible T cell kinase (ITK) [217], while negatively regulating the type E3 ubiquitin ligase Cbl-b [218], which restrains the PI3K activity [219]. Of relevance, PKC θ facilitates the engagement of LFA-1 to its own ligand intercellular adhesion molecule 1 (ICAM-1), expressed on activated APCs [216], then

facilitating the generation of a more stable IS. Moreover, the increased adhesion potential to the endothelium delivered by the LFA-1 and LFA1-ICAM engagement with cancer cells may serve as a mechanism entrapping activated CD8⁺ T cells in the tumor site [220], thus potentially contributing to the generation of a more inflamed TME.

The enrolment of these molecules is supported by the engagement of PKC θ with the cytoplasmatic tail of the co-stimulatory molecule CD28 [221], required for its own translocation to the membrane [222], followed by interaction with AKT kinase, which preserves its critical role as IS rheostat [223]. In T cells, in the absence of CD28, PKC θ is diffused throughout the synapse, indicating that CD28 is specifically required for PKC θ localization to the central (c)-SMAC region and the establishment of a mature IS [222]. This is of critical importance since CD28 represents the main down-stream target of PD-1-mediated inhibition through the SH2 domain-containing protein tyrosine phosphatase 2 (SHP-2) [224] and is required for T cell re-invigoration following PD-1 blockade [225]. A nonconventional PI3K- and Vav-associated signaling pathway has also been reported to facilitate a specific PKC θ membrane recruitment and activation by anti-CD3/CD28 stimulation in T lymphocytes [226]. Of note, PKC θ represents, along with CD3 ζ -associated protein of 70 kD (Zap70), another direct target of the inhibition to the TCR downstream signaling resulting from PD-1 engagement in T cells [227], and leading to impaired activation, proliferation, cytokine production and metabolic reprogramming [228]. This identifies PKC θ as a sensible therapeutic target to increase the effect of ICB and overcome therapeutic resistance in selected patients.

Among the mechanisms operating upstream PKC θ , MAP4K3 GCK-like kinase (GLK) is responsible for kinase Thr538 phosphorylation [229], a prerequisite for the activation of IL-2 promoter by NF- κ B and NFAT in mature T cells [230], and for retaining PKC θ at the IS. A further level of control downstream of TCR is represented by the DG kinases (DGK) α and ζ , which facilitate DAG consumption, thus impairing the availability required for PKC θ activation [231].

The assessment of polyfunctionality, as defined by the contemporary/sequential release of different cytokines by activated T lymphocytes [232], finely mirrors an ongoing and effective anti-tumor T cell functional activity. PKC has been shown to play a critical role in the orchestrated release of effector cytokines TNF- α , IFN- γ and IL-2, through the involvement of distinctive mechanisms [233]. Following an appropriate stimulus, while an early yet short-lived TNF- α production has been described, the release of IFN- γ has been reported as more persistent, and IL-2 production mainly depending on de novo gene transcription. Nevertheless, while PKC drives TNF- α translation without stabilizing its mRNA, the permanence of IFN- γ and IL-2 transcripts is sustained by the kinase. Since the PKC isoenzymes involved in sequential cytokine production are not specified, these observations suggest that a better comprehension of the involvement of the different PKC isoforms in the mechanisms regulating distinctive cytokine generation can contribute to improving the quality of polyfunctional anti-tumor responses.

Nevertheless, a normal protective Th1 immune response, with an intact CD8⁺ effector memory T cell activity, has also been observed in PKC θ -deficient mice [234], which suggests a redundant control by other kinases. At variance, the absence of PKC θ has been associated with severe defects in both Th17 and Th2 responses, the latter likely associated with the PKC θ -mediated expression of the Th2 differentiation controller GATA-3 [235].

PKC- θ has also been involved in the molecular mechanisms regulating the rapid NK cell discrimination between healthy and malignant cells. A recent original study by Ben-Shmuel et al. [236] has established a role for PKC θ in fine-tuning the balance between stimulatory and inhibitory signals by controlling SHP-1 phosphatase, in the early stages of activation and/or inhibition of NK cell synapse. In particular, the phosphorylation of SHP-1 on the Ser591 residue by PKC θ supports a repressed SHP-1 state, while neutralization of PKC θ has been reported to preserve SHP-1 into an active conformation, reducing NK cell activation and cytotoxicity, thus promoting tumor progression in vivo. This is of relevance since SHP-1 can provide PD-1-mediated downstream dephosphorylation in the absence of

SHP-2 [237], while another IC molecule, the B and tumor activity of T cells T lymphocyte attenuator (BTLA) [238], has been reported to engage SHP-1 in preference to SHP-2 [239] to impair lymphocyte functionality.

Human T cells can proliferate to a limited extent before entering replicative senescence [240,241], characterized by a progressive telomere shortening, following each round of antigen (Ag)-induced duplications [242] that can be overcome by the enzyme telomerase, which is activated by T cell stimulation [243]. The activation of telomerase in stimulated T cells has been shown to require the PKC-dependent stimulation of the hTERT catalytic subunit expression [244], although T lymphocytes activated for different lengths of time may employ distinctive mechanisms to express hTERT. PKC θ -induced expression of hTERT is indirectly mediated by NF- κ B through an increased binding of c-Myc and Sp1 transcription factors to their sites on the hTERT promoter [245], thus providing a proliferative advantage for Ag-specific T cells.

PKC θ expression has been previously restricted to the lymphoid lineage, while more recent investigations have defined a role in the response of macrophages to infection [246], suggesting that it also impacts myeloid features by modulating cytokine release and the potential for antigen (Ag) presentation.

Immunosuppression may partially be mediated through the recruitment and induction of FoxP3⁺ regulatory T (Treg) cells that provide the required maintenance of the balance amid tolerance to self-Ags and an effective anti-tumor response [247].

Like for conventional T cells, TCR signals are also critical for the development and activation of Treg-mediated inhibitory function. At variance with functional effector T cells, in Tregs, PKC θ is segregated from the central domain of the IS [248]. Of note, through this differential positioning within the IS, PKC θ would potentially promote the activation of effector T cell functions over Treg inhibitory activity [249]. Accordingly, Ma et al. [250] have proposed that the differentiation of induced (i)Treg cells is inhibited by the PKC θ -mediated AKT-Foxo1/3A pathway [250], while an increase in iTreg-mediated cell immunosuppression has been reported following kinase neutralization [251].

At variance, Gupta et al. showed a substantial reduction in the number of natural (n)CD4⁺Foxp3⁺ Treg cells in mice deficient in PKC θ [252]. The kinase has been reported to control the generation of Tregs, likely through the activation of the calcineurin/NFAT-dependent Ikaros, required for an effectual suppression [253]. Also, PKC θ appears to be required for the effective generation of immunoregulatory CD4⁺ T cells expressing IL-10 [254], thus contributing to the preservation of peripheral tolerance.

Therefore, according to these apparently contrasting results, the precise impact of PKC θ on the signaling controlling effector versus Treg phenotype development has not been completely elucidated and requires further research. However, opposing roles appear to be played by PKC θ in the generation of natural and peripherally induced Tregs.

4.1.2. PKC α

Alongside PKC θ , the conventional PKC α also plays an important role in promoting an effective T cell-mediated immune response, firstly through a vigorous impact on the differentiation and expansion of immature thymocytes. PKC α is also directly involved in the activation of the PI3K/AKT pathway following TCR activation, by inducing the Ser473 phosphorylation of AKT [210], critical for the kinase full activation. AKT represents a main molecular target of the PD-1 inhibitory activity in T lymphocytes [255,256] and determines a polyfunctional phenotype in Ag-specific CD8⁺ T cells derived from the peripheral blood of melanoma patients [257].

However, in discriminating redundant versus individual functional activities, PKC α has been reported to play a beneficial role in T cell activation, either along with PKC θ , e.g., through the κ B/NF- κ B axis, or via the engagement in distinctive pathways [258]. A fast and transient engagement to the IS in the DG-based signalosome induced by Ag recognition has also been described for PKC α , leading to the activation of Ras/ERK pathway and shedding of CD62L (L-selectin) [259], favoring the progenitor differentiation into effector memory

T cells (TEM), and their migration toward peripheral tissues [260], including tumor sites. Moreover, T cells defective for PKC α fail to stimulate the TCR/NFAT/AP-1 axis, which is involved in the activation of IL-2 and IL-17A promoters [261]. The non-redundancy of roles played by the two kinases in the regulation of T cell development and activation is further advocated by the strong immunosuppressive phenotype derived by the dual PKC θ /PKC α inhibition with sotrastaurin [262].

4.1.3. PKC δ

Among the other isozymes, PKC δ has been reported to control B cell growth and negatively control T cell responses [263]. Gruber et al. demonstrated an increase in terms of both proliferation and IL-2 release in T cells isolated from PKC δ -deficient mice [264], while the interaction of PKC δ with CARMA1 has been reported to impair NF- κ B activation [265]. A critical function for PKC δ in supporting T cell apoptosis has also been reported, following the cytokine deficiency and engagement of Fas, leading to a caspase 3-mediated proteolytic activation [266]. Indeed, when activated, PKC δ translocates to the nucleus, where it supports T cell apoptosis via delivery of cytochrome c, PARP cleavage, histone phosphorylation and caspase 3 stimulation [267].

However, besides these negative regulatory effects, the Thr505-phosphorylated form of PKC δ has been reported to support CD8⁺ cytotoxic T cell response by co-localizing with secretory lysosomes and mediating granules' mobilization and exocytosis in response to TCR signals [268]. More recent studies have suggested that both processes, namely microtubule-organizing center (MTOC) polarization to the IS and granule exocytosis, are controlled by PKC δ , likely through two distinctive and coordinated pathways, involving the reorganization of F-actin at the IS and at the centrosomal area, respectively [269]. Authors have suggested that the existence of two regulatory mechanisms coordinated by PKC δ can establish a fine-tuned production of regulatory checkpoint molecules, supporting a critical role for PKC δ in maintaining T cell homeostasis. Two main types of vesicles have recently been identified based on their content and the requirements of the signal for degranulation: light vesicles carrying FasL and 15 kDa granulysin, released in a PKC-dependent and Ca²⁺-independent mode and dense granules containing perforin, GRZ and 9 kDa granulysin, which require additional Ca²⁺-mediated signals [270,271]. Notably, both types of vesicles also convey several other immunomodulatory proteins including MHC class I and II, costimulatory and adhesion molecules, enzymes (i.e., CD26/DPP4), also endowed with co-stimulatory functions [272] or cytokines, indicating a wider spectrum of influences on different aspects of T cell functional activity.

Of note, by using PRKCD-defective mice, a critical role for PKC δ in limiting the autoimmune features of SLE by restraining the accumulation of autoreactive B cells has been established, thus proving human PKC δ deficiency as crucially involved in autoimmunity generation [273]. Indeed, CD4⁺ T cells from PKC δ defective mice also display distinctive defects, including impaired ERK signaling, reduced DNA methyltransferase 1 (DNMT1) expression and the increased methylation of genes implicated in the amplified immune response scenario representative of lupus [274], supporting a critical role for PKC δ as an immune gatekeeper, as suggested by Salzer et al. [273].

4.1.4. PKC ϵ

At variance with PKC δ , an anti-apoptotic role has been suggested for novel kinase PKC ϵ through the inactivation of BAD, mediated by p90Rsk-dependent phosphorylation [275]. Numerous studies have shown a redundant role for PKC ϵ in terms of the positive regulation of the NF- κ B/NFAT/AP1 pathway [210] and in the recruitment at the center of the IS and MTOC [276], shared with PKC- θ . At variance, the regulation of T cell proliferation and the contribution to a reduced T cell sensitivity to TGF β 1, shown by Mirandola et al. [277] are reasonably not redundant. This is of critical interest, considering the role of TGF β 1 in promoting both the generation of Tregs [278] and T lymphocytes with features of tissue-residency, the latter through the induction of integrin CD103 [279,280].

A considerable fraction of tumor-infiltrating CD8⁺ T lymphocytes is represented by this tissue resident memory cell (T_{RM}) population, which has emerged as one of the key tumor-reactive T cell subgroups able to exert optimal protective immunity. Accordingly, a key role for CD103⁺CD8⁺ T_{RM} has also been described in terms of response to PD-1 blockade [281].

T_{RM} accumulate in different human cancers, including NSCLC, and are characterized by the expression, besides CD103, also of C-type lectin CD69, which both contribute to their residency features [282]. A seminal work by Le Floch [283] described the involvement of the PLC/PKC signaling pathways in CD103-dependent TCR-mediated cytotoxicity. A role for PKC δ in MTOC cytolytic granule polarization and degranulation has also been described above [268]. Of note, the engagement of CD103 in tumor-specific cytotoxic T cells with its own ligand E-cadherin has been reported to increase the interaction with the target cell, likely lowering the threshold for the TCR/CD3 signal activation while supporting polarization and granule delocalization throughout the stimulation of PLC/PKC.

4.1.5. PKC η

PKC η , another member of the novel PKC subfamily, is also highly expressed in T cells, endowed with several redundant functions shared with PKC θ . Notably, this isoform is recruited to the IS upon TCR stimulation, but unlike PKC θ , which is concentrated at the central region of the synapse, PKC η diffuses over the whole synapse area [284], as described for PKC θ in the absence of CD28. Since T cell differentiation correlates with the loss of co-stimulatory molecule CD28 [285], distinctive and/or cooperative roles for the two isoforms in the TCR-associated signalosome according to the differentiative status of T cells can be hypothesized.

PKC η -deficient Treg cells have shown defective suppressive activity. Of note, PKC η associates with and recruits CTLA-4, required for contact-dependent suppression, along with the GIT2- α PIX-PAK complex. The defective activation of this complex in PKC η -deficient Tregs has been associated with a reduced depletion of the co-stimulatory molecule CD86 from APCs, promoted by CTLA-4, implicating this pathway as a potential anti-cancer immunotherapeutic target [286]. Accordingly, the reduced development of both B16-F10 melanoma and TRAMP-C1 adenocarcinoma tumors have been reported in the preclinical models of PKC η defective Tregs, in association with a less immunosuppressive TME, increased the frequency and functionality of tumor-infiltrating CD8⁺ effector T cells and an elevated expression of CD86 on intra-tumoral DCs. At variance, PKC η defective CD8⁺ T cells have not been reported to impact either tumor growth or the frequency and functionality of CD8⁺ effector T cells [287], proving that the acquisition of a more inflamed TME can be achieved by indirectly targeting intra-tumor Treg PKC η .

4.1.6. PKC ζ and PKC ι

The PKC ζ isotype has also been directly involved in the differentiation of Th2 T cells [288] and in IL-2-mediated proliferation [289], thus showing redundancy but also cooperation with PKC θ , especially in the activation of NF- κ B [218,261].

A redundant role for PKC ζ and PKC ι , both required for T cell motility and the ability to scan DCs for chemokine receptors has been suggested [290]. PKC ζ has also been reported to post-transcriptionally control the telomerase enzyme, through the phosphorylation of hTERT [291], thus contributing to a long-term proliferative potential of Ag-specific T cells through telomere elongation. The impact of PKC isoforms on T cell activity is summarized in Figure 1.

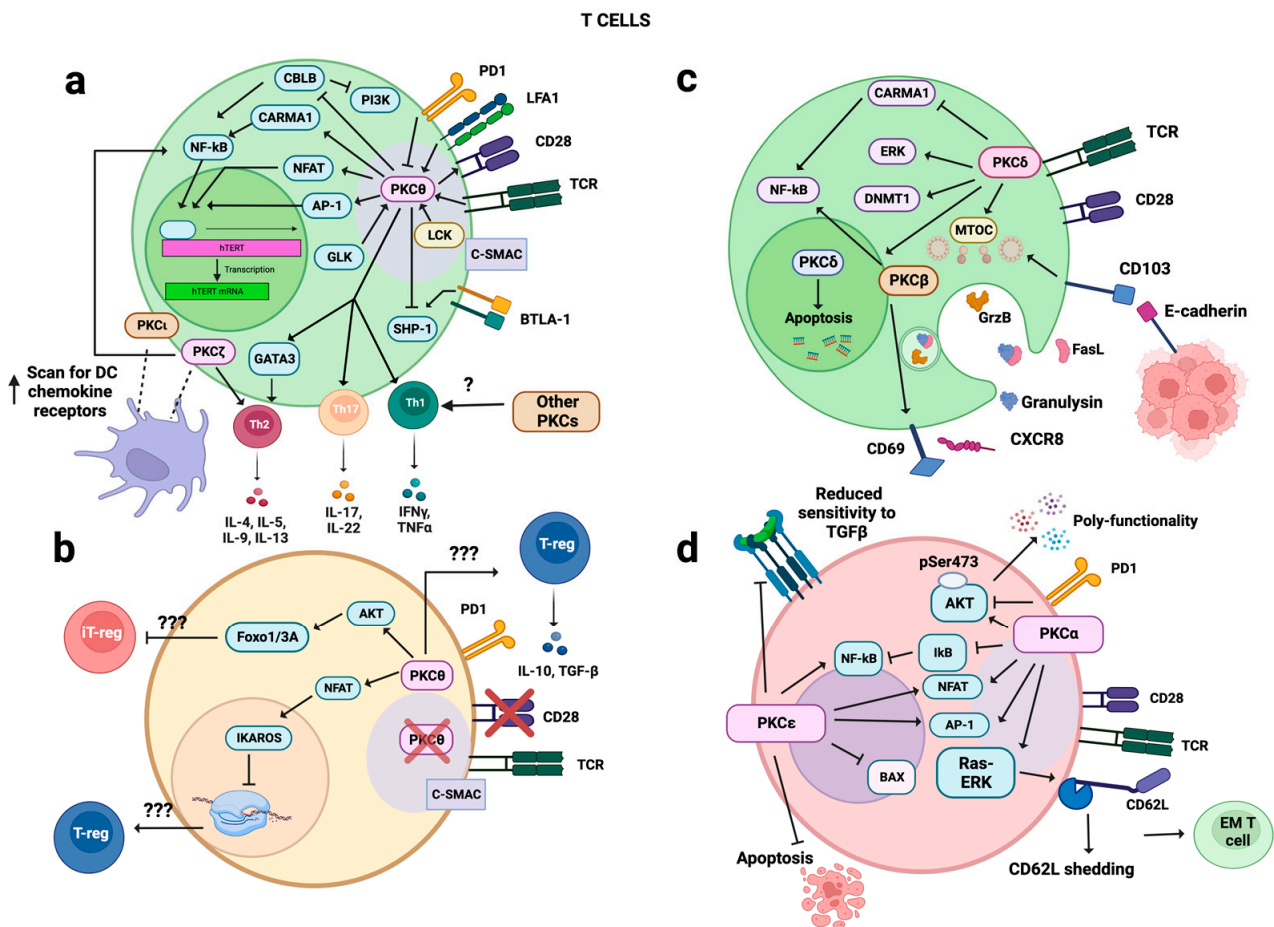


Figure 1. Impact of the main PKC isoforms on different aspects and inter-players of T cell functionality. (a) The main roles of PKCθ and interactions with inter-players involved in T cell activation; localization of PKCθ within the cSMAC in the presence of CD28; role of PKCθ in T cell differentiation; role of PKCζ and PKCι in terms of DC scan for chemokine receptors and of PKCζ in terms of Th2 cell differentiation. (b) Localization of PKCθ outside the cSMAC in the absence of CD28 and in Tregs; impact of PKCθ in terms of either favoring/inhibiting Treg differentiation. (c) Negative impact of PKCδ on T cell activation and positive influence on MTOC polarization and degranulation, positive impact of PKCβ on T cell activation. (d) Positive effect of PKCα on T cell activation and on TEM development via CD62L shedding; positive effect of PKCε on T cell activation and protective effects from T cell apoptosis; induction of reduced sensitivity to the effects of TGFβ. Created with <https://www.biorender.com> (accessed on 28 June 2023).

Among the multiple PKC isoforms expressed by B cells, PKCβI and PKCβII play a critical role in B cell development, activation/proliferation, and guide the microtubule polarization resulting from LFA-1 engagement in the IS [292–295]. PKCβ has also been reported to be implicated in either *IL2* gene transcription and/or release [295,296] in T cells, through the activation of MAPK/NF-κB/NFAT pathway, while at variance, another study only provided evidence of an involvement of PKCβ in *IL-2* exocytosis. A PKCβ involvement in the increase in CD69 levels was involved in tissue residency [297] was also suggested, along with the production of CXCL8 chemokine [298], the latter reported as pro-tumorigenic in the TME by supporting tumor persistence, EMT, angiogenesis and impairment of anti-tumor responses [299].

4.2. Potential Impact of PKC on TME Features and Immunotherapies

4.2.1. Impact of PKC on Intra-Tumor Macrophage Polarization

ICB agents work by reinvigorating anti-tumor T cell responses and have revolutionized cancer therapy showing unprecedented antitumor responses [300]. However, most patients do not respond adequately, especially to monotherapies. Therefore, a deeper knowledge of the mechanisms underlying resistance is strongly required.

Favorable clinical responses to immunotherapy have been correlated with a highly infiltrated inflamed TME [301]. However, the degree of spontaneous immune infiltration in tumors varies extensively between individual patients; therefore, tailored patient-specific therapeutic manipulations can potentially improve the extent of intra-tumor T cell infiltration. Patients not responding to immunotherapy show high levels of circulating myeloid-derived suppressor cells (MDSCs), an immunosuppressive innate cell population which expands in pathological settings including cancer, comprising two subgroups: the polymorphonuclear MDSCs (PMN-MDSCs) and the monocytic MDSCs (M-MDSCs) [302].

According to a pre-print research report by Chaib et al. [303], PKC δ is highly expressed in mononuclear phagocytes involved in cancer growth. The absence of PKC δ in the preclinical models of knock-out mice was associated with reduced tumor development and a higher responsiveness to PD-1 blockade. Moreover, the absence of PKC δ in M2-like macrophages has been related to higher T cell activation than in the presence of wild-type M2-like macrophages, delayed tumor growth and an immune landscape skewed towards a Th1 phenotype. Lastly, the loss of PKC δ has been shown to increase Ag presenting competence in macrophages and DCs and trigger type I and type II interferon signaling, proposing PKC δ that is a reasonable target to reprogram mononuclear phagocytes and increase intra-tumor T cell migration while improving the PD-1 blockade efficacy [303].

Similarly, in hepatocellular carcinoma (HCC) patients, a high expression of PKC α has been reported to stimulate the M2-like polarization of macrophages, accompanied by immune escape and a lack of response to the anti-PD1 blockade by promoting the nuclear import of ZFP64 [304].

At variance, the employment of a syngeneic mouse model has demonstrated how the pharmacological stimulation of PKC with the plant extract ingenol mebutate (PEP005) or prostratin PKC agonists is able to reduce the MDSC development from cellular precursors while stimulating the development of a cDC1-associated APC-like phenotype via the activation of p38MAPK [305], thus impairing the MDSC suppressive function. Of note, the combined activation of PKC and CD40 has been reported to significantly reduce breast cancer growth while increasing intra-tumor CD8⁺ T cell activation and T_{RM} frequency in a mouse preclinical model. This apparent discrepancy between the two studies from Chaib et al. [303,305] prompts the requirement for more specific PKC modulators, with either an inhibitory or agonistic effect, not able to target other PKC isoforms sharing structure resemblances, which can impair the expected outcomes.

Among cancers poorly responding to ICB therapy, the EGFR-mutated lung tumor has been described to achieve a modest advantage in clinical settings [306,307], likely due to an insufficient intra-tumor T cell recruitment, speaking in favor of a non-inflamed tumor site. Small-molecule inhibitors of tyrosine kinase EGFR represent the favorite first-line approach for EGFR-mutant NSCLC. Nevertheless, frequent drug resistance severely restrains stable therapeutic effectiveness, although successful alternative approaches are not presently available. Of relevance, PKC δ represents one of the immune rheostats responsible for the establishment of non-inflamed phenotype in EGFR-mutated lung cancer, also by increasing the expression of PD-1 ligand PD-L1 on tumor cells [308], leading to immune exclusion and cancer escape from T cell surveillance. Accordingly, PKC δ blockade has been shown to improve intra-tumor T cell infiltration and inhibit tumor expansion while increasing tumor susceptibility to ICB therapy in both in vitro and in vivo settings.

4.2.2. Impact of PKC on Tumor-Infiltrating T Cells

While the normal function of PKC θ in T cells is well established, a deeper knowledge about its roles in immunotherapy resistance and dysfunctionality of T cells is strongly required. PKC θ can be endowed with both cytoplasmic and nuclear functions, and nuclear chromatin-associated PKC θ is increasingly acknowledged as pathogenic in cancer settings, while its cytoplasmic roles are relevant in normal T cell functions. Nuclear chromatin-associated is enriched in PKC θ in circulating tumor cells in patients with triple-negative breast cancer (TNBC) brain metastases and immunotherapy-resistant metastatic melanoma and has been associated with poor survival in immunotherapy-resistant disease. Furthermore, increased levels of nuclear PKC θ associated with the transcription factor ZEB1 have been detected within CD8 $^+$ T cells isolated from immunotherapy-resistant metastatic cancer patients. Based on the previous identification of a nuclear localization signal motif in PKC θ [309], a novel PKC θ inhibitor (nPKC- θ i2) that specifically inhibits nuclear translocation of PKC θ without interrupting normal catalytic signaling in healthy T cells has recently been described [310]. The inhibition of nuclear PKC θ partially overcomes metastatic tumor growth by inhibiting mesenchymal signatures in murine TNBCs. In addition, nPKC- θ i2 has been shown to impair the ZEB1/PKC θ complex while inducing cytokine release in CD8 $^+$ T cells isolated from immunotherapy-resistant patients. Overall, targeting nuclear PKC θ could represent a combinatorial approach able to re-invigorate dysfunctional T cells in immunotherapy-resistant patients.

Unfortunately, this could not be the case for some T cell NHL patients who have experienced hyper progression following PD-1 blockade, due to a significant re-invigoration of CD4 $^+$ malignant T cells expressing high levels of expressions of activated p-PKC θ (Thr538), leading to the hyper activation of the oncogenic TCR-associated pathway [311].

Lymphocyte activation gene 3 (LAG-3, also known as CD223) is an IC belonging to the immunoglobulin superfamily (IgSF) [312], strictly associated with human tumor prognosis, mostly negative, but also to positive outcomes, like in gastric carcinoma and melanoma [313]. LAG-3 is expressed by both effector T cells and Tregs [314] under continuous Ag stimulation, contributing to T cell exhaustion and increase in Treg immunosuppressive functions. Both the upregulation and the transport to the T cell surface of LAG-3 are mediated by PKC [315], although the distinctive kinase isoform involved is not specified in the study. While the reported PKC-mediated down-regulation of CD4 expression is mediated by a direct Ser phosphorylation and endocytosis [316,317], PKC may induce a conformational change of the adaptor molecule interacting with LAG-3, which leads to the IC translocation to the cell surface. This prompted the authors to propose that PKC signaling may act as one of the switches to turn off T cell activation to achieve T cell homeostasis.

According to the negative impact demonstrated by the seminal studies described above, a single-cell RNA sequencing (RNA-seq) study by Cron et al. [318] demonstrated that a single-nucleotide polymorphism (SNP) mutation, associated with a lower expression of PKC δ and implying a loss-of-function phenotype, results in a reduced B16.SIY melanoma growth, along with an increased intra-tumor infiltration of CD8 $^+$ T cells at the endpoint and better response to anti-PD-L1 therapy [318]. However, confirming previous studies, PKC δ loss has mostly been shown to modify gene expression in myeloid cell subsets, leading to the increased expression of M1-associated genes and the decreased expression of M2-associated genes in PKC $\delta^{-/-}$ chimeras.

These findings establish that germline modifications in immune regulatory genes can profoundly affect anti-tumor immunity and the efficacy of PD-1/PD-L1 blockade, as described previously, in the case of decreased expression/activity of PKC δ in myeloid lineage mediating improved anti-tumor immunity by altering the M1/M2 ratio.

Among other isoforms, PKC η has been shown to potentially synergize with CTLA-4 to mediate immune tolerance, by mediating the regulatory Treg function downstream of the checkpoint molecule [286], PKC η induces anti-inflammatory cytokine transcription by activating NF- κ B downstream of the cascade [319]. Accordingly, the PKC η defect in murine

models has been shown to reduce the tumor-suppressive activity of Tregs in the absence of autoimmune reactions [286] while reducing tumor growth [320].

Of note, a valuable study was conducted by Abdelatty et al. [321] by employing the single-cell gene set enrichment analysis and the ESTIMATE methods to analyze the tumor-infiltrating lymphocytes (TILs) and the immune components found within 28 cancer types, and correlating response to immunotherapies with PKC levels, based on human leukocytic antigen gene enrichment scores and PD-L1 expression. Univariate and multivariate Cox analysis was performed to evaluate the prognostic role of PKC genes in a pan-cancer analysis, and PKC isoenzymes were found to be solid biomarkers for the tumor immune status, with a distinctive PKC gene expression differently impacting the clinical outcome of cancer patients after immunotherapies. Altogether, the transcripts coding for PKC β , PKC ϵ and PKC θ were positively related to the response to immunotherapies, while PKC ι and PKC ζ proved mainly detrimental in most cancers.

Also, most PKC isoforms were directly related to intra-tumor PD-L1 expression, with the exception of PKC θ that instead showed a reversed correspondence with PD-L1 in 23 out of the 28 tumors analyzed.

Accordingly, atypical PKC ι has been shown to condition the tumor microenvironment via the YAP1 factor by reducing T cell infiltration and suppressing the host immune response in ovarian [322] and pancreatic adenocarcinoma (PDAC) [323]. Of note, PKC ι -YAP1 signaling has been reported to increase the expression of PD-L1 in PDAC through STAT3 phosphorylation at Tyr705, contributing to PDAC resistance against cytotoxic NK cells [323].

Tumor-infiltrating CD8⁺ T cells expressing high levels of CD226, previously known as DNAX accessory molecule-1 (DNAM-1), possess greater self-renewal capacity and responsiveness [324]. PKC(ζ)-mediated phosphorylation of Ser329 [325] is critically required for CD226 adhesion and the association with lipid rafts and LFA [326], a prerequisite for phosphorylation at Tyr322-dependent full activation. Immune checkpoint T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) affects CD8⁺ T and NK cell functionality [327] by engaging with CD226, similarly to the reported commitment between PD-1 and CD28 [224,225], and the blockade of TIGIT has been shown to improve CD8⁺ T cell responses selectively affecting CD226hiCD8⁺ T cells by promoting CD226 phosphorylation at Tyr322 [328]. Since CD226 agonist antibody-mediated activation of CD226 augments the effect of TIGIT blockade on CD8⁺ T cell responses, PKC can potentially represent a pharmacological target to stimulate intra-tumor CD8⁺ T cells to promote CD226 migration to the lipid raft to facilitate activation by phosphorylation at Tyr322.

As previously discussed, DGK ζ facilitates DAG consumption, limiting PKC-dependent T cell activation and cytotoxic T cell responses. By reducing DAG consumption, the absence of DGK ζ has been shown to improve the associated transcriptional programs, fostering IL-2 release and partly neutralizing the PD-1 repressive impact. In particular, DGK ζ neutralization has been related to the decreased PD-1 expression, increase in cytotoxic CD8⁺ T cells, and reduced MC38 adenocarcinoma growth [329], outlining a task for DGK ζ as a regulator of PD-1 expression.

Of note, the expression of PD-L1 has been associated with reduced aPKC λ levels and poor OS in cutaneous angiosarcoma (CAS) patients, along with the impaired phosphorylation of FoxO1 at Ser218 [330], which is mediated by the kinase [331]. Moreover, the inhibition of aPKC λ has been demonstrated to reduce the PD-L1 expression in cultured endothelial cells, suggesting that the combined treatment with ICIs and aPKC λ inhibitors could represent a therapeutic strategy for CAS patients.

The impact of the PKC β on B cell functionality and the influence of PKC isoforms on the response to ICB are schematized in Figure 2.

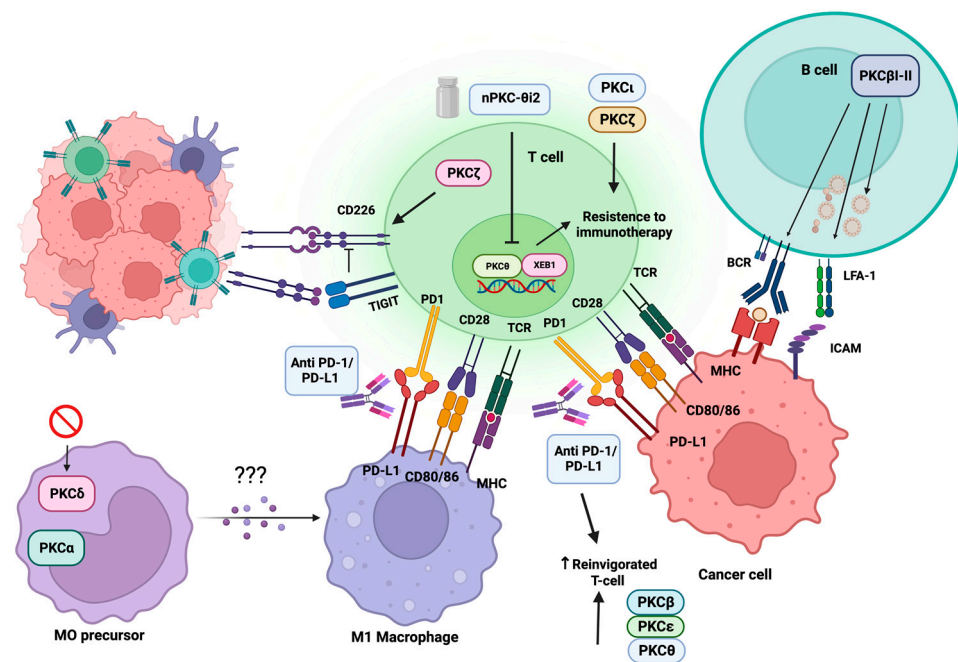


Figure 2. Effect of PKC on B cell activation and response to ICB. Effect of PKC β on B cell activation and MTOC polarization; potential effects of PKC δ on intra-tumor macrophages polarization toward an M2 phenotype and response to ICB; negative impact of intra-nuclear PKC θ (via interaction with the chromatin) in terms of immunotherapy resistance: role of the nPKC- θ i2 compound; impact of PKC ζ on the activation of CD226, critical for competition with the inhibitory molecule TIGIT and for responsiveness to TIGIT blockade; prognostic role of different PKC isoforms in terms of either immunotherapy response/resistance. Created with <https://www.biorender.com> (accessed on 28 June 2023).

5. Conclusions

Our focus on PKC isoforms, while underlining their prevalent oncogenic roles, also highlights controversial aspects mainly attributed to PKC δ and to the suppressor role of PKC ζ . This picture is further complicated by the occurrence of mutations that can either increase or impair the activity of these kinases. Rare variants with significant clinical impact are reported by the ClinVar database. In particular, the mutation 501 of PKC δ is reportedly of uncertain significance (<https://www.ncbi.nlm.nih.gov/clinvar/>, accessed on 15 July 2023). An interesting PKC ι mutation has been reported as pathogenic in SCLC [55], while of relevance, the R480C dPKC ι mutation is one of the most detected in tumors [56]. Different alterations (i.e., single point mutations, splicing variants, fusion proteins) can potentially represent useful markers for the diagnosis of specific tumors, in some cases even targetable with selective drugs, as in the case of enzastaurin, employed to treat melanoma and characterized by the presence of spliced PKC β isoforms.

The complications and setbacks faced in the pharmacology of PKC have generated a difficult perception of the true impact of PKCs in the context of anticancer therapies. After almost three decades of clinical trials with PKC inhibitors, it is clear that the inhibition of PKC alone provides little or no clinical benefit in the treatment of cancer. Furthermore, most of these drugs have not only shown no significant clinical benefit, but in some cases have even worsened patient outcomes. Indeed, as reported by an extensive meta-analysis [332], the combination of enzastaurin [171,172] or aprinocarsen [203] with standard chemotherapy (pemetrexed, erlotinib, gemcitabine, cisplatin, carboplatin) has provided lower response rates and greater adverse effects as compared with chemotherapy alone in recurrent or malignant NSCLC patients [332].

In contrast, clinical studies with midostaurin plus standard chemotherapy in patients with FLT3-mutated AML [158], or with midostaurin alone in patients with advanced

mast cell lymphoma [160] have shown significant clinical advantages, including improved overall response rates, longer event-free survival times and low toxicities.

Whether these midostaurin-induced clinical benefits are due to tyrosine kinase inhibition alone or to the impairment of both, tyrosine kinase and PKC, needs to be evaluated by further investigations.

The failure of the pharmacological inhibition of PKCs in most clinical studies can be explained by the complex biological functions regulated by PKC isoenzymes and their significant expression heterogeneity in different types of cancer [333,334]. Whereas PKCs have generally been considered pro-oncogenic kinases, different isoenzymes are inactivated by loss-of-function mutations in a variety of cancers, thus supporting a potential tumor-suppressive rather than tumor-promoting role for distinctive PKC isoenzymes [334]. In fact, specific PKC isoforms have been implicated in various biological activities in tumor cells, including tumorigenic and anti-tumorigenic, anti-apoptotic or pro-apoptotic, proliferative or anti-proliferative activities [18,335]. Non-specific PKC isoenzymatic inhibitors, particularly those ATP-competitive, can thus block the activation of different PKC isoforms associated with both carcinogenic and antitumor effects, not leading to the expected therapeutic benefit.

A deeper understanding of the expression levels, the mutational status and of the role of distinct PKC isoforms in different cancers may aid in the identification of patients who may benefit from kinase-targeted therapies. Notably, the failure of aprinocarsen, which specifically targets PKC α , is not surprising, given the anti-growth/tumor-suppressive activity of PKC α in leukemia and colorectal, ovarian and possibly NSCL cancer models. Thus, a growing body of evidence suggests that the therapeutic exploitation of PKC α signaling in many cancers will require interventions that enhance rather than suppress PKC α function.

Although PKC inhibitors block the pro-proliferative and apoptotic functions of PKC, which are significantly activated in cancer settings, other cellular signals (e.g., AKT) that promote proliferation and are anti-apoptotic, may be able to replace the PKCs. Noteworthy, some inhibitors of PI3K, which is upstream of PKC and AKT, show significant clinical benefit in cancer treatment [336].

These considerations highlight the need for a better understanding of the pathways involved and the development of new PKC inhibitors for use in clinical practice, with higher isoenzyme specificity.

Furthermore, despite the current use of ICB agents to treat different cancers based on their ability to stimulate tumor-specific T cells, a substantial fraction of patients fails to respond adequately, thus supporting the need for combined therapeutic strategies. Of note, mechanisms produced by the distinctive PKC isoforms described in this review have the potential to support or inhibit ICB-mediated immune recovery. Relevant results could potentially be achieved by inhibiting PKC δ in intratumoral myeloid cells, strongly biased towards the generation of immunosuppressive M2 macrophages. The resulting switch to a preferential M1 generation may ultimately lead to an increased intra-tumor CD8⁺ T cell infiltration [318], one of the prerequisites underlying the success of ICB therapy.

Furthermore, interesting compounds such as nPKC- θ i2, by specifically targeting nuclear PKC θ without disturbing the normal catalytic signaling in T cells [310], can potentially help to prevent the development and metastatization of recalcitrant tumors such as TNBCs, while promoting CD8⁺ T cell function. Therefore, compounds of this type potentially represent promising therapeutic agents to be tested in combination with ICB in tumors that are otherwise poorly responsive to immunotherapies. Of note, the distinctive inhibition of specific forms of PKC with intracellular localizations linked to pathogenic states, may, at least in part, compensate for the current lack of isoform-selective inhibitors.

We can therefore envision that a comprehensive examination of the molecular features of the tumor, in terms of either the expression of distinctive PKC isoenzymes or mutated forms, could contribute to improving the clinical outcome of the PKC blockade. This exploration could also suggest novel and feasible patient-specific immune landscapes

featuring novel targets of PKC inhibition or stimulation. Indeed, individual PKC isoforms can also be potentially predictive of ICB response in several cancer types [321] or could be selectively modulated in immune cell subsets to promote antitumor responses and improve clinical outcomes after immunotherapies. Further investigations, aiming to better elucidate the interactions and the roles, either divergent or collaborative of the different isoforms in antitumor immune responses, may contribute to a better use of PKC both as a therapeutic target and as a biomarker of response to immunotherapies.

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References

1. Takai, Y.; Yamamoto, M.; Inoue, M.; Kishimoto, A.; Nishizuka, Y.A. Proenzyme of Cyclic Nucleotide-Independent Protein Kinase and Its Activation by Calcium-Dependent Neutral Protease from Rat Liver. *Biochem. Biophys. Res. Commun.* **1977**, *77*, 542–550. [[CrossRef](#)] [[PubMed](#)]
2. Mellor, H.; Parker, P.J. The Extended Protein Kinase C Superfamily. *Biochem. J.* **1998**, *332*, 281–292. [[CrossRef](#)] [[PubMed](#)]
3. Stahelin, R.V.; Digman, M.A.; Medkova, M.; Ananthanarayanan, B.; Rafter, J.D.; Melowic, H.R.; Cho, W. Mechanism of diacylglycerol-induced membrane targeting and activation of protein kinase Cdelta. *J. Biol. Chem.* **2004**, *279*, 29501–29512. [[CrossRef](#)]
4. Nishizuka, Y.; Nakamura, S. Lipid Mediators and Protein Kinase C For Intracellular Signalling. *Clin. Exp. Pharmacol. Physiol. Suppl.* **1995**, *22*, S202–S203. [[CrossRef](#)]
5. Newton, A.C. Protein kinase C: Structural and spatial regulation by phosphorylation, cofactors, and macromolecular interactions. *Chem. Rev.* **2001**, *101*, 2353–2364. [[CrossRef](#)]
6. Kajimoto, T.; Caliman, A.D.; Tobias, I.S.; Okada, T.; Pilo, C.A.; Van, A.-A.N.; Andrew McCammon, J.; Nakamura, S.; Newton, A.C. Activation of Atypical Protein Kinase C by Sphingosine 1-Phosphate Revealed by an aPKC-Specific Activity Reporter. *Sci. Signal* **2019**, *12*, aat6662. [[CrossRef](#)]
7. Velnati, S.; Centonze, S.; Girivetto, F.; Capello, D.; Biondi, R.M.; Bertoni, A.; Cantello, R.; Ragnoli, B.; Malerba, M.; Graziani, A.; et al. Identification of Key Phospholipids That Bind and Activate Atypical PKCs. *Biomedicines* **2021**, *9*, 45. [[CrossRef](#)]
8. Reyland, M.E. Protein Kinase C Isoforms: Multi-Functional Regulators of Cell Life and Death. *Front. Biosci.* **2009**, *14*, 2386–2399. [[CrossRef](#)]
9. He, S.; Li, Q.; Huang, Q.; Cheng, J. Targeting Protein Kinase C for Cancer Therapy. *Cancers* **2022**, *14*, 1104. [[CrossRef](#)] [[PubMed](#)]
10. Newton, A.C. Protein Kinase C: Perfectly Balanced. *Crit. Rev. Biochem. Mol.* **2018**, *53*, 208–230. [[CrossRef](#)]
11. Baffi, T.R.; Van, A.-A.N.; Zhao, W.; Mills, G.B.; Newton, A.C. Protein Kinase C Quality Control by Phosphatase PHLPP1 Unveils Loss-of-Function Mechanism in Cancer. *Mol. Cell* **2019**, *74*, 378–392.e5. [[CrossRef](#)] [[PubMed](#)]
12. Castagna, M.; Takai, Y.; Kaibuchi, K.; Sano, K.; Kikkawa, U.; Nishizuka, Y. Direct Activation of Calcium-Activated, Phospholipid-Dependent Protein Kinase by Tumor-Promoting Phorbol Esters. *J. Biol. Chem.* **1982**, *257*, 7847–7851. [[CrossRef](#)] [[PubMed](#)]
13. De Vries, D.J.; Herald, C.L.; Pettit, G.R.; Blumberg, P.M. Demonstration of Sub-Nanomolar Affinity of Bryostatin 1 for the Phorbol Ester Receptor in Rat Brain. *Biochem. Pharmacol.* **1988**, *37*, 4069–4073. [[CrossRef](#)] [[PubMed](#)]
14. Abb, J.; Bayliss, G.J.; Deinhardt, F. Lymphocyte Activation by the Tumor-Promoting Agent 12-O-Tetradecanoylphorbol-13-Acetate (TPA). *J. Immunol.* **1979**, *122*, 1639–1642. [[CrossRef](#)]
15. Kawano, T.; Inokuchi, J.; Eto, M.; Murata, M.; Kang, J.-H. Activators and Inhibitors of Protein Kinase C (PKC): Their Applications in Clinical Trials. *Pharmaceutics* **2021**, *13*, 1748. [[CrossRef](#)]
16. Parker, P.J.; Brown, S.J.; Calleja, V.; Chakravarty, P.; Cobbaut, M.; Linch, M.; Marshall, J.J.T.; Martini, S.; McDonald, N.Q.; Soliman, T.; et al. Equivocal, Explicit and Emergent Actions of PKC Isoforms in Cancer. *Nat. Rev. Cancer* **2021**, *21*, 51–63. [[CrossRef](#)]
17. Newton, A.C.; Brognard, J. Reversing the Paradigm: Protein Kinase C as a Tumor Suppressor. *Trends Pharmacol. Sci.* **2017**, *38*, 438–447. [[CrossRef](#)]
18. Garg, R.; Benedetti, L.G.; Abera, M.B.; Wang, H.; Abba, M.; Kazanietz, M.G. Protein kinase C and cancer: What we know and what we do not. *Oncogene* **2014**, *33*, 5225–5237. [[CrossRef](#)]

19. Regala, R.P.; Weems, C.; Jamieson, L.; Khor, A.; Edell, E.S.; Lohse, C.M.; Fields, A.P. Atypical Protein Kinase C ϵ Is an Oncogene in Human Non-Small Cell Lung Cancer. *Cancer Res.* **2005**, *65*, 8905–8911. [[CrossRef](#)]
20. Zhang, L.; Huang, J.; Yang, N.; Liang, S.; Barchetti, A.; Giannakakis, A.; Cadungog, M.G.; O'Brien-Jenkins, A.; Massobrio, M.; Roby, K.F.; et al. Integrative Genomic Analysis of Protein Kinase C (PKC) Family Identifies PKC ϵ as a Biomarker and Potential Oncogene in Ovarian Carcinoma. *Cancer Res.* **2006**, *66*, 4627–4635. [[CrossRef](#)]
21. Cacace, A.M.; Guadagno, S.N.; Krauss, R.S.; Fabbro, D.; Weinstein, I.B. The epsilon isoform of protein kinase C is an oncogene when overexpressed in rat fibroblasts. *Oncogene* **1993**, *8*, 2095–2104. [[PubMed](#)]
22. Reyland, M.E. Protein kinase Cdelta and apoptosis. *Biochem. Soc. Trans.* **2007**, *35*, 1001–1004. [[CrossRef](#)] [[PubMed](#)]
23. Ma, L.; Tao, Y.; Duran, A.; Llado, V.; Galvez, A.; Barger, J.F.; Castilla, E.A.; Chen, J.; Yajima, T.; Porollo, A.; et al. Control of Nutrient Stress-Induced Metabolic Reprogramming by PKC ζ in Tumorigenesis. *Cell* **2013**, *152*, 599–611. [[CrossRef](#)]
24. Cerami, E.; Gao, J.; Dogrusoz, U.; Gross, B.E.; Sumer, S.O.; Aksoy, B.A.; Jacobsen, A.; Byrne, C.J.; Heuer, M.L.; Larsson, E.; et al. The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* **2012**, *2*, 401–404. [[CrossRef](#)]
25. Antal, C.E.; Hudson, A.M.; Kang, E.; Zanca, C.; Wirth, C.; Stephenson, N.L.; Trotter, E.W.; Gallegos, L.L.; Miller, C.J.; Furnari, F.B.; et al. Cancer-Associated Protein Kinase C Mutations Reveal Kinase's Role as Tumor Suppressor. *Cell* **2015**, *160*, 489–502. [[CrossRef](#)]
26. Prévostel, C.; Alvaro, V.; de Boisvilliers, F.; Martin, A.; Jaffiol, C.; Joubert, D. The natural protein kinase C alpha mutant is present in human thyroid neoplasms. *Oncogene* **1995**, *11*, 669–674.
27. Zhu, Y.; Dong, Q.; Tan, B.J.; Lim, W.G.; Zhou, S.; Duan, W. The PKCalpha-D294G mutant found in pituitary and thyroid tumors fails to transduce extracellular signals. *Cancer Res.* **2005**, *65*, 4520–4524. [[CrossRef](#)]
28. Assert, R.; Kötter, R.; Schiemann, U.; Goretzki, P.; Pfeiffer, A.F. Effects of the putatively oncogenic protein kinase Calpha D294G mutation on enzymatic activity and cell growth and its occurrence in human thyroid neoplasias. *Horm. Metabol. Res.* **2022**, *34*, 311–317. [[CrossRef](#)]
29. Goode, B.; Mondal, G.; Hyun, M.; Ruiz, D.G.; Lin, Y.H.; Van Ziffle, J.; Joseph, N.M.; Onodera, C.; Talevich, E.; Grenert, J.P.; et al. A recurrent kinase domain mutation in PRKCA defines chordoid glioma of the third ventricle. *Nat. Commun.* **2018**, *9*, 810–818. [[CrossRef](#)]
30. Rosenberg, S.; Simeonova, I.; Bielle, F.; Verreault, M.; Bance, B.; Le Roux, I.; Daniau, M.; Nadaradjane, A.; Gleize, V.; Paris, S.; et al. A recurrent point mutation in PRKCA is a hallmark of chordoid gliomas. *Nat. Commun.* **2018**, *9*, 2371. [[CrossRef](#)] [[PubMed](#)]
31. Callender, J.A.; Yang, Y.; Lordén, G.; Stephenson, N.L.; Jones, A.C.; Brognard, J.; Newton, A.C. Protein kinase C α gain-of-function variant in Alzheimer's disease displays enhanced catalysis by a mechanism that evades down-regulation. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E5497–E5505. [[CrossRef](#)] [[PubMed](#)]
32. Bridge, J.A.; Liu, X.Q.; Sumegi, J.; Nelson, M.; Reyes, C.; Bruch, L.A.; Rosenblum, M.; Puccioni, M.J.; Bowdino, B.S.; McComb, R.D. Identification of a novel, recurrent SLC44A1-PRKCA fusion in papillary glioneuronal tumor. *Brain Pathol.* **2013**, *23*, 121–128. [[CrossRef](#)] [[PubMed](#)]
33. Lordén, G.; Wozniak, J.M.; Doré, K.; Dozier, L.E.; Cates-Gatto, C.; Patrick, G.N.; Gonzalez, D.J.; Roberts, A.J.; Tanzi, R.E.; Newton, A.C. Enhanced activity of Alzheimer disease-associated variant of protein kinase C α drives cognitive decline in a mouse model. *Nat. Commun.* **2022**, *13*, 7200. [[CrossRef](#)]
34. Płaszczycza, A.; Nilsson, J.; Magnusson, L.; Brosjö, O.; Larsson, O.; Vult von Steyern, F.; Domanski, H.A.; Lilljebjörn, H.; Fioretos, T.; Tayebwa, J.; et al. Fusions involving protein kinase C and membrane-associated proteins in benign fibrous histiocytoma. *Int. J. Biochem. Cell Biol.* **2014**, *53*, 475–481. [[CrossRef](#)] [[PubMed](#)]
35. Pavlovic, Z.; Zhu, L.; Pereira, L.; Singh, R.K.; Cornell, R.B.; Bakovic, M. Isoform-specific and protein kinase C-mediated regulation of CTP: Phosphoethanolamine cytidylyltransferase phosphorylation. *J. Biol. Chem.* **2014**, *289*, 9053–9064. [[CrossRef](#)] [[PubMed](#)]
36. Lee, S.H.; Chen, T.; Zhou, J.; Hofmann, J.; Beppler, G. Protein kinase C-beta gene variants, pathway activation, and enzastaurin activity in lung cancer. *Clin. Lung Cancer* **2010**, *1*, 169–175. [[CrossRef](#)]
37. Voris, J.P.; Sitailo, L.A.; Rahn, H.R.; Defnet, A.; Gerds, A.T.; Sprague, R.; Yadav, V.; Caroline Le Poole, I.; Denning, M.F. Functional alterations in protein kinase C beta II expression in melanoma. *Pigment. Cell Melanoma Res.* **2010**, *23*, 216–224. [[CrossRef](#)]
38. Lintas, C.; Sacco, R.; Garbett, K.; Mirnics, K.; Militerni, R.; Bravaccio, C.; Curatolo, P.; Manzi, B.; Schneider, C.; Melmed, R.; et al. Involvement of the PRKCB1 gene in autistic disorder: Significant genetic association and reduced neocortical gene expression. *Mol. Psychiatry* **2009**, *14*, 705–718. [[CrossRef](#)]
39. Gould, C.M.; Kannan, N.; Taylor, S.S.; Newton, A.C. The Chaperones Hsp90 and Cdc37 Mediate the Maturation and Stabilization of Protein Kinase C through a Conserved PXXP Motif in the C-Terminal Tail. *J. Biol. Chem.* **2009**, *284*, 4921–4935. [[CrossRef](#)]
40. Mouradov, D.; Sloggett, C.; Jorissen, R.N.; Love, C.G.; Li, S.; Burgess, A.W.; Arango, D.; Strausberg, R.L.; Buchanan, D.; Wormald, S.; et al. Colorectal cancer cell lines are representative models of the main molecular subtypes of primary cancer. *Cancer Res.* **2014**, *74*, 3238–3247. [[CrossRef](#)]
41. Abaan, O.D.; Polley, E.C.; Davis, S.R.; Zhu, Y.J.; Bilke, S.; Walker, R.L.; Pineda, M.; Gindin, Y.; Jiang, Y.; Reinhold, W.; et al. The exomes of the NCI-60 panel: A genomic resource for cancer biology and systems pharmacology. *Cancer Res.* **2013**, *73*, 4372–4382. [[CrossRef](#)]
42. Kataoka, K.; Nagata, Y.; Kitanaka, A.; Shiraishi, Y.; Shimamura, T.; Yasunaga, J.; Totoki, Y.; Chiba, K.; Sato-Otsubo, A.; Nagae, G. Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nat. Genet.* **2015**, *47*, 1304–1315. [[CrossRef](#)] [[PubMed](#)]

43. Lacy, S.E.; Barrans, S.L.; Beer, P.A.; Painter, D.; Smith, A.G.; Roman, E.; Cooke, S.L.; Ruiz, C.; Glover, P.; Van Hoppe, S.J.L.; et al. Targeted sequencing in DLBCL, molecular subtypes, and outcomes: A Haematological Malignancy Research Network report. *Blood* **2020**, *135*, 1759–1771. [[CrossRef](#)] [[PubMed](#)]
44. Yamagishi, M.; Kubokawa, M.; Kuze, Y.; Suzuki, A.; Yokomizo, A.; Kobayashi, S.; Nakashima, M.; Makiyama, J.; Iwanaga, M.; Fukuda, T.; et al. Chronological genome and single-cell transcriptome integration characterizes the evolutionary process of adult T cell leukemia-lymphoma. *Nat. Commun.* **2021**, *12*, 4821. [[CrossRef](#)]
45. Sakihama, S.; Morichika, K.; Saito, R.; Miyara, M.; Miyagi, T.; Hayashi, M.; Uchihara, J.; Tomoyose, T.; Ohshiro, K.; Nakayama, S.; et al. Genetic profile of adult T-cell leukemia/lymphoma in Okinawa: Association with prognosis, ethnicity, and HTLV-1 strains. *Cancer Sci.* **2021**, *112*, 1300–1309. [[CrossRef](#)]
46. Wang, L.; Ni, X.; Covington, K.R.; Yang, B.Y.; Shiu, J.; Zhang, X.; Xi, L.; Meng, Q.; Langridge, T.; Drummond, J.; et al. Genomic profiling of Sézary syndrome identifies alterations of key T cell signaling and differentiation genes. *Nat. Genet.* **2015**, *47*, 1426–1434. [[CrossRef](#)]
47. Kan, Z.; Jaiswal, B.S.; Stinson, J.; Janakiraman, V.; Bhatt, D.; Stern, H.M.; Yue, P.; Haverty, P.M.; Bourgon, R.; Zheng, J.; et al. Diverse Somatic Mutation Patterns and Pathway Alterations in Human Cancers. *Nature* **2010**, *466*, 869–873. [[CrossRef](#)]
48. Creixell, P.; Schoof, E.M.; Simpson, C.D.; Longden, J.; Miller, C.J.; Lou, H.J.; Perryman, L.; Cox, T.R.; Zivanovic, N.; Palmeri, A.; et al. Kinome-Wide Decoding of Network-Attacking Mutations Rewiring Cancer Signaling. *Cell* **2015**, *163*, 202–217. [[CrossRef](#)] [[PubMed](#)]
49. Guo, Y.; Li, W.; Qian, M.; Jiang, T.; Guo, P.; Du, Q.; Lin, N.; Xie, X.; Wu, Z.; Lin, D.; et al. D-4F Ameliorates Contrast Media-Induced Oxidative Injuries in Endothelial Cells via the AMPK/PKC Pathway. *Front. Pharmacol.* **2021**, *11*, 556074–556089. [[CrossRef](#)]
50. Guo, X. Studying potential PKC δ loss of function mutation and its downstream effects in gastric cancer progression. In Proceedings of the 2nd International Academic Conference on Energy Conservation, Environmental Protection and Energy Science (ICEPE 2021), E3S Web of Conferences, Dali, China, 11–12 November 2021; Volume 271. [[CrossRef](#)]
51. Ghosh, P.M.; Bedolla, R.; Mikhailova, M.; Kreisberg, J.I. RhoA-dependent murine prostate cancer cell proliferation and apoptosis: Role of protein kinase Czeta. *Cancer Res.* **2002**, *62*, 2630–2636. [[PubMed](#)]
52. Whyte, J.; Thornton, L.; McNally, S.; McCarthy, S.; Lanigan, F.; Gallagher, W.M.; Stein, T.; Martin, F. PKCzeta regulates cell polarisation and proliferation restriction during mammary acinus formation. *J. Cell Sci.* **2010**, *123*, 3316–3328. [[CrossRef](#)]
53. Lakshmi, J.; Alvarez-Perez, J.C.; Rosselot, C.; Casinelli, G.P.; Stamateris, R.E.; Rausell-Palamos, F.; O'Donnell, C.P.; Vasavada, R.C.; Scott, D.K.; Alonso, L.C.; et al. PKC ζ Is Essential for Pancreatic β -Cell Replication During Insulin Resistance by Regulating mTOR and Cyclin-D2. *Diabetes* **2016**, *65*, 1283–1296. [[CrossRef](#)] [[PubMed](#)]
54. Bensen, R.; Brognard, J. New Therapeutic Opportunities for the Treatment of Squamous Cell Carcinomas: A Focus on Novel Driver Kinases. *Int. J. Mol. Sci.* **2021**, *22*, 2831. [[CrossRef](#)]
55. Rudin, C.M.; Durinck, S.; Stawiski, E.W.; Poirier, J.T.; Modrusan, Z.; Shames, D.S.; Bergbower, E.A.; Guan, Y.; Shin, J.; Guillory, J.; et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat. Genet.* **2012**, *44*, 1111–1116. [[CrossRef](#)] [[PubMed](#)]
56. Reina-Campos, M.; Diaz-Meco, M.T.; Moscat, J. The Dual Roles of the Atypical Protein Kinase Cs in Cancer. *Cancer Cell* **2019**, *36*, 218–235. [[CrossRef](#)] [[PubMed](#)]
57. Linch, M.; Sanz-Garcia, M.; Soriano, E.; Zhang, Y.; Riou, P.; Rosse, C.; Cameron, A.; Knowles, P.; Purkiss, A.; Kjaer, S.; et al. A Cancer-Associated Mutation in Atypical Protein Kinase C ι Occurs in a Substrate-Specific Recruitment Motif. *Sci. Signal* **2013**, *6*, ra82. [[CrossRef](#)]
58. Gwak, J.; Jung, S.-J.; Kang, D.-I.; Kim, E.-Y.; Don Kim, D.-E.; Chung, Y.-H.; Shin, J.-G.; Oh, S. Stimulation of Protein Kinase C- α Suppresses Colon Cancer Cell Proliferation by Down-Regulation of beta-Catenin. *J. Cell Mol. Med.* **2009**, *13*, 2171–2180. [[CrossRef](#)]
59. Oster, H.; Leitges, M. Protein Kinase C α but Not PKC ζ , Suppresses Intestinal Tumor Formation in ApcMin/+ Mice. *Cancer Res.* **2006**, *66*, 6955–6963. [[CrossRef](#)] [[PubMed](#)]
60. Hill, K.S.; Erdogan, E.; Khor, A.; Walsh, M.P.; Leitges, M.; Murray, N.R.; Fields, A.P. Protein Kinase C α Suppresses Kras-Mediated Lung Tumor Formation through Activation of a P38 MAPK-TGF β Signaling Axis. *Oncogene* **2013**, *33*, 2134–2144. [[CrossRef](#)]
61. Lin, S.C.; Chen, W.Y.; Lin, K.Y.; Chen, S.H.; Chang, C.C.; Lin, S.E.; Fang, C.L. Clinicopathological correlation and prognostic significance of protein kinase α overexpression in human gastric carcinoma. *PLoS ONE* **2013**, *8*, e56675. [[CrossRef](#)]
62. Kong, C.; Zhu, Y.; Liu, D.; Yu, M.; Li, S.; Li, Z.; Sun, Z.; Liu, G. Role of protein kinase C- α in superficial bladder carcinoma recurrence. *Urology* **2005**, *65*, 1228–1232. [[CrossRef](#)] [[PubMed](#)]
63. Haughian, J.M.; Bradford, A.P. Protein kinase C α (PKC α) regulates growth and invasion of endometrial cancer cells. *J. Cell Physiol.* **2009**, *220*, 112–118. [[CrossRef](#)] [[PubMed](#)]
64. Frankel, L.B.; Lykkesfeldt, A.E.; Hansen, J.B.; Stenvang, J. Protein Kinase C α is a marker for antiestrogen resistance and is involved in the growth of tamoxifen resistant human breast cancer cells. *Breast Cancer Res. Treat.* **2007**, *104*, 165–179. [[CrossRef](#)] [[PubMed](#)]
65. Tam, W.L.; Lu, H.; Buikhuisen, J.; Soh, B.S.; Lim, E.; Reinhardt, F.; Wu, Z.J.; Krall, J.A.; Bierie, B.; Guo, W.; et al. Protein Kinase C α Is a Central Signaling Node and Therapeutic Target for Breast Cancer Stem Cells. *Cancer Cell* **2013**, *24*, 347–364. [[CrossRef](#)]
66. Tonetti, D.A.; Chisamore, M.J.; Grdina, W.; Schurz, H.; Jordan, V.C. Stable Transfection of Protein Kinase C Alpha cDNA in Hormone-Dependent Breast Cancer Cell Lines. *Br. J. Cancer* **2000**, *83*, 782–791. [[CrossRef](#)]

67. Chisamore, M.J.; Ahmed, Y.; Bentrem, D.J.; Jordan, V.C.; Tonetti, D.A. Novel antitumor effect of estradiol in athymic mice injected with a T47D breast cancer cell line overexpressing protein kinase Calpha. *Clinical Cancer Res.* **2001**, *7*, 3156–3165.
68. Yun, J.; Pannuti, A.; Espinoza, I.; Zhu, H.; Hicks, C.; Zhu, X.; Caskey, M.; Rizzo, P.; D'Souza, G.; Backus, K.; et al. Crosstalk between PKC α and Notch-4 in Endocrine-Resistant Breast Cancer Cells. *Oncogenesis* **2013**, *2*, e60. [[CrossRef](#)] [[PubMed](#)]
69. Assender, J.W.; Gee, J.M.W.; Lewis, I.; Ellis, I.O.; Robertson, J.F.R.; Nicholson, R.I. Protein Kinase C Isoform Expression as a Predictor of Disease Outcome on Endocrine Therapy in Breast Cancer. *J. Clin. Pathol.* **2007**, *60*, 1216–1221. [[CrossRef](#)]
70. Tonetti, D.A.; Morrow, M.; Kidwai, N.; Gupta, A.; Badve, S. Elevated Protein Kinase C Alpha Expression May Be Predictive of Tamoxifen Treatment Failure. *Br. J. Cancer* **2003**, *88*, 1400–1402. [[CrossRef](#)]
71. Tan, M.; Li, P.; Sun, M.; Yin, G.; Yu, D. Upregulation and Activation of PKC α by ErbB2 through Src Promotes Breast Cancer Cell Invasion That Can Be Blocked by Combined Treatment with PKC α and Src Inhibitors. *Oncogene* **2006**, *25*, 3286–3295. [[CrossRef](#)]
72. Kim, S.; Han, J.; Lee, S.K.; Choi, M.-Y.; Kim, J.; Lee, J.; Jung, S.P.; Kim, J.S.; Kim, J.-H.; Choe, J.-H.; et al. Berberine Suppresses the TPA-Induced MMP-1 and MMP-9 Expressions Through the Inhibition of PKC- α in Breast Cancer Cells. *J. Surg. Res.* **2012**, *176*, e21–e29. [[CrossRef](#)] [[PubMed](#)]
73. Baltuch, G.H.; Dooley, N.P.; Rostworowski, K.M.; Villemure, J.-G.; Yong, V.W. Protein Kinase C Isoform? Overexpression in C6 Glioma Cells and Its Role in Cell Proliferation. *J. Neuro-Oncol.* **1995**, *24*, 241–250. [[CrossRef](#)] [[PubMed](#)]
74. Mut, M.; Amos, S.; Hussaini, I.M. Pkc Alpha Phosphorylates Cytosolic Nf-Kappab/P65 and Pkc Delta Delays Nuclear Translocation of Nf-Kappab/P65 in U1242 Glioblastoma Cells. *Turk. Neurosurg.* **2010**, *20*, 277–285. [[CrossRef](#)]
75. Cameron, A.J.; Procyk, K.J.; Leitges, M.; Parker, P.J. PKC Alpha Protein but Not Kinase Activity Is Critical for Glioma Cell Proliferation and Survival. *Int. J. Cancer* **2008**, *123*, 769–779. [[CrossRef](#)] [[PubMed](#)]
76. Davidson, L.A.; Aymond, C.M.; Jiang, Y.H.; Turner, N.D.; Lupton, J.R.; Chapkin, R.S. Non-invasive detection of fecal protein kinase C betaII and zeta messenger RNA: Putative biomarkers for colon cancer. *Carcinogenesis* **1998**, *19*, 253–257. [[CrossRef](#)]
77. Spindler, K.-L.G.; Lindebjerg, J.; Lahn, M.; Kjaer-Frifeldt, S.; Jakobsen, A. Protein Kinase C-Beta II (PKC- β II) Expression in Patients with Colorectal Cancer. *Int. J. Colorectal Dis.* **2009**, *24*, 641–645. [[CrossRef](#)]
78. Murray, N.R.; Davidson, L.A.; Chapkin, R.S.; Clay Gustafson, W.; Schattenberg, D.G.; Fields, A.P. Overexpression of Protein Kinase C β II Induces Colonic Hyperproliferation and Increased Sensitivity to Colon Carcinogenesis. *J. Cell Biol.* **1999**, *145*, 699–711. [[CrossRef](#)]
79. Yu, W.; Murray, N.R.; Weems, C.; Chen, L.; Guo, H.; Ethridge, R.; Ceci, J.D.; Evers, B.M.; Thompson, E.A.; Fields, A.P. Role of Cyclooxygenase 2 in Protein Kinase C β II-Mediated Colon Carcinogenesis. *J. Biol. Chem.* **2003**, *278*, 11167–11174. [[CrossRef](#)]
80. Calcagno, S.R.; Li, S.; Colon, M.; Kreinest, P.A.; Thompson, E.A.; Fields, A.P.; Murray, N.R. OncogenicK-Ras Promotes Early Carcinogenesis in the Mouse Proximal Colon. *Int. J. Cancer* **2008**, *122*, 2462–2470. [[CrossRef](#)]
81. Zhang, J.; Anastasiadis, P.Z.; Liu, Y.; Thompson, E.A.; Fields, A.P. Protein Kinase C (PKC) β II Induces Cell Invasion through a Ras/Mek-, PKC ζ /Rac 1-Dependent Signaling Pathway. *J. Biol. Chem.* **2004**, *279*, 22118–22123. [[CrossRef](#)]
82. Garczarzyk, D.; Szeker, K.; Galfi, P.; Csordas, A.; Hofmann, J. Protein kinase Cgamma in colon cancer cells: Expression, Thr514 phosphorylation and sensitivity to butyrate-mediated upregulation as related to the degree of differentiation. *Chem. Biol. Interact.* **2010**, *185*, 25–33. [[CrossRef](#)] [[PubMed](#)]
83. Alothaim, T.; Charbonneau, M.; Tang, X. HDAC6 inhibitors sensitize non-mesenchymal triple-negative breast cancer cells to cysteine deprivation. *Sci. Rep.* **2021**, *11*, 10956. [[CrossRef](#)] [[PubMed](#)]
84. Barretina, J.; Caponigro, G.; Stransky, N.; Venkatesan, K.; Margolin, A.A.; Kim, S.; Wilson, C.J.; Lehár, J.; Kryukov, G.V.; Sonkin, D.; et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature* **2012**, *483*, 603–607. [[CrossRef](#)] [[PubMed](#)]
85. Nussinov, R.; Tsai, C.J.; Jang, H. Autoinhibition can identify rare driver mutations and advise pharmacology. *FASEB* **2020**, *34*, 16–29. [[CrossRef](#)] [[PubMed](#)]
86. Parsons, M.; Adams, J.C. Rac regulates the interaction of fascin with protein kinase C in cell migration. *J. Cell Sci.* **2008**, *121*, 2805–2813. [[CrossRef](#)]
87. Mazzoni, E.; Adam, A.; Bal de Kier Joffe, E.; Aguirre-Ghiso, J.A. Immortalized mammary epithelial cells overexpressing protein kinase C gamma acquire a malignant phenotype and become tumorigenic in vivo. *Mol. Cancer Res.* **2003**, *1*, 776–787.
88. Belot, A.; Kasher, P.R.; Trotter, E.W.; Foray, A.-P.; Debaud, A.-L.; Rice, G.I.; Szykiewicz, M.; Zobot, M.-T.; Rouvet, I.; Bhaskar, S.S.; et al. Protein Kinase C δ Deficiency Causes Mendelian Systemic Lupus Erythematosus with B Cell-Defective Apoptosis and Hyperproliferation. *Arthritis Rheum.* **2013**, *65*, 2161–2171. [[CrossRef](#)]
89. Martiny-Baron, G.; Kazanietz, M.G.; Mischak, H.; Blumberg, P.M.; Kochs, G.; Hug, H.; Marmé, D.; Schächtele, C. Selective Inhibition of Protein Kinase C Isozymes by the Indolocarbazole Gö 6976. *J. Biol. Chem.* **1993**, *268*, 9194–9197. [[CrossRef](#)]
90. Villar, J.; Arenas, M.I.; MacCarthy, C.M.; Blánquez, M.J.; Tirado, O.M.; Notario, V. PCPH/ENTPD5 Expression Enhances the Invasiveness of Human Prostate Cancer Cells by a Protein Kinase C δ -Dependent Mechanism. *Cancer Res.* **2007**, *67*, 10859–10868. [[CrossRef](#)]
91. Kim, J.; Koyanagi, T.; Mochly-Rosen, D. PKC δ Activation Mediates Angiogenesis via NADPH Oxidase Activity in PC-3 Prostate Cancer Cells. *Prostate* **2011**, *71*, 946–954. [[CrossRef](#)]
92. McKiernan, E.; O'Brien, K.; Grebenchtchikov, N.; Geurts-Moespot, A.; Sieuwerts, A.M.; Martens, J.W.M.; Magdolen, V.; Evoy, D.; McDermott, E.; Crown, J.; et al. Protein Kinase C δ Expression in Breast Cancer as Measured by Real-Time PCR, Western Blotting and ELISA. *Br. J. Cancer* **2008**, *99*, 1644–1650. [[CrossRef](#)]

93. Grossoni, V.C.; Falbo, K.B.; Kazanietz, M.G.; de Kier Joffé, E.D.B.; Urtreger, A.J. Protein Kinase C δ Enhances Proliferation and Survival of Murine Mammary Cells. *Mol. Carcinog.* **2007**, *46*, 381–390. [[CrossRef](#)]
94. Nakagawa, M.; Oliva, J.L.; Kothapalli, D.; Fournier, A.; Assoian, R.K.; Kazanietz, M.G. Phorbol Ester-Induced G1 Phase Arrest Selectively Mediated by Protein Kinase C δ -Dependent Induction of P21. *J. Biol. Chem.* **2005**, *280*, 33926–33934. [[CrossRef](#)]
95. Santiago-Walker, A.E.; Fikaris, A.J.; Kao, G.D.; Brown, E.J.; Kazanietz, M.G.; Meinkoth, J.L. Protein Kinase C δ Stimulates Apoptosis by Initiating G1 Phase Cell Cycle Progression and S Phase Arrest. *J. Biol. Chem.* **2005**, *280*, 32107–32114. [[CrossRef](#)]
96. Irie, K.; Yanagita, R.C.; Nakagawa, Y. Challenges to the Development of Bryostatins-Type Anticancer Drugs Based on the Activation Mechanism of Protein Kinase C δ . *Med. Res. Rev.* **2012**, *32*, 518–535. [[CrossRef](#)]
97. DeVries, T.A.; Neville, M.C.; Reyland, M.E. Nuclear Import of PKC δ Is Required for Apoptosis: Identification of a Novel Nuclear Import Sequence. *EMBO J.* **2002**, *21*, 6050–6060. [[CrossRef](#)]
98. Tanaka, Y.; Gavrielides, M.V.; Mitsuchi, Y.; Fujii, T.; Kazanietz, M.G. Protein Kinase C Promotes Apoptosis in LNCaP Prostate Cancer Cells through Activation of P38 MAPK and Inhibition of the Akt Survival Pathway. *J. Biol. Chem.* **2004**, *278*, 33753–33762. [[CrossRef](#)]
99. Xiao, L.; Eto, M.; Kazanietz, M.G. ROCK Mediates Phorbol Ester-Induced Apoptosis in Prostate Cancer Cells via p21Cip1 Up-Regulation and JNK. *J. Biol. Chem.* **2009**, *284*, 29365–29375. [[CrossRef](#)]
100. Gonzalez-Guerrico, A.M.; Kazanietz, M.G. Phorbol ester-induced apoptosis in prostate cancer cells via autocrine activation of the extrinsic apoptotic cascade: A key role for protein kinase C delta. *J. Biol. Chem.* **2005**, *280*, 38982–38991. [[CrossRef](#)]
101. Xiao, L.; Caino, M.C.; von Burstin, V.A.; Oliva, J.L.; Kazanietz, M.G. Phorbol ester-induced apoptosis and senescence in cancer cell models. *Methods Enzymol.* **2008**, *446*, 123–139. [[CrossRef](#)]
102. Xiao, L.; Gonzalez-Guerrico, A.; Kazanietz, M.G. PKC-Mediated Secretion of Death Factors in LNCaP Prostate Cancer Cells Is Regulated by Androgens. *Mol. Carcinog.* **2009**, *48*, 187–195. [[CrossRef](#)]
103. Cacace, A.M.; Ueffing, M.; Philipp, A.; Han, E.K.; Kolch, W.; Weinstein, I.B. PKC epsilon functions as an oncogene by enhancing activation of the Raf kinase. *Oncogene* **1996**, *13*, 2517–2526.
104. Hamilton, M.; Liao, J.; Cathcart, M.K.; Wolfman, A. Constitutive Association of C-N-Ras with c-Raf-1 and Protein Kinase C ϵ in Latent Signaling Modules. *J. Biol. Chem.* **2001**, *276*, 29079–29090. [[CrossRef](#)]
105. Cacace, A.M.; Ueffing, M.; Han, E.K.; Marmè, D.; Weinstein, I.B. Overexpression of PKCepsilon in R6 fibroblasts causes increased production of active TGFbeta. *J. Cell Physiol.* **1998**, *175*, 314–322. [[CrossRef](#)]
106. Pan, Q.; Bao, L.W.; Kleer, C.G.; Sabel, M.S.; Griffith, K.A.; Teknos, T.N.; Merajver, S.D. Protein kinase C epsilon is a predictive biomarker of aggressive breast cancer and a validated target for RNA interference anticancer therapy. *Cancer Res.* **2005**, *65*, 8366–8371. [[CrossRef](#)]
107. Lu, J.; Rho, O.; Wilker, E.; Beltran, L.; Digiovanni, J. Activation of epidermal akt by diverse mouse skin tumor promoters. *Mol. Cancer Res.* **2007**, *5*, 1342–1352. [[CrossRef](#)]
108. Bae, K.M.; Wang, H.; Jiang, G.; Chen, M.G.; Lu, L.; Xiao, L. Protein kinase C epsilon is overexpressed in primary human non-small cell lung cancers and functionally required for proliferation of non-small cell lung cancer cells in a p21/Cip1-dependent manner. *Cancer Res.* **2007**, *67*, 6053–6063. [[CrossRef](#)]
109. Aziz, M.H.; Manoharan, H.T.; Church, D.R.; Dreckschmidt, N.E.; Zhong, W.; Oberley, T.D.; Wilding, G.; Verma, A.K. Protein kinase Cepsilon interacts with signal transducers and activators of transcription 3 (Stat3), phosphorylates Stat3Ser727, and regulates its constitutive activation in prostate cancer. *Cancer Res.* **2007**, *67*, 8828–8838. [[CrossRef](#)]
110. Basu, A.; Sivaprasad, U. Protein kinase Cepsilon makes the life and death decision. *Cell Signal.* **2007**, *19*, 1633–1642. [[CrossRef](#)]
111. Meshki, J.; Caino, M.C.; von Burstin, V.A.; Griner, E.; Kazanietz, M.G. Regulation of prostate cancer cell survival by protein kinase Cepsilon involves bad phosphorylation and modulation of the TNFalpha/JNK pathway. *J. Biol. Chem.* **2010**, *285*, 26033–26040. [[CrossRef](#)]
112. Pan, Q.; Bao, L.W.; Teknos, T.N.; Merajver, S.D. Targeted disruption of protein kinase C epsilon reduces cell invasion and motility through inactivation of RhoA and RhoC GTPases in head and neck squamous cell carcinoma. *Cancer Res.* **2006**, *66*, 9379–9384. [[CrossRef](#)] [[PubMed](#)]
113. McJilton, M.A.; Van Sikes, C.; Wescott, G.G.; Wu, D.; Foreman, T.L.; Gregory, C.W.; Weidner, D.A.; Harris Ford, O.; Morgan Lasater, A.; Mohler, J.L.; et al. Protein kinase Cepsilon interacts with Bax and promotes survival of human prostate cancer cells. *Oncogene* **2003**, *22*, 7958–7968. [[CrossRef](#)] [[PubMed](#)]
114. Wu, D.; Thakore, C.U.; Wescott, G.G.; McCubrey, J.A.; Terrian, D.M. Integrin Signaling Links Protein Kinase C ϵ to the Protein Kinase B/Akt Survival Pathway in Recurrent Prostate Cancer Cells. *Oncogene* **2004**, *23*, 8659–8672. [[CrossRef](#)] [[PubMed](#)]
115. Hafeez, B.B.; Zhong, W.; Weichert, J.; Dreckschmidt, N.E.; Jamal, M.S.; Verma, A.K. Genetic ablation of PKC epsilon inhibits prostate cancer development and metastasis in transgenic mouse model of prostate adenocarcinoma. *Cancer Res.* **2011**, *71*, 2318–2327. [[CrossRef](#)] [[PubMed](#)]
116. Besson, A.; Davy, A.; Robbins, S.M.; Yong, V.W. Differential Activation of ERKs to Focal Adhesions by PKC ϵ Is Required for PMA-Induced Adhesion and Migration of Human Glioma Cells. *Oncogene* **2001**, *20*, 7398–7407. [[CrossRef](#)]
117. Caino, M.C.; Lopez-Haber, C.; Kissil, J.L.; Kazanietz, M.G. Non-Small Cell Lung Carcinoma Cell Motility, Rac Activation and Metastatic Dissemination Are Mediated by Protein Kinase C Epsilon. *PLoS ONE* **2012**, *7*, e31714. [[CrossRef](#)]
118. Selbie, L.A.; Schmitz-Peiffer, C.; Sheng, Y.; Biden, T.J. Molecular Cloning and Characterization of PKC Iota, an Atypical Isoform of Protein Kinase C Derived from Insulin-Secreting Cells. *J. Biol. Chem.* **1993**, *268*, 24296–24302. [[CrossRef](#)]

119. Ono, Y.; Fujii, T.; Ogita, K.; Kikkawa, U.; Igarashi, K.; Nishizuka, Y. Protein Kinase C Zeta Subspecies from Rat Brain: Its Structure, Expression, and Properties. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 3099–3103. [[CrossRef](#)] [[PubMed](#)]
120. Mustafi, R.; Cerda, S.; Chumsangsri, A.; Fichera, A.; Bissonnette, M. Protein Kinase- ζ Inhibits Collagen I-Dependent and Anchorage-Independent Growth and Enhances Apoptosis of Human Caco-2 Cells. *Mol. Cancer Res.* **2006**, *4*, 683–694. [[CrossRef](#)] [[PubMed](#)]
121. Nazarenko, I.; Jenny, M.; Keil, J.; Gieseler, C.; Weisshaupt, K.; Sehouli, J.; Legewie, S.; Herbst, L.; Weichert, W.; Darb-Esfahani, S.; et al. Atypical Protein Kinase C ζ Exhibits a Proapoptotic Function in Ovarian Cancer. *Mol. Cancer Res.* **2010**, *8*, 919–934. [[CrossRef](#)] [[PubMed](#)]
122. Galvez, A.S.; Duran, A.; Linares, J.F.; Pathrose, P.; Castilla, E.A.; Abu-Baker, S.; Leitges, M.; Diaz-Meco, M.T.; Moscat, J. Protein Kinase C ζ Represses the Interleukin-6 Promoter and Impairs Tumorigenesis In Vivo. *Mol. Cell Biol.* **2009**, *29*, 104–115. [[CrossRef](#)] [[PubMed](#)]
123. Kim, J.Y.; Valencia, T.; Abu-Baker, S.; Linares, J.; Lee, S.J.; Yajima, T.; Chen, J.; Eroshkin, A.; Castilla, E.A.; Brill, L.M.; et al. C-Myc Phosphorylation by PKC ζ Represses Prostate Tumorigenesis. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 6418–6423. [[CrossRef](#)] [[PubMed](#)]
124. Murray, N.R.; Jamieson, L.; Yu, W.; Zhang, J.; Gökmen-Polar, Y.; Sier, D.; Anastasiadis, P.; Gatalica, Z.; Thompson, E.A.; Fields, A.P. Protein Kinase C ι Is Required for Ras Transformation and Colon Carcinogenesis in Vivo. *J. Cell Biol.* **2004**, *164*, 797–802. [[CrossRef](#)]
125. Murray, N.R.; Kalari, K.R.; Fields, A.P. Protein kinase C ι expression and oncogenic signaling mechanisms in cancer. *J. Cell. Physiol.* **2011**, *226*, 879–887. [[CrossRef](#)]
126. Eder, A.M.; Sui, X.; Rosen, D.G.; Nolden, L.K.; Cheng, K.W.; Lahad, J.P.; Kango-Singh, M.; Lu, K.H.; Warneke, C.L.; Atkinson, E.N.; et al. Atypical PKC ι Contributes to Poor Prognosis through Loss of Apical-Basal Polarity and Cyclin E Overexpression in Ovarian Cancer. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 12519–12524. [[CrossRef](#)] [[PubMed](#)]
127. Nanjundan, M.; Nakayama, Y.; Cheng, K.W.; Lahad, J.; Liu, J.; Lu, K.; Kuo, W.-L.; Smith-McCune, K.; Fishman, D.; Gray, J.W.; et al. Amplification of MDS1/EVI1 and EVI1, Located in the 3q26.2 Amplicon, Is Associated with Favorable Patient Prognosis in Ovarian Cancer. *Cancer Res.* **2007**, *67*, 3074–3084. [[CrossRef](#)]
128. Justilien, V.; Jameison, L.; Der, C.J.; Rossman, K.L.; Fields, A.P. Oncogenic Activity of Ect2 Is Regulated through Protein Kinase C ι -Mediated Phosphorylation. *J. Biol. Chem.* **2011**, *286*, 8149–8157. [[CrossRef](#)]
129. Win, H.Y.; Acevedo-Duncan, M. Atypical Protein Kinase C Phosphorylates IKK $\alpha\beta$ in Transformed Non-Malignant and Malignant Prostate Cell Survival. *Cancer Lett.* **2008**, *270*, 302–311. [[CrossRef](#)]
130. Ishiguro, H.; Akimoto, K.; Nagashima, Y.; Kojima, Y.; Sasaki, T.; Ishiguro-Imagawa, Y.; Nakaigawa, N.; Ohno, S.; Kubota, Y.; Uemura, H. aPKC λ/ι Promotes Growth of Prostate Cancer Cells in an Autocrine Manner through Transcriptional Activation of Interleukin-6. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 16369–16374. [[CrossRef](#)]
131. Abdelatty, A.; Fang, D.; Wei, G.; Wu, F.; Zhang, C.; Xu, H.; Yao, C.; Wang, Y.; Xia, H. PKC ι Is a Promising Prognosis Biomarker and Therapeutic Target for Pancreatic Cancer. *Pathobiology* **2022**, *89*, 370–381. [[CrossRef](#)]
132. Scotti, M.L.; Bamlet, W.R.; Smyrk, T.C.; Fields, A.P.; Murray, N.R. Protein kinase Ciota is required for pancreatic cancer cell transformed growth and tumorigenesis. *Cancer Res.* **2010**, *70*, 2064–2074. [[CrossRef](#)]
133. Kawano, T.; Inokuchi, J.; Eto, M.; Murata, M.; Kang, J.-H. Protein Kinase C (PKC) Isozymes as Diagnostic and Prognostic Biomarkers and Therapeutic Targets for Cancer. *Cancers* **2022**, *14*, 5425. [[CrossRef](#)] [[PubMed](#)]
134. Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. Staurosporine, a potent inhibitor of phospholipid/Ca⁺⁺ dependent protein kinase. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397–402. [[CrossRef](#)] [[PubMed](#)]
135. Takahashi, I.; Kobayashi, E.; Nakano, H.; Murakata, C.; Saitoh, H.; Suzuki, K.; Tamaoki, T. Potent selective inhibition of 7-O-methyl UCN-01 against protein kinase C. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 1218–1221. [[PubMed](#)]
136. Mizuno, K.; Noda, K.; Ueda, Y.; Hanaki, H.; Saido, T.C.; Ikuta, T.; Kuroki, T.; Tamaoki, T.; Hirai, S.; Osada, S.; et al. UCN-01, an anti-tumor drug, is a selective inhibitor of the conventional PKC subfamily. *FEBS Lett.* **1995**, *359*, 259–261. [[CrossRef](#)]
137. Seynaeve, C.M.; Stetler-Stevenson, M.; Sebers, S.; Kaur, G.; Sausville, E.A.; Worland, P.J. Cell cycle arrest and growth inhibition by the protein kinase antagonist UCN-01 in human breast carcinoma cells. *Cancer Res.* **1993**, *53*, 2081–2086.
138. Husain, A.; Yan, X.J.; Rosales, N.; Aghajanian, C.; Schwartz, G.K.; Spriggs, D.R. UCN-01 in Ovary cancer cells: Effective as a single agent and in combination with cis-diamminedichloroplatinum(II) independent of p53 status. *Clin. Cancer Res.* **1997**, *3*, 2089–2097.
139. Kortmansky, J.; Shah, M.A.; Kaubisch, A.; Weyerbacher, A.; Yi, S.; Tong, W.; Sowers, R.; Gonen, M.; O'Reilly, E.; Kemeny, N.; et al. Phase I Trial of the Cyclin-Dependent Kinase Inhibitor and Protein Kinase C Inhibitor 7-Hydroxystaurosporine in Combination with Fluorouracil in Patients with Advanced Solid Tumors. *J. Clin. Oncol.* **2005**, *23*, 1875–1884. [[CrossRef](#)]
140. Lara, P.N.; Mack, P.C.; Synold, T.; Frankel, P.; Longmate, J.; Gumerlock, P.H.; Doroshow, J.H.; Gandara, D.R. The Cyclin-Dependent Kinase Inhibitor UCN-01 Plus Cisplatin in Advanced Solid Tumors: A California Cancer Consortium Phase I Pharmacokinetic and Molecular Correlative Trial. *Clin. Cancer Res.* **2005**, *11*, 4444–4450. [[CrossRef](#)]
141. Sausville, E.A.; Arbuck, S.G.; Messmann, R.; Headlee, D.; Bauer, K.S.; Lush, R.M.; Murgo, A.; Figg, W.D.; Lahusen, T.; Jaken, S.; et al. Phase I Trial of 72-Hour Continuous Infusion UCN-01 in Patients with Refractory Neoplasms. *J. Clin. Oncol.* **2001**, *19*, 2319–2333. [[CrossRef](#)]

142. Welch, S.; Hirte, H.W.; Carey, M.S.; Hotte, S.J.; Tsao, M.S.; Brown, S.; Pond, G.R.; Dancey, J.E.; Oza, A.M. UCN-01 in combination with topotecan in patients with advanced recurrent ovarian cancer: A study of the Princess Margaret Hospital Phase II consortium. *Gynecol. Oncol.* **2007**, *106*, 305–310. [[CrossRef](#)] [[PubMed](#)]
143. Edelman, M.J.; Bauer, K.S., Jr.; Wu, S.; Smith, R.; Bisaccia, S.; Dancey, J. Phase I and pharmacokinetic study of 7-hydroxystaurosporine and carboplatin in advanced solid tumors. *Clin. Cancer Res.* **2007**, *13*, 2667–2674. [[CrossRef](#)]
144. Fracasso, P.M.; Williams, K.J.; Chen, R.C.; Picus, J.; Ma, C.X.; Ellis, M.J.; Tan, B.R.; Pluard, T.J.; Adkins, D.R.; Naughton, M.J.; et al. A phase 1 study of UCN-01 in combination with irinotecan in patients with resistant solid tumor malignancies. *Cancer Chemoth. Pharm.* **2011**, *67*, 1225–1237. [[CrossRef](#)]
145. Ma, C.X.; Ellis, M.J.; Petroni, G.R.; Guo, Z.; Cai, S.R.; Ryan, C.E.; Craig Lockhart, A.; Naughton, M.J.; Pluard, T.J.; Brenin, C.M.; et al. A phase II study of UCN-01 in combination with irinotecan in patients with metastatic triple negative breast cancer. *Breast Cancer Res. Treat.* **2013**, *137*, 483–492. [[CrossRef](#)] [[PubMed](#)]
146. Kummar, S.; Gutierrez, M.E.; Gardner, E.R.; Figg, W.D.; Melillo, G.; Dancey, J.; Sausville, E.A.; Conley, B.A.; Murgu, A.J.; Doroshow, J.H. A phase I trial of UCN-01 and prednisone in patients with refractory solid tumors and lymphomas. *Cancer Chemoth. Pharm.* **2010**, *65*, 383–389. [[CrossRef](#)]
147. Gojo, I.; Perl, A.; Luger, S.; Baer, M.R.; Norsworthy, K.J.; Bauer, K.S.; Tidwell, M.; Fleckinger, S.; Carroll, M.; Sausville, E.A. Phase I study of UCN-01 and perifosine in patients with relapsed and refractory acute leukemias and high-risk myelodysplastic syndrome. *Investig. New Drug* **2013**, *31*, 1217–1227. [[CrossRef](#)]
148. Marti, G.E.; Stetler-Stevenson, M.; Grant, N.D.; White, T.; Figg, W.D.; Tohnya, T.; Jaffe, E.S.; Dunleavy, K.; Janik, J.E.; Steinberg, S.M.; et al. Phase I trial of 7-hydroxystaurosporine and fludarabine phosphate: In vivo evidence of 7-hydroxystaurosporine-induced apoptosis in chronic lymphocytic leukemia. *Leuk. Lymphoma* **2011**, *52*, 2284–2292. [[CrossRef](#)] [[PubMed](#)]
149. Weisberg, E.; Boulton, C.; Kelly, L.M.; Manley, P.; Fabbro, D.; Meyer, T.; Gilliland, D.G.; Griffin, J.D. Inhibition of mutant FLT3 receptors in leukemia cells by the small molecule tyrosine kinase inhibitor PKC412. *Cancer Cell* **2002**, *1*, 433–443. [[CrossRef](#)]
150. Utz, I.; Hofer, S.; Regenass, U.; Hilbe, W.; Thaler, J.; Grunicke, H.; Hofmann, J. The protein kinase C inhibitor CGP 41251, a staurosporine derivative with antitumor activity, reverses multidrug resistance. *Int. J. Cancer* **1994**, *57*, 104–110. [[CrossRef](#)]
151. Ikegami, Y.; Yano, S.; Nakao, K. Antitumor Effect of CGP41251, a New Selective Protein Kinase C Inhibitor, on Human Non-Small Cell Lung Cancer Cells. *Jpn. J. Pharmacol.* **1996**, *70*, 65–72. [[CrossRef](#)]
152. Yoshikawa, N.; Nakamura, K.; Yamaguchi, Y.; Kagota, S.; Shinozuka, K.; Kunitomo, M. Effect of PKC412, a Selective Inhibitor of Protein Kinase C, on Lung Metastasis in Mice Injected with B16 Melanoma Cells. *Life Sci.* **2003**, *72*, 1377–1387. [[CrossRef](#)] [[PubMed](#)]
153. Fabbro, D.; Ruetz, S.; Bodis, S.; Pruschy, M.; Csermak, K.; Man, A.; Campochiaro, P.; Wood, J.; O'Reilly, T.; Meyer, T. PKC412—a protein kinase inhibitor with a broad therapeutic potential. *Anti-Cancer Drug Des.* **2000**, *15*, 17–28.
154. Ge, X.; Chen, J.; Li, L.; Ding, P.; Wang, Q.; Zhang, W.; Li, L.; Lv, X.; Zhou, D.; Jiang, Z.; et al. Midostaurin potentiates rituximab antitumor activity in Burkitt's lymphoma by inducing apoptosis. *Cell Death Dis.* **2018**, *10*, 8–20. [[CrossRef](#)] [[PubMed](#)]
155. Gallogly, M.M.; Lazarus, H.M. Midostaurin: An emerging treatment for acute myeloid leukemia patients. *J. Blood Med.* **2016**, *7*, 73–83. [[CrossRef](#)]
156. Millward, M.J.; House, C.; Bowtell, D.; Webster, L.; Olver, I.N.; Gore, M.; Copeman, M.; Lynch, K.; Yap, A.; Wang, Y.; et al. The multikinase inhibitor midostaurin (PKC412A) lacks activity in metastatic melanoma: A phase IIA clinical and biologic study. *Br. J. Cancer* **2006**, *95*, 829–834. [[CrossRef](#)] [[PubMed](#)]
157. Daver, N.; Schlenk, R.F.; Russell, N.H.; Levis, M.J. Targeting FLT3 mutations in AML: Review of current knowledge and evidence. *Leukemia* **2019**, *33*, 299–312. [[CrossRef](#)]
158. Gueta, I.; Marcu-Malina, V.; Avigdor, A.; Shimoni, A.; Loebstein, R.; Canaani, J. Real-World Efficacy Outcomes of FLT3-ITD Acute Myeloid Leukemia Patients Treated with Midostaurin in Combination with Intensive Induction. *Clin. Lymph. Myelom Leuk.* **2023**, *23*, 154–157. [[CrossRef](#)]
159. Weinbergerová, B.; Čerňan, M.; Kabut, T.; Semerád, L.; Podstavková, N.; Szotkowski, T.; Ježíšková, I.; Mayer, J. Gemtuzumab Ozogamicin plus Midostaurin in Conjunction with Standard Intensive Therapy for FLT3-Mutated Acute Myeloid Leukemia Patients—Czech Center Experience. *Haematologica* **2023**. [[CrossRef](#)]
160. DeAngelo, D.J.; George, T.I.; Linder, A.; Langford, C.; Perkins, C.; Ma, J.; Westervelt, P.; Merker, J.D.; Berube, C.; Coutre, S.; et al. Efficacy and Safety of Midostaurin in Patients with Advanced Systemic Mastocytosis: 10-Year Median Follow-up of a Phase II Trial. *Leukemia* **2018**, *32*, 470–478. [[CrossRef](#)]
161. Wagner, J.; von Matt, P.; Sedrani, R.; Albert, R.; Cooke, N.; Ehrhardt, C.; Geiser, M.; Rummel, G.; Stark, W.; Strauss, A.; et al. Discovery of 3-(1H-Indol-3-Yl)-4-[2-(4-Methylpiperazin-1-Yl)Quinazolin-4-Yl]Pyrrole-2,5-Dione (AEB071), a Potent and Selective Inhibitor of Protein Kinase C Isoforms. *J. Med. Chem.* **2009**, *52*, 6193–6196. [[CrossRef](#)]
162. Wu, X.; Li, J.; Zhu, M.; Fletcher, J.A.; Hodi, F.S. Protein Kinase C Inhibitor AEB071 Targets Ocular Melanoma Harboring GNAQ Mutations via Effects on the PKC/Erk1/2 and PKC/NF-κB Pathways. *Mol. Cancer Ther.* **2012**, *11*, 1905–1914. [[CrossRef](#)]
163. Musi, E.; Ambrosini, G.; de Stanchina, E.; Schwartz, G.K. The Phosphoinositide 3-Kinase α Selective Inhibitor BYL719 Enhances the Effect of the Protein Kinase C Inhibitor AEB071 in GNAQ/GNA11-Mutant Uveal Melanoma Cells. *Mol. Cancer Ther.* **2014**, *13*, 1044–1053. [[CrossRef](#)] [[PubMed](#)]
164. Van Raamsdonk, C.D.; Griewank, K.G.; Crosby, M.B.; Garrido, M.C.; Vemula, S.; Wiesner, T.; Obenauf, A.C.; Wackernagel, W.; Green, G.; Bouvier, N.; et al. Mutations in GNA11 in uveal melanoma. *N. Engl. J. Med.* **2010**, *363*, 2191–2199. [[CrossRef](#)] [[PubMed](#)]

165. Silva-Rodríguez, P.; Fernández-Díaz, D.; Bande, M.; Pardo, M.; Loidi, L.; Blanco-Teijeiro, M.J. GNAQ and GNA11 Genes: A Comprehensive Review on Oncogenesis, Prognosis and Therapeutic Opportunities in Uveal Melanoma. *Cancers* **2022**, *14*, 3066. [[CrossRef](#)] [[PubMed](#)]
166. Piperno-Neumann, S.; Larkin, J.; Carvajal, R.D.; Luke, J.J.; Schwartz, G.K.; Hodi, F.S.; Sablin, M.P.; Shoushtari, A.N.; Szpakowski, S.; Chowdhury, N.R.; et al. Genomic profiling of metastatic uveal melanoma and clinical results of a phase I study of the protein kinase C inhibitor AEB071. *Mol. Cancer Ther.* **2020**, *19*, 1031–1039. [[CrossRef](#)]
167. Shoushtari, A.N.; Khan, S.; Komatsubara, K.; Feun, L.; Acquavella, N.; Singh-Kandah, S.; Negri, T.; Nesson, A.; Abbate, K.; Cremers, S.; et al. A Phase Ib Study of Sotrastaurin, a PKC Inhibitor, and Alpelisib, a PI3K α Inhibitor, in Patients with Metastatic Uveal Melanoma. *Cancers* **2021**, *13*, 5504. [[CrossRef](#)] [[PubMed](#)]
168. Piperno-Neumann, S.; Carlino, M.S.; Boni, V.; Loirat, D.; Speetjens, F.M.; Park, J.J.; Calvo, E.; Carvajal, R.D.; Nyakas, M.; Gonzalez-Maffe, J.; et al. A Phase I Trial of LXS196, a Protein Kinase C (PKC) Inhibitor, for Metastatic Uveal Melanoma. *Br. J. Cancer* **2023**, *128*, 1040–1051. [[CrossRef](#)] [[PubMed](#)]
169. Graff, J.R.; McNulty, A.M.; Hanna, K.R.; Konicek, B.W.; Lynch, R.L.; Bailey, S.N.; Banks, C.; Capen, A.; Goode, R.; Lewis, J.E.; et al. The Protein Kinase C β -Selective Inhibitor, Enzastaurin (LY317615.HCl), Suppresses Signaling through the AKT Pathway, Induces Apoptosis, and Suppresses Growth of Human Colon Cancer and Glioblastoma Xenografts. *Cancer Res.* **2005**, *65*, 7462–7469. [[CrossRef](#)]
170. Mukohara, T.; Nagai, S.; Koshiji, M.; Yoshizawa, K.; Minami, H. Phase I Dose Escalation and Pharmacokinetic Study of Oral Enzastaurin (LY317615) in Advanced Solid Tumors. *Cancer Sci.* **2010**, *101*, 2193–2199. [[CrossRef](#)]
171. Clément-Duchêne, C.; Natale, R.B.; Jahan, T.; Krupitskaya, Y.; Osarogiagbon, R.; Sanborn, R.E.; Bernstein, E.D.; Dudek, A.Z.; Latz, J.E.; Shi, P.; et al. A phase II study of enzastaurin in combination with erlotinib in patients with previously treated advanced non-small cell lung cancer. *Lung Cancer* **2012**, *78*, 57–62. [[CrossRef](#)]
172. Chiappori, A.; Bepler, G.; Barlesi, F.; Soria, J.C.; Reck, M.; Bearz, A.; Barata, F.; Scagliotti, G.; Park, K.; Wagle, A.; et al. Phase II, double-blinded, randomized study of enzastaurin plus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer. *J. Thorac. Oncol.* **2010**, *5*, 369–375. [[CrossRef](#)]
173. Oda, Y.; Iwamoto, F.M.; Moustakas, A.; Fraum, T.J.; Salgado, C.A.; Li, A.; Kreisl, T.N.; Sul, J.; Butman, J.A.; Fine, H.A. A phase II trial of enzastaurin (LY317615) in combination with bevacizumab in adults with recurrent malignant gliomas. *J. Neuro-Oncol.* **2016**, *127*, 127–135. [[CrossRef](#)] [[PubMed](#)]
174. Butowski, N.; Chang, S.M.; Lamborn, K.R.; Polley, M.Y.; Pieper, R.; Costello, J.F.; Vandenberg, S.; Parvataneni, R.; Nicole, A.; Sneed, P.K.; et al. Phase II and pharmacogenomics study of enzastaurin plus temozolomide during and following radiation therapy in patients with newly diagnosed glioblastoma multiforme and gliosarcoma. *Neuro-Oncology* **2011**, *13*, 1331–1338. [[CrossRef](#)] [[PubMed](#)]
175. Dreicer, R.; Garcia, J.; Rini, B.; Vogelzang, N.; Srinivas, S.; Somer, B.; Shi, P.; Kania, M.; Raghavan, D. A randomized, double-blind, placebo-controlled, Phase II study with and without enzastaurin in combination with docetaxel-based chemotherapy in patients with castration-resistant metastatic prostate cancer. *Investig. New Drug* **2013**, *31*, 1044–1050. [[CrossRef](#)] [[PubMed](#)]
176. Vergote, I.B.; Chakerov, R.; Amant, F.; Harter, P.; Casado, A.; Emerich, J.; Bauknecht, T.; Mansouri, K.; Myrand, S.P.; Nguyen, T.S.; et al. Randomized, phase II, placebo-controlled, double-blind study with and without enzastaurin in combination with paclitaxel and carboplatin as first-line treatment followed by maintenance treatment in advanced ovarian cancer. *J. Clin. Oncol.* **2013**, *31*, 3127–3132. [[CrossRef](#)] [[PubMed](#)]
177. Jourdan, E.; Leblond, V.; Maisonneuve, H.; Benhadji, K.A.; Hossain, A.M.; Nguyen, T.S.; Wooldridge, J.E.; Moreau, P. A multicenter phase II study of single-agent enzastaurin in previously treated multiple myeloma. *Leuk. Lymphoma* **2014**, *55*, 2013–2017. [[CrossRef](#)]
178. Grønberg, B.H.; Ciuleanu, T.; Fløtten, Ø.; Knuutila, A.; Abel, E.; Langer, S.W.; Krejcy, K.; Liepa, A.M.; Munoz, M.; HahkaKempinen, M.; et al. A placebo-controlled, randomized phase II study of maintenance enzastaurin following whole brain radiation therapy in the treatment of brain metastases from lung cancer. *Lung Cancer* **2012**, *78*, 63–69. [[CrossRef](#)]
179. Usha, L.; Sill, M.W.; Darcy, K.M.; Benbrook, D.M.; Hurteau, J.A.; Michelin, D.P.; Mannel, R.S.; Hanjani, P.; De Geest, K.; Godwin, A.K. A Gynecologic Oncology Group phase II trial of the protein kinase C- β inhibitor, enzastaurin and evaluation of markers with potential predictive and prognostic value in persistent or recurrent epithelial ovarian and primary peritoneal malignancies. *Gynecol. Oncol.* **2011**, *121*, 455–461. [[CrossRef](#)]
180. Morschhauser, F.; Seymour, J.F.; Kluin-Nelemans, H.C.; Grigg, A.; Wolf, M.; Pfreundschuh, M.; Tilly, H.; Raemaekers, J.; van't Veer, M.B.; Milpied, N.; et al. A phase II study of enzastaurin, a protein kinase C β inhibitor, in patients with relapsed or refractory mantle cell lymphoma. *Ann. Oncol.* **2008**, *19*, 247–253. [[CrossRef](#)]
181. Mina, L.; Krop, I.; Zon, R.T.; Isakoff, S.J.; Schneider, C.J.; Yu, M.; Johnson, C.; Vaughn, L.G.; Wang, Y.; Hristova-Kazmierski, M.; et al. A phase II study of oral enzastaurin in patients with metastatic breast cancer previously treated with an anthracycline and a taxane containing regimen. *Investig. New Drug* **2009**, *27*, 565–570. [[CrossRef](#)]
182. Querfeld, C.; Kuzel, T.M.; Kim, Y.H.; Porcu, P.; Duvic, M.; Musiek, A.; Rook, A.H.; Mark, L.A.; Pinter-Brown, L.; Hamid, O.; et al. Multicenter phase II trial of enzastaurin in patients with relapsed or refractory advanced cutaneous T-cell lymphoma. *Leuk. Lymphoma* **2011**, *52*, 1474–1480. [[CrossRef](#)]

183. Nowakowski, G.S.; Zhu, J.; Zhang, Q.; Brody, J.; Sun, X.; Maly, J.; Song, Y.; Rizvi, S.; Song, Y.; Lansigan, F.; et al. ENGINE: A Phase III Randomized Placebo Controlled Study of Enzastaurin/R-CHOP as Frontline Therapy in High-Risk Diffuse Large B-Cell Lymphoma Patients with the Genomic Biomarker DGM1. *Future Oncol.* **2020**, *16*, 991–999. [[CrossRef](#)] [[PubMed](#)]
184. Kazanietz, M.G.; Lewin, N.E.; Gao, F.; Pettit, G.R.; Blumberg, P.M. Binding of [26-3H]bryostatin 1 and analogs to calcium dependent and calcium-independent protein kinase C isozymes. *Mol. Pharmacol.* **1994**, *46*, 374–379.
185. Schaar, D.; Goodell, L.; Aisner, J.; Cui, X.X.; Han, Z.T.; Chang, R.; Martin, J.; Grospe, S.; Dudek, L.; Riley, J.; et al. A phase I clinical trial of 12-O-tetradecanoylphorbol-13-acetate for patients with relapsed/refractory malignancies. *Cancer Chemoth. Pharm.* **2006**, *57*, 789–795. [[CrossRef](#)] [[PubMed](#)]
186. Tozer, R.G.; Burdette-Radoux, S.; Berlinger, K.; Davis, M.L.; Lohmann, R.C.; Rusthoven, J.R.; Wainman, N.; Zee, B.; Seymour, L.; National Cancer Institute of Canada Clinical Trials Group. A randomized phase II study of two schedules of bryostatin-1 (NSC339555) in patients with advanced malignant melanoma: A National Cancer Institute of Canada Clinical Trials Group Study. *Investig. New Drug* **2002**, *20*, 407–412. [[CrossRef](#)] [[PubMed](#)]
187. Peterson, A.C.; Harlin, H.; Karrison, T.; Vogelzang, N.J.; Knost, J.A.; Kugler, J.W.; Lester, E.; Vokes, E.; Gajewski, T.F.; Stadler, W.M.; et al. A randomized phase II trial of interleukin-2 in combination with four different doses of bryostatin-1 in patients with renal cell carcinoma. *Investig. New Drug* **2006**, *24*, 141–149. [[CrossRef](#)] [[PubMed](#)]
188. Zonder, J.A.; Shields, A.F.; Zalupski, M.; Chaplen, R.; Heilbrun, L.K.; Arlauskas, P.; Philip, P.A. A phase II trial of bryostatin 1 in the treatment of metastatic colorectal cancer. *Clin. Cancer Res.* **2001**, *7*, 38–42.
189. Blackhall, F.H.; Ranson, M.; Radford, J.A.; Hancock, B.W.; Soukop, M.; McGown, A.T.; Robbins, A.; Halbert, G.; Jayson, G.C.; Cancer Research Campaign Phase I/II Committee. A phase II trial of bryostatin 1 in patients with non-Hodgkin's lymphoma. *Br. J. Cancer* **2001**, *84*, 465–469. [[CrossRef](#)]
190. Varterasian, M.L.; Pemberton, P.A.; Hulburd, K.; Rodriguez, D.H.; Murgu, A.; Al-Katib, A.M. Phase II study of bryostatin 1 in patients with relapsed multiple myeloma. *Investig. New Drug* **2001**, *19*, 245–247. [[CrossRef](#)]
191. Pfister, D.G.; McCaffrey, J.; Zahalsky, A.J.; Schwartz, G.K.; Lis, E.; Gerald, W.; Huvos, A.; Shah, J.; Kraus, D.; Shaha, A.; et al. A phase II trial of bryostatin-1 in patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *Investig. New Drug* **2002**, *20*, 123–127. [[CrossRef](#)]
192. Nezhat, F.; Wadler, S.; Muggia, F.; Mandeli, J.; Goldberg, G.; Rahaman, J.; Runowicz, C.; Murgu, A.J.; Gardner, G.J. Phase II trial of the combination of bryostatin-1 and cisplatin in advanced or recurrent carcinoma of the cervix: A New York Gynecologic Oncology Group study. *Gynecol. Oncol.* **2004**, *93*, 144–148. [[CrossRef](#)]
193. Morgan, R.J.; Leong, L.; Chow, W.; Gandara, D.; Frankel, P.; Garcia, A.; Lenz, H.J.; Doroshow, J.H. Phase II trial of bryostatin-1 in combination with cisplatin in patients with recurrent or persistent epithelial ovarian cancer: A California cancer consortium study. *Investig. New Drug* **2012**, *30*, 723–728. [[CrossRef](#)]
194. Lam, A.P.; Sparano, J.A.; Vinciguerra, V.; Ocean, A.J.; Christos, P.; Hochster, H.; Camacho, F.; Goel, S.; Mani, S.; Kaubisch, A. Phase II study of paclitaxel plus the protein kinase C inhibitor bryostatin-1 in advanced pancreatic carcinoma. *Am. J. Clin. Oncol.* **2010**, *33*, 121–124. [[CrossRef](#)] [[PubMed](#)]
195. Winegarden, J.D.; Mauer, A.M.; Gajewski, T.F.; Hoffman, P.C.; Krauss, S.; Rudin, C.M.; Vokes, E.E. A phase II study of bryostatin-1 and paclitaxel in patients with advanced non-small cell lung cancer. *Lung Cancer* **2003**, *39*, 191–196. [[CrossRef](#)]
196. Ajani, J.A.; Jiang, Y.; Faust, J.; Chang, B.B.; Ho, L.; Yao, J.C.; Rousey, S.; Dakhil, S.; Cherny, R.C.; Craig, C.; et al. A multicenter phase II study of sequential paclitaxel and bryostatin-1 (NSC 339555) in patients with untreated, advanced gastric or gastroesophageal junction adenocarcinoma. *Investig. New Drug* **2006**, *24*, 353–357. [[CrossRef](#)]
197. Ku, G.Y.; Ilson, D.H.; Schwartz, L.H.; Capanu, M.; O'Reilly, E.; Shah, M.A.; Kelsen, D.P.; Schwartz, G.K. Phase II trial of sequential paclitaxel and 1 h infusion of bryostatin-1 in patients with advanced esophageal cancer. *Cancer Chemoth. Pharm.* **2008**, *62*, 875–880. [[CrossRef](#)] [[PubMed](#)]
198. Barr, P.M.; Lazarus, H.M.; Cooper, B.W.; Schluchter, M.D.; Panneerselvam, A.; Jacobberger, J.W.; Hsu, J.W.; Janakiraman, N.; Simic, A.; Dowlati, A.; et al. Phase II study of bryostatin 1 and vincristine for aggressive non-Hodgkin lymphoma relapsing after an autologous stem cell transplant. *Am. J. Hematol.* **2009**, *84*, 484–487. [[CrossRef](#)] [[PubMed](#)]
199. Castanotto, D.; Stein, C.A. Antisense oligonucleotides in cancer. *Curr. Opin. Oncol.* **2014**, *26*, 584–589. [[CrossRef](#)] [[PubMed](#)]
200. Black, A.R.; Black, J.D. The complexities of PKC α signaling in cancer. *Adv. Biol. Regul.* **2021**, *80*, 100769–100823. [[CrossRef](#)] [[PubMed](#)]
201. Lahn, M.; Sundell, K.; Moore, S. Targeting protein kinase C-alpha (PKC- α) in cancer with the phosphorothioate antisense oligonucleotide aprinocarsen. *Ann. N. Y. Acad. Sci.* **2003**, *1002*, 263–270. [[CrossRef](#)]
202. Grossman, S.A.; Alavi, J.B.; Supko, J.G.; Carson, K.A.; Priet, R.; Dorr, F.A.; Grundy, J.S.; Holmlund, J.T. Efficacy and toxicity of the antisense oligonucleotide aprinocarsen directed against protein kinase C- α delivered as a 21-day continuous intravenous infusion in patients with recurrent high-grade astrocytomas. *Neuro-Oncol.* **2005**, *7*, 32–40. [[CrossRef](#)]
203. Paz-Ares, L.; Douillard, J.Y.; Koralewski, P.; Manegold, C.; Smit, E.F.; Reyes, J.M.; Chang, G.C.; John, W.J.; Peterson, P.M.; Obasaju, C.K.; et al. Phase III study of gemcitabine and cisplatin with or without aprinocarsen, a protein kinase C-alpha antisense oligonucleotide, in patients with advanced-stage non-small-cell lung cancer. *J. Clin. Oncol.* **2006**, *24*, 1428–1434. [[CrossRef](#)]
204. Advani, R.; Peethambaram, P.; Lum, B.L.; Fisher, G.A.; Hartmann, L.; Long, H.J.; Halsey, J.; Holmlund, J.T.; Dorr, A.; Sikic, B.I. A Phase II trial of aprinocarsen, an antisense oligonucleotide inhibitor of protein kinase C α , administered as a 21-day infusion to patients with advanced ovarian carcinoma. *Cancer* **2004**, *100*, 321–326. [[CrossRef](#)]

205. Tolcher, A.W.; Reyno, L.; Venner, P.M.; Ernst, S.D.; Moore, M.; Geary, R.S.; Chi, K.; Hall, S.; Walsh, W.; Dorr, A.; et al. A randomized phase II and pharmacokinetic study of the antisense oligonucleotides ISIS 3521 and ISIS 5132 in patients with hormone-refractory prostate cancer. *Clin. Cancer Res.* **2002**, *8*, 2530–2535. [[PubMed](#)]
206. Roychowdhury, D.; Lahn, M. Antisense therapy directed to protein kinase C-alpha (Affinitak, LY900003/ISIS 3521): Potential role in breast cancer. *Semin. Oncol.* **2003**, *30*, 30–33. [[CrossRef](#)]
207. Marshall, J.L.; Eisenberg, S.G.; Johnson, M.D.; Hanfelt, J.; Dorr, F.A.; El-Ashry, D.; Oberst, M.; Fuxman, Y.; Holmlund, J.; Malik, S. A phase II trial of ISIS 3521 in patients with metastatic colorectal cancer. *Clin. Clin. Color. Cancer* **2004**, *4*, 268–274. [[CrossRef](#)] [[PubMed](#)]
208. Rao, S.; Watkins, D.; Cunningham, D.; Dunlop, D.; Johnson, P.; Selby, P.; Hancock, B.W.; Fegan, C.; Culligan, D.; Schey, S.; et al. Phase II study of ISIS 3521, an antisense oligodeoxynucleotide to protein kinase C alpha, in patients with previously treated low-grade non-Hodgkin's lymphoma. *Ann. Oncol.* **2004**, *15*, 1413–1418. [[CrossRef](#)] [[PubMed](#)]
209. Kelland, L. Discontinued drugs in 2005: Oncology drugs. *Expert Opin. Investig. Drugs* **2006**, *15*, 1309–1318. [[CrossRef](#)]
210. Pfeifhofer-Obermair, C.; Thuille, N.; Baier, G. Involvement of Distinct PKC Gene Products in T Cell Functions. *Front. Immunol.* **2012**, *3*, 220–232. [[CrossRef](#)]
211. Shiravand, Y.; Khodadadi, F.; Kashani, S.M.A.; Hosseini-Fard, S.R.; Hosseini, S.; Sadeghirad, H.; Ladwa, R.; O'Byrne, K.; Kulasinghe, A. Immune Checkpoint Inhibitors in Cancer Therapy. *Curr. Oncol.* **2022**, *29*, 3044–3060. [[CrossRef](#)]
212. Zhang, E.Y.; Kong, K.-F.; Altman, A. The Yin and Yang of Protein Kinase C-Theta (PKC θ). *Adv. Pharmacol.* **2013**, 267–312. [[CrossRef](#)]
213. Wang, D.; You, Y.; Case, S.M.; McAllister-Lucas, L.M.; Wang, L.; DiStefano, P.S.; Nuñez, G.; Bertin, J.; Lin, X. A Requirement for CARMA1 in TCR-Induced NF- κ B Activation. *Nat. Immunol.* **2002**, *3*, 830–835. [[CrossRef](#)] [[PubMed](#)]
214. Ghosh, S.; Karin, M. Missing pieces in the NF- κ B puzzle. *Cell* **2002**, *109*, S81–S96. [[CrossRef](#)]
215. Liu, Y.; Witte, S.; Liu, Y.-C.; Doyle, M.; Elly, C.; Altman, A. Regulation of Protein Kinase C θ Function during T Cell Activation by Lck-Mediated Tyrosine Phosphorylation. *J. Biol. Chem.* **2000**, *275*, 3603–3609. [[CrossRef](#)]
216. Letschka, T.; Kollmann, V.; Pfeifhofer-Obermair, C.; Lutz-Nicoladoni, C.; Obermair, G.J.; Fresser, F.; Leitges, M.; Hermann-Kleiter, N.; Kaminski, S.; Baier, G. PKC- θ Selectively Controls the Adhesion-Stimulating Molecule Rap1. *Blood* **2008**, *112*, 4617–4627. [[CrossRef](#)] [[PubMed](#)]
217. Thuille, N.; Lutz-Nicoladoni, C.; Letschka, T.; Hermann-Kleiter, N.; Heit, I.; Baier, G. PKC θ and Itk Functionally Interact during Primary Mouse CD3+ T Cell Activation. *Immunol. Lett.* **2009**, *126*, 54–59. [[CrossRef](#)] [[PubMed](#)]
218. Gruber, T.; Hermann-Kleiter, N.; Hinterleitner, R.; Fresser, F.; Schneider, R.; Gastl, G.; Penninger, J.M.; Baier, G. PKC- θ Modulates the Strength of T Cell Responses by Targeting Cbl-b for Ubiquitination and Degradation. *Sci. Signal.* **2009**, *2*, ra30. [[CrossRef](#)]
219. Fang, D.; Liu, Y.-C. Proteolysis-Independent Regulation of PI3K by Cbl-b-Mediated Ubiquitination in T Cells. *Nat. Immunol.* **2001**, *2*, 870–875. [[CrossRef](#)]
220. Yanguas, A.; Garasa, S.; Teijeira, Á.; Aubá, C.; Melero, I.; Rouzaut, A. ICAM-1-LFA-1 Dependent CD8+ T-Lymphocyte Aggregation in Tumor Tissue Prevents Recirculation to Draining Lymph Nodes. *Front. Immunol.* **2018**, *9*, 2084–2098. [[CrossRef](#)]
221. Kong, K.-F.; Yokosuka, T.; Canonigo-Balancio, A.J.; Isakov, N.; Saito, T.; Altman, A. A Motif in the V3 Domain of the Kinase PKC- θ Determines Its Localization in the Immunological Synapse and Functions in T Cells via Association with CD28. *Nat. Immunol.* **2011**, *12*, 1105–1112. [[CrossRef](#)]
222. Huang, J.; Lo, P.-F.; Žal, T.; Gascoigne, N.R.J.; Smith, B.A.; Levin, S.D.; Grey, H.M. CD28 Plays a Critical Role in the Segregation of PKC θ within the Immunologic Synapse. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 9369–9373. [[CrossRef](#)] [[PubMed](#)]
223. Dustin, M.L. The Cellular Context of T Cell Signaling. *Immunity* **2009**, *30*, 482–492. [[CrossRef](#)]
224. Hui, E.; Cheung, J.; Zhu, J.; Su, X.; Taylor, M.J.; Wallweber, H.A.; Sasmal, D.K.; Huang, J.; Kim, J.M.; Mellman, I.; et al. T Cell Costimulatory Receptor CD28 Is a Primary Target for PD-1-Mediated Inhibition. *Science* **2017**, *355*, 1428–1433. [[CrossRef](#)] [[PubMed](#)]
225. Kamphorst, A.O.; Wieland, A.; Nasti, T.; Yang, S.; Zhang, R.; Barber, D.L.; Konieczny, B.T.; Daugherty, C.Z.; Koenig, L.; Yu, K.; et al. Rescue of Exhausted CD8 T Cells by PD-1-Targeted Therapies Is CD28-Dependent. *Science* **2017**, *355*, 1423–1427. [[CrossRef](#)]
226. Villalba, M.; Bi, K.; Hu, J.; Altman, Y.; Bushway, P.; Reits, E.; Neefjes, J.; Baier, G.; Abraham, R.T.; Altman, A. Translocation of PKC θ in T Cells Is Mediated by a Nonconventional, PI3-K- and Vav-Dependent Pathway, but Does Not Absolutely Require Phospholipase C. *J. Cell Biol.* **2002**, *157*, 253–263. [[CrossRef](#)]
227. Sheppard, K.-A.; Fitz, L.J.; Lee, J.M.; Benander, C.; George, J.A.; Wooters, J.; Qiu, Y.; Jussif, J.M.; Carter, L.L.; Wood, C.R.; et al. PD-1 Inhibits T-Cell Receptor Induced Phosphorylation of the ZAP70/CD3 ζ Signalosome and Downstream Signaling to PKC θ . *FEBS Lett.* **2004**, *574*, 37–41. [[CrossRef](#)]
228. Patsoukis, N.; Bardhan, K.; Chatterjee, P.; Sari, D.; Liu, B.; Bell, L.N.; Karoly, E.D.; Freeman, G.J.; Petkova, V.; Seth, P.; et al. PD-1 Alters T-Cell Metabolic Reprogramming by Inhibiting Glycolysis and Promoting Lipolysis and Fatty Acid Oxidation. *Nat. Commun.* **2015**, *6*, 6692–6705. [[CrossRef](#)] [[PubMed](#)]
229. Chuang, H.-C.; Lan, J.-L.; Chen, D.-Y.; Yang, C.-Y.; Chen, Y.-M.; Li, J.-P.; Huang, C.-Y.; Liu, P.-E.; Wang, X.; Tan, T.-H. The Kinase GLK Controls Autoimmunity and NF- κ B Signaling by Activating the Kinase PKC- θ in T Cells. *Nat. Immunol.* **2011**, *12*, 1113–1118. [[CrossRef](#)] [[PubMed](#)]

230. Sun, Z.; Arendt, C.W.; Ellmeier, W.; Schaeffer, E.M.; Sunshine, M.J.; Gandhi, L.M.; Annes, J.; Petrzilka, D.; Kupfer, A.; Schwartzberg, P.L.; et al. PKC- θ is required for TCR-induced NF- κ B activation in mature but not immature T lymphocytes. *Nature* **2000**, *404*, 402–407. [[CrossRef](#)] [[PubMed](#)]
231. Prinz, P.U.; Mendler, A.N.; Masouris, I.; Durner, L.; Oberneder, R.; Noessner, E. High DGK- α and Disabled MAPK Pathways Cause Dysfunction of Human Tumor-Infiltrating CD8⁺ T Cells That Is Reversible by Pharmacologic Intervention. *J. Immunol.* **2012**, *188*, 5990–6000. [[CrossRef](#)]
232. Han, Q.; Bagheri, N.; Bradshaw, E.M.; Hafler, D.A.; Lauffenburger, D.A.; Love, J.C. Polyfunctional Responses by Human T Cells Result from Sequential Release of Cytokines. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 1607–1612. [[CrossRef](#)] [[PubMed](#)]
233. Salerno, F.; Paolini, N.A.; Stark, R.; von Lindern, M.; Wolkers, M.C. Distinct PKC-Mediated Posttranscriptional Events Set Cytokine Production Kinetics in CD8⁺ T Cells. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 9677–9682. [[CrossRef](#)]
234. Marsland, B.J.; Soos, T.J.; Späth, G.; Littman, D.R.; Kopf, M. Protein Kinase C θ Is Critical for the Development of In Vivo T Helper (Th)2 Cell but Not Th1 Cell Responses. *J. Exp. Med.* **2004**, *200*, 181–189. [[CrossRef](#)]
235. Mowen, K.A.; Glimcher, L.H. Signaling Pathways in Th2 Development. *Immunol. Rev.* **2004**, *202*, 203–222. [[CrossRef](#)]
236. Ben-Shmuel, A.; Sabag, B.; Puthenveetil, A.; Biber, G.; Levy, M.; Jubany, T.; Awwad, F.; Roy, R.K.; Joseph, N.; Matalon, O.; et al. Inhibition of SHP-1 Activity by PKC- θ Regulates NK Cell Activation Threshold and Cytotoxicity. *eLife* **2022**, *11*, e73282. [[CrossRef](#)]
237. Celis-Gutierrez, J.; Blattmann, P.; Zhai, Y.; Jarmuzynski, N.; Ruminski, K.; Grégoire, C.; Ounoughene, Y.; Fiore, F.; Aebbersold, R.; Roncagalli, R.; et al. Quantitative Interactions in Primary T Cells Provides a Rationale for Concomitant PD-1 and BTLA Coinhibitor Blockade in Cancer Immunotherapy. *Cell Rep.* **2019**, *27*, 3315–3330. [[CrossRef](#)] [[PubMed](#)]
238. Watanabe, N.; Gavrieli, M.; Sedy, J.R.; Yang, J.; Fallarino, F.; Loftin, S.K.; Hurchla, M.A.; Zimmerman, N.; Sim, J.; Zang, X.; et al. BTLA Is a Lymphocyte Inhibitory Receptor with Similarities to CTLA-4 and PD-1. *Nat. Immunol.* **2003**, *4*, 670–679. [[CrossRef](#)] [[PubMed](#)]
239. Xu, X.; Hou, B.; Fulzele, A.; Masubuchi, T.; Zhao, Y.; Wu, Z.; Hu, Y.; Jiang, Y.; Ma, Y.; Wang, H.; et al. PD-1 and BTLA Regulate T Cell Signaling Differentially and Only Partially through SHP1 and SHP2. *J. Cell Biol.* **2020**, *219*, e201905085. [[CrossRef](#)]
240. Valenzuela, H.F.; Effros, R.B. Divergent Telomerase and CD28 Expression Patterns in Human CD4 and CD8 T Cells Following Repeated Encounters with the Same Antigenic Stimulus. *Clin. Immunol.* **2002**, *105*, 117–125. [[CrossRef](#)]
241. Comandini, A.; Naro, C.; Adamo, R.; Akbar, A.N.; Lanna, A.; Bonmassar, E.; Franzese, O. Molecular Mechanisms Involved in HIV-1-Tat Mediated Inhibition of Telomerase Activity in Human CD4⁺ T Lymphocytes. *Mol. Immunol.* **2013**, *54*, 181–192. [[CrossRef](#)]
242. Greider, C.W. Telomere Length Regulation. *Annu. Rev. Biochem.* **1996**, *65*, 337–365. [[CrossRef](#)]
243. Weng, N.; Hathcock, K.S.; Hodes, R.J. Regulation of Telomere Length and Telomerase in T and B Cells. *Immunity* **1998**, *9*, 151–157. [[CrossRef](#)] [[PubMed](#)]
244. Reed, J.C.; Alpers, J.D.; Nowell, P.C.; Hoover, R.G. Sequential Expression of Protooncogenes during Lectin-Stimulated Mitogenesis of Normal Human Lymphocytes. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 3982–3986. [[CrossRef](#)] [[PubMed](#)]
245. Sheng, W.-Y.; Chen, Y.-R.; Wang, T.-C.V. A Major Role of PKC θ and NF κ B in the Regulation of hTERT in Human T Lymphocytes. *FEBS Lett.* **2006**, *580*, 6819–6824. [[CrossRef](#)] [[PubMed](#)]
246. Pfeifhofer-Obermair, C.; Albrecht-Schgoer, K.; Peer, S.; Nairz, M.; Siegmund, K.; Klepsch, V.; Haschka, D.; Thuille, N.; Hermann-Kleiter, N.; Gruber, T.; et al. Role of PKC θ in Macrophage-Mediated Immune Response to Salmonella Typhimurium Infection in Mice. *Cell Commun. Signal* **2016**, *14*, 14–22. [[CrossRef](#)]
247. Sakaguchi, S.; Yamaguchi, T.; Nomura, T.; Ono, M. Regulatory T Cells and Immune Tolerance. *Cell* **2008**, *133*, 775–787. [[CrossRef](#)]
248. Sumoza-Toledo, A.; Eaton, A.D.; Sarukhan, A. Regulatory T Cells Inhibit Protein Kinase C θ Recruitment to the Immune Synapse of Naive T Cells with the Same Antigen Specificity. *J. Immunol.* **2006**, *176*, 5779–5787. [[CrossRef](#)]
249. Roybal, K.T.; Wülfing, C. Inhibiting the Inhibitor of the Inhibitor: Blocking PKC- θ to Enhance Regulatory T Cell Function. *Sci. Signal.* **2010**, *3*, pe24. [[CrossRef](#)]
250. Ma, J.; Ding, Y.; Fang, X.; Wang, R.; Sun, Z. Protein Kinase C- θ Inhibits Inducible Regulatory T Cell Differentiation via an AKT-Foxo1/3a-Dependent Pathway. *J. Immunol.* **2012**, *188*, 5337–5347. [[CrossRef](#)]
251. Ozay, E.I.; Shanthalingam, S.; Sherman, H.L.; Torres, J.A.; Osborne, B.A.; Tew, G.N.; Minter, L.M. Cell-Penetrating Anti-Protein Kinase C Theta Antibodies Act Intracellularly to Generate Stable, Highly Suppressive Regulatory T Cells. *Mol. Ther.* **2020**, *28*, 1987–2006. [[CrossRef](#)]
252. Gupta, S.; Manicassamy, S.; Vasu, C.; Kumar, A.; Shang, W.; Sun, Z. Differential Requirement of PKC- θ in the Development and Function of Natural Regulatory T Cells. *Mol. Immunol.* **2008**, *46*, 213–224. [[CrossRef](#)]
253. Shin, D.S.; Jordan, A.; Basu, S.; Thomas, R.M.; Bandyopadhyay, S.; de Zoeten, E.F.; Wells, A.D.; Macian, F. Regulatory T Cells Suppress CD4⁺ T Cells through NFAT-dependent Transcriptional Mechanisms. *EMBO Rep.* **2014**, *15*, 991–999. [[CrossRef](#)]
254. Britton, G.J.; Mitchell, R.E.; Burton, B.R.; Wraith, D.C. Protein Kinase C Theta Is Required for Efficient Induction of IL-10-Secreting T Cells. *PLoS ONE* **2017**, *12*, e0171547. [[CrossRef](#)]
255. Henson, S.M.; Macaulay, R.; Franzese, O.; Akbar, A.N. Reversal of Functional Defects in Highly Differentiated Young and Old CD8 T Cells by PDL Blockade. *Immunology* **2012**, *135*, 355–363. [[CrossRef](#)]
256. Franzese, O.; Torino, F.; Fuggetta, M.P.; Aquino, A.; Roselli, M.; Bonmassar, E.; Giuliani, A.; D’Atri, S. Tumor Immunotherapy: Drug-Induced Neoantigens (Xenogenization) and Immune Checkpoint Inhibitors. *Oncotarget* **2017**, *8*, 41641–41669. [[CrossRef](#)] [[PubMed](#)]

257. Franzese, O.; Palermo, B.; Di Donna, C.; Sperduti, I.; Ferraresi, V.; Stabile, H.; Gismondi, A.; Santoni, A.; Nisticò, P. Polyfunctional Melan-A-Specific Tumor-Reactive CD8⁺T Cells Elicited by Dacarbazine Treatment before Peptide-Vaccination Depends on AKT Activation Sustained by ICOS. *Oncol Immunology* **2016**, *5*, e1114203. [[CrossRef](#)] [[PubMed](#)]
258. Trushin, S.A.; Pennington, K.N.; Carmona, E.M.; Asin, S.; Savoy, D.N.; Billadeau, D.D.; Paya, C.V. Protein Kinase C α (PKC α) Acts Upstream of PKC θ To Activate I κ B Kinase and NF- κ B in T Lymphocytes. *Mol. Cell Biol.* **2003**, *23*, 7068–7081. [[CrossRef](#)] [[PubMed](#)]
259. Gharbi, S.I.; Avila-Flores, A.; Soutar, D.; Orive, A.; Koretzky, G.A.; Albar, J.P.; Mérida, I. Transient PKC α Shuttling to the Immunological Synapse Is Governed by (DGK) ζ and Regulates L-Selectin Shedding. *J. Cell Sci.* **2013**, *126*, 2176–2186. [[CrossRef](#)]
260. Galkina, E.; Tanousis, K.; Preece, G.; Tolaini, M.; Kioussis, D.; Florey, O.; Haskard, D.O.; Tedder, T.F.; Ager, A. L-Selectin Shedding Does Not Regulate Constitutive T Cell Trafficking but Controls the Migration Pathways of Antigen-Activated T Lymphocytes. *J. Exp. Med.* **2003**, *198*, 1323–1335. [[CrossRef](#)]
261. Gruber, T.; Hermann-Kleiter, N.; Pfeifhofer-Obermair, C.; Lutz-Nicoladoni, C.; Thuille, N.; Letschka, T.; Barsig, J.; Baudler, M.; Li, J.; Metzler, B.; et al. PKC θ Cooperates with PKC α in Alloimmune Responses of T Cells in Vivo. *Mol. Immunol.* **2009**, *46*, 2071–2079. [[CrossRef](#)]
262. Baier, G.; Wagner, J. PKC Inhibitors: Potential in T Cell-Dependent Immune Diseases. *Curr. Opin. Cell Biol.* **2009**, *21*, 262–267. [[CrossRef](#)]
263. Mecklenbräuker, I.; Saijo, K.; Zheng, N.-Y.; Leitges, M.; Tarakhovskiy, A. Protein Kinase C δ Controls Self-Antigen-Induced B-Cell Tolerance. *Nature* **2002**, *416*, 860–865. [[CrossRef](#)]
264. Gruber, T.; Barsig, J.; Pfeifhofer, C.; Ghaffari-Tabrizi, N.; Tinhofer, I.; Leitges, M.; Baier, G. PKC δ Is Involved in Signal Attenuation in CD3⁺ T Cells. *Immunol. Lett.* **2005**, *96*, 291–293. [[CrossRef](#)]
265. Liu, Y.; Song, R.; Gao, Y.; Li, Y.; Wang, S.; Liu, H.-Y.; Wang, Y.; Hu, Y.-H.; Shu, H.-B. Protein Kinase C- δ Negatively Regulates T Cell Receptor-Induced NF- κ B Activation by Inhibiting the Assembly of CARMA1 Signalosome. *J. Biol. Chem.* **2012**, *287*, 20081–20087. [[CrossRef](#)]
266. Scheel-Toellner, D.; Pilling, D.; Akbar, A.N.; Hardie, D.; Lombardi, G.; Salmon, M.; Lord, J.M. Inhibition of T Cell Apoptosis by IFN- β Rapidly Reverses Nuclear Translocation of Protein Kinase C- δ . *Eur. J. Immunol.* **1999**, *29*, 2603–2612. [[CrossRef](#)]
267. DeVries-Seimon, T.A.; Ohm, A.M.; Humphries, M.J.; Reyland, M.E. Induction of Apoptosis Is Driven by Nuclear Retention of Protein Kinase C δ . *J. Biol. Chem.* **2007**, *282*, 22307–22314. [[CrossRef](#)]
268. Ma, J.S.Y.; Monu, N.; Shen, D.T.; Mecklenbräuker, I.; Radoja, N.; Haydar, T.F.; Leitges, M.; Frey, A.B.; Vukmanović, S.; Radoja, S. Protein Kinase C δ Regulates Antigen Receptor-Induced Lytic Granule Polarization in Mouse CD8⁺ CTL. *J. Immunol.* **2007**, *178*, 7814–7821. [[CrossRef](#)] [[PubMed](#)]
269. Bello-Gamboa, A.; Velasco, M.; Moreno, S.; Herranz, G.; Ilie, R.; Huetos, S.; Dávila, S.; Sánchez, A.; Bernardino De La Serna, J.; Calvo, V.; et al. Actin Reorganization at the Centrosomal Area and the Immune Synapse Regulates Polarized Secretory Traffic of Multivesicular Bodies in T Lymphocytes. *J. Extracell. Vesicles* **2020**, *9*, 1759926–1759947. [[CrossRef](#)] [[PubMed](#)]
270. Lettau, M.; Armbrust, F.; Dohmen, K.; Drews, L.; Poch, T.; Dietz, M.; Kabelitz, D.; Janssen, O. Mechanistic Peculiarities of Activation-Induced Mobilization of Cytotoxic Effector Proteins in Human T Cells. *Int. Immunol.* **2018**, *30*, 215–228. [[CrossRef](#)] [[PubMed](#)]
271. Lettau, M.; Dietz, M.; Dohmen, K.; Leippe, M.; Kabelitz, D.; Janssen, O. Granulysin Species Segregate to Different Lysosome-Related Effector Vesicles (LREV) and Get Mobilized by Either Classical or Non-Classical Degranulation. *Mol. Immunol.* **2019**, *107*, 44–53. [[CrossRef](#)]
272. Hatano, R.; Ohnuma, K.; Yamamoto, J.; Dang, N.H.; Morimoto, C. CD26-Mediated Co-Stimulation in Human CD8⁺T Cells Provokes Effector Function via pro-Inflammatory Cytokine Production. *Immunology* **2013**, *138*, 165–172. [[CrossRef](#)]
273. Salzer, E.; Santos-Valente, E.; Keller, B.; Warnatz, K.; Boztug, K. Protein Kinase C δ : A Gatekeeper of Immune Homeostasis. *J. Clin. Immunol.* **2016**, *36*, 631–640. [[CrossRef](#)]
274. Gorelik, G.; Sawalha, A.H.; Patel, D.; Johnson, K.; Richardson, B. T Cell PKC δ Kinase Inactivation Induces Lupus-like Autoimmunity in Mice. *Clin. Immunol.* **2015**, *158*, 193–203. [[CrossRef](#)]
275. Bertolotto, C.; Maulon, L.; Filippa, N.; Baier, G.; Auberger, P. Protein Kinase C θ and ϵ Promote T-Cell Survival by a Rsk-Dependent Phosphorylation and Inactivation of BAD. *J. Biol. Chem.* **2000**, *275*, 37246–37250. [[CrossRef](#)]
276. Quann, E.J.; Liu, X.; Altan-Bonnet, G.; Huse, M. A Cascade of Protein Kinase C Isozymes Promotes Cytoskeletal Polarization in T Cells. *Nat. Immunol.* **2011**, *12*, 647–654. [[CrossRef](#)]
277. Mirandola, P.; Gobbi, G.; Masselli, E.; Micheloni, C.; Di Marcantonio, D.; Queirolo, V.; Chiodera, P.; Meschi, T.; Vitale, M. Protein Kinase C ϵ Regulates Proliferation and Cell Sensitivity to TGF-1 β of CD4⁺ T Lymphocytes: Implications for Hashimoto Thyroiditis. *J. Immunol.* **2011**, *187*, 4721–4732. [[CrossRef](#)]
278. Chen, W.; Jin, W.; Hardegen, N.; Lei, K.; Li, L.; Marinos, N.; McGrady, G.; Wahl, S.M. Conversion of Peripheral CD4⁺CD25⁻ Naive T Cells to CD4⁺CD25⁺ Regulatory T Cells by TGF- β Induction of Transcription Factor Foxp3. *J. Exp. Med.* **2003**, *198*, 1875–1886. [[CrossRef](#)]
279. Zhang, N.; Bevan, M.J. Transforming Growth Factor- β Signaling Controls the Formation and Maintenance of Gut-Resident Memory T Cells by Regulating Migration and Retention. *Immunity* **2013**, *39*, 687–696. [[CrossRef](#)] [[PubMed](#)]
280. Qiu, Z.; Chu, T.H.; Sheridan, B.S. TGF- β : Many Paths to CD103⁺ CD8 T Cell Residency. *Cells* **2021**, *10*, 989. [[CrossRef](#)] [[PubMed](#)]

281. Banchereau, R.; Chitre, A.S.; Scherl, A.; Wu, T.D.; Patil, N.S.; de Almeida, P.; Kadel, E.E., III; Madireddi, S.; Au-Yeung, A.; Takahashi, C.; et al. Intratumoral CD103+ CD8+ T Cells Predict Response to PD-L1 Blockade. *J. Immunother. Cancer* **2021**, *9*, e002231. [[CrossRef](#)] [[PubMed](#)]
282. Corgnac, S.; Boutet, M.; Kfoury, M.; Naltet, C.; Mami-Chouaib, F. The Emerging Role of CD8+ Tissue Resident Memory T (TRM) Cells in Antitumor Immunity: A Unique Functional Contribution of the CD103 Integrin. *Front. Immunol.* **2018**, *9*, 1904–1913. [[CrossRef](#)] [[PubMed](#)]
283. Floc'h, A.L.; Jalil, A.; Franciszkiwicz, K.; Validire, P.; Vergnon, I.; Mami-Chouaib, F. Minimal Engagement of CD103 on Cytotoxic T Lymphocytes with an E-Cadherin-Fc Molecule Triggers Lytic Granule Polarization via a Phospholipase C γ -Dependent Pathway. *Cancer Res.* **2011**, *71*, 328–338. [[CrossRef](#)] [[PubMed](#)]
284. Fu, G.; Gascoigne, N.R.J. The Role of Protein Kinase C η in T Cell Biology. *Front. Immunol.* **2012**, *3*, 177–185. [[CrossRef](#)] [[PubMed](#)]
285. Franzese, O.; Henson, S.M.; Naro, C.; Bonmassar, E. Defect in HSP90 Expression in Highly Differentiated Human CD8+ T Lymphocytes. *Cell Death Dis.* **2014**, *5*, e1294. [[CrossRef](#)] [[PubMed](#)]
286. Kong, K.-F.; Fu, G.; Zhang, Y.; Yokosuka, T.; Casas, J.; Canonigo-Balancio, A.J.; Becart, S.; Kim, G.; Yates, J.R.; Kronenberg, M.; et al. Protein Kinase C- η Controls CTLA-4-Mediated Regulatory T Cell Function. *Nat. Immunol.* **2014**, *15*, 465–472. [[CrossRef](#)] [[PubMed](#)]
287. Liu, H.-Y.; Pedros, C.; Kong, K.-F.; Canonigo-Balancio, A.J.; Xue, W.; Altman, A. Leveraging the Treg-Intrinsic CTLA4-PKC η Signaling Pathway for Cancer Immunotherapy. *J. Immunother. Cancer* **2021**, *9*, e002792. [[CrossRef](#)]
288. Martin, P.; Villares, R.; Rodriguez-Mascarenhas, S.; Zaballos, A.; Leitges, M.; Kovac, J.; Sizing, I.; Rennert, P.; Márquez, G.; Martínez-Alonso, C.; et al. Control of T Helper 2 Cell Function and Allergic Airway Inflammation by PKC ζ . *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 9866–9871. [[CrossRef](#)]
289. San-Antonio, B.; Iñiguez, M.A.; Fresno, M. Protein kinase Czeta phosphorylates nuclear factor of activated T cells and regulates its transactivating activity. *J. Biol. Chem.* **2002**, *277*, 27073–27080. [[CrossRef](#)]
290. Real, E.; Faure, S.; Donnadieu, E.; Delon, J. Cutting Edge: Atypical PKCs Regulate T Lymphocyte Polarity and Scanning Behavior. *J. Immunol.* **2007**, *179*, 5649–5652. [[CrossRef](#)]
291. Sheng, W.-Y.; Chien, Y.-L.; Wang, T.-C.V. The Dual Role of Protein Kinase C in the Regulation of Telomerase Activity in Human Lymphocytes. *FEBS Lett.* **2003**, *540*, 91–95. [[CrossRef](#)]
292. Mischak, H.; Kolch, W.; Goodnight, J.; Davidson, W.F.; Rapp, U.; Rose-John, S.; Mushinski, J.F. Expression of Protein Kinase C Genes in Hemopoietic Cells Is Cell-Type- and B Cell-Differentiation Stage Specific. *J. Immunol.* **1991**, *147*, 3981–3987. [[CrossRef](#)]
293. Su, T.T.; Guo, B.; Kawakami, Y.; Sommer, K.; Chae, K.; Humphries, L.A.; Kato, R.M.; Kang, S.; Patrone, L.; Wall, R.; et al. PKC- β Controls I κ B Kinase Lipid Raft Recruitment and Activation in Response to BCR Signaling. *Nat. Immunol.* **2002**, *3*, 780–786. [[CrossRef](#)] [[PubMed](#)]
294. Saijo, K.; Mecklenbräuker, I.; Santana, A.; Leitger, M.; Schmedt, C.; Tarakhovsky, A. Protein Kinase C β Controls Nuclear Factor κ B Activation in B Cells Through Selective Regulation of the I κ B Kinase α . *J. Exp. Med.* **2002**, *195*, 1647–1652. [[CrossRef](#)] [[PubMed](#)]
295. Volkov, Y.; Long, A.; McGrath, S.; Eidhin, D.N.; Kelleher, D. Crucial Importance of PKC- β (I) in LFA-1-Mediated Locomotion of Activated T Cells. *Nat. Immunol.* **2001**, *2*, 508–514. [[CrossRef](#)]
296. Dreikhausen, U.E. Protein Kinase C 1, a Major Regulator of TCR-CD28-Activated Signal Transduction Leading to IL-2 Gene Transcription and Secretion. *Int. Immunol.* **2003**, *15*, 1089–1098. [[CrossRef](#)] [[PubMed](#)]
297. Walsh, D.A.; Borges da Silva, H.; Beura, L.K.; Peng, C.; Hamilton, S.E.; Masopust, D.; Jameson, S.C. The Functional Requirement for CD69 in Establishment of Resident Memory CD8+ T Cells Varies with Tissue Location. *J. Immunol.* **2019**, *203*, 946–955. [[CrossRef](#)] [[PubMed](#)]
298. Cervino, M.C.; Lopez-Lago, M.A.; Vinuela, J.E.; Barja, P. Specific inhibition of protein kinase C β expression by antisense RNA affects the activation of Jurkat T lymphoma cells. *J. Biol. Regul. Homeost. Agents* **2010**, *24*, 273–285.
299. Xiong, X.; Liao, X.; Qiu, S.; Xu, H.; Zhang, S.; Wang, S.; Ai, J.; Yang, L. CXCL8 in Tumor Biology and Its Implications for Clinical Translation. *Front. Mol. Biosci.* **2022**, *9*, 723846–723859. [[CrossRef](#)]
300. Korman, A.J.; Garrett-Thomson, S.C.; Lonberg, N. The Foundations of Immune Checkpoint Blockade and the Ipilimumab Approval Decennial. *Nat. Rev. Drug Discov.* **2022**, *21*, 509–528. [[CrossRef](#)]
301. Morad, G.; Helmink, B.A.; Sharma, P.; Wargo, J.A. Hallmarks of Response, Resistance, and Toxicity to Immune Checkpoint Blockade. *Cell* **2022**, *185*, 576–593. [[CrossRef](#)]
302. Gabilovich, D.I. Myeloid-Derived Suppressor Cells. *Cancer Immunol. Res.* **2017**, *5*, 3–8. [[CrossRef](#)]
303. Chaib, M.; Holt, J.; Sipe, L.M.; Bohm, M.S.; Clarice, S.J.; Yarbro, J.R.; Tanveer, U.; Hollingsworth, T.J.; Wei, Q.; Thomas, P.G.; et al. Protein Kinase C Delta Regulates Mononuclear Phagocytes and Hinders Response to Immunotherapy in Cancer. *bioRxiv* **2022**. [[CrossRef](#)]
304. Wei, C.-Y.; Zhu, M.-X.; Zhang, P.-F.; Huang, X.-Y.; Wan, J.-K.; Yao, X.-Z.; Hu, Z.-T.; Chai, X.-Q.; Peng, R.; Yang, X.; et al. PKC α /ZFP64/CSF1 Axis Resets the Tumor Microenvironment and Fuels Anti-PD1 Resistance in Hepatocellular Carcinoma. *J. Hepatol.* **2022**, *77*, 163–176. [[CrossRef](#)] [[PubMed](#)]
305. Chaib, M.; Sipe, L.M.; Yarbro, J.R.; Bohm, M.S.; Counts, B.R.; Tanveer, U.; Pingili, A.K.; Daria, D.; Marion, T.N.; Carson, J.A.; et al. PKC Agonism Restricts Innate Immune Suppression, Promotes Antigen Cross-Presentation and Synergizes with Agonistic CD40 Antibody Therapy to Activate CD8+ T Cells in Breast Cancer. *Cancer Lett.* **2022**, *531*, 98–108. [[CrossRef](#)] [[PubMed](#)]

306. To, K.K.W.; Fong, W.; Cho, W.C.S. Immunotherapy in Treating EGFR-Mutant Lung Cancer: Current Challenges and New Strategies. *Front. Oncol.* **2021**, *11*, 635007–635024. [[CrossRef](#)]
307. Gainor, J.F.; Shaw, A.T.; Sequist, L.V.; Fu, X.; Azzoli, C.G.; Piotrowska, Z.; Huynh, T.G.; Zhao, L.; Fulton, L.; Schultz, K.R.; et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. *Clin. Cancer Res.* **2016**, *22*, 4585–4593. [[CrossRef](#)] [[PubMed](#)]
308. Zuo, Y.-H.; Gao, W.-N.; Xie, Y.-J.; Yang, S.-Y.; Zhou, J.-T.; Liang, H.-H.; Fan, X.-X. Tumor PKC δ Instigates Immune Exclusion in EGFR-Mutated Non-Small Cell Lung Cancer. *BMC Med.* **2022**, *20*, 470–484. [[CrossRef](#)] [[PubMed](#)]
309. Sutcliffe, E.L.; Li, J.; Zafar, A.; Hardy, K.; Ghildyal, R.; McCuaig, R.; Norris, N.; Lim, P.S.; Milburn, P.J.; Casarotto, M.; et al. Chromatinized Protein Kinase C- θ : Can It Escape the Clutches of NF- κ B? *Front. Immunol.* **2012**, *3*, 260. [[CrossRef](#)]
310. Dunn, J.; McCuaig, R.D.; Tan, A.H.Y.; Tu, W.J.; Wu, F.; Wagstaff, K.M.; Zafar, A.; Ali, S.; Diwakar, H.; Dahlstrom, J.E.; et al. Selective Targeting of Protein Kinase C (PKC)- θ Nuclear Translocation Reduces Mesenchymal Gene Signatures and Reinvigorates Dysfunctional CD8⁺ T Cells in Immunotherapy-Resistant and Metastatic Cancers. *Cancers* **2022**, *14*, 1596. [[CrossRef](#)]
311. Gao, Y.; Hu, S.; Li, R.; Jin, S.; Liu, F.; Liu, X.; Li, Y.; Yan, Y.; Liu, W.; Gong, J.; et al. Hyperprogression of Cutaneous T Cell Lymphoma after Anti-PD-1 Treatment. *JCI Insight* **2023**, *8*, e164793. [[CrossRef](#)]
312. Triebel, F. LAG-3: A Regulator of T-Cell and DC Responses and Its Use in Therapeutic Vaccination. *Trends Immunol.* **2003**, *24*, 619–622. [[CrossRef](#)]
313. Shi, A.-P.; Tang, X.-Y.; Xiong, Y.-L.; Zheng, K.-F.; Liu, Y.-J.; Shi, X.-G.; Lv, Y.; Jiang, T.; Ma, N.; Zhao, J.-B. Immune Checkpoint LAG3 and Its Ligand FGL1 in Cancer. *Front. Immunol.* **2021**, *12*, 785091–785102. [[CrossRef](#)]
314. Maruhashi, T.; Sugiura, D.; Okazaki, I.; Okazaki, T. LAG-3: From Molecular Functions to Clinical Applications. *J. Immunother. Cancer* **2020**, *8*, e001014. [[CrossRef](#)]
315. Bae, J.; Lee, S.J.; Park, C.-G.; Lee, Y.S.; Chun, T. Trafficking of LAG-3 to the Surface on Activated T Cells via Its Cytoplasmic Domain and Protein Kinase C Signaling. *J. Immunol.* **2014**, *193*, 3101–3112. [[CrossRef](#)] [[PubMed](#)]
316. Sleckman, B.P.; Shin, J.; Igras, V.E.; Collins, T.L.; Strominger, J.L.; Burakoff, S.J. Disruption of the CD4-P56lck Complex Is Required for Rapid Internalization of CD4. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 7566–7570. [[CrossRef](#)] [[PubMed](#)]
317. Sleckman, B.P.; Bigby, M.; Greenstein, J.L.; Burakoff, S.J.; Sy, M.S. Requirements for Modulation of the CD4 Molecule in Response to Phorbol Myristate Acetate. Role of the Cytoplasmic Domain. *J. Immunol.* **1989**, *142*, 1457–1462. [[CrossRef](#)]
318. Cron, K.; Sivan, A.; Aquino-Michaels, K.; Higgs, E.; Fessler, J.; Lee, S.; Sweis, R.; Gajewski, T. 642 Decreased Host PKC-Delta Is Associated with the T Cell-Inflamed Tumor Microenvironment and Improves Anti-Tumor Immunity. *J. Immunother. Cancer* **2021**, *9*, A671. [[CrossRef](#)]
319. Diaz-Meco, M.T.; Moscat, J. The Atypical PKCs in Inflammation: NF- κ B and Beyond. *Immunol. Rev.* **2012**, *246*, 154–167. [[CrossRef](#)] [[PubMed](#)]
320. Pedros, C.; Canonigo-Balancio, A.J.; Kong, K.-F.; Altman, A. Requirement of Treg-Intrinsic CTLA4/PKC η Signaling Pathway for Suppressing Tumor Immunity. *JCI Insight* **2017**, *2*, e95692. [[CrossRef](#)]
321. Abdelatty, A.; Sun, Q.; Hu, J.; Wu, F.; Wei, G.; Xu, H.; Zhou, G.; Wang, X.; Xia, H.; Lan, L. Pan-Cancer Study on Protein Kinase C Family as a Potential Biomarker for the Tumors Immune Landscape and the Response to Immunotherapy. *Front. Cell Dev. Biol.* **2022**, *9*, 798319–798336. [[CrossRef](#)]
322. Sarkar, S.; Bristow, C.A.; Dey, P.; Rai, K.; Perets, R.; Ramirez-Cardenas, A.; Malasi, S.; Huang-Hobbs, E.; Haemmerle, M.; Wu, S.Y.; et al. PRKCI Promotes Immune Suppression in Ovarian Cancer. *Genes. Dev.* **2017**, *31*, 1109–1121. [[CrossRef](#)]
323. Zhang, H.; Zhu, Y.; Wang, J.; Weng, S.; Zuo, F.; Li, C.; Zhu, T. PKC ι Regulates the Expression of PDL1 through Multiple Pathways to Modulate Immune Suppression of Pancreatic Cancer Cells. *Cell Signal.* **2021**, *86*, 110115–110130. [[CrossRef](#)] [[PubMed](#)]
324. Huang, H.; Huang, Z.; Ge, J.; Yang, J.; Chen, J.; Xu, B.; Wu, S.; Zheng, X.; Chen, L.; Zhang, X.; et al. CD226 Identifies Functional CD8⁺T Cells in the Tumor Microenvironment and Predicts a Better Outcome for Human Gastric Cancer. *Front. Immunol.* **2023**, *14*, 1150803. [[CrossRef](#)]
325. Shibuya, A.; Lanier, L.L.; Phillips, J.H. Protein Kinase C Is Involved in the Regulation of Both Signaling and Adhesion Mediated by DNAX Accessory Molecule-1 Receptor. *J. Immunol.* **1998**, *161*, 1671–1676. [[CrossRef](#)]
326. Shirakawa, J. Requirement of the Serine at Residue 329 for Lipid Raft Recruitment of DNAM-1 (CD226). *Int. Immunol.* **2005**, *17*, 217–223. [[CrossRef](#)]
327. Johnston, R.J.; Comps-Agrar, L.; Hackney, J.; Yu, X.; Huseni, M.; Yang, Y.; Park, S.; Javinal, V.; Chiu, H.; Irving, B.; et al. The Immunoreceptor TIGIT Regulates Antitumor and Antiviral CD8⁺ T Cell Effector Function. *Cancer Cell* **2014**, *26*, 923–937. [[CrossRef](#)] [[PubMed](#)]
328. Jin, H.; Ko, M.; Choi, D.; Kim, J.H.; Lee, D.; Kang, S.-H.; Kim, I.; Lee, H.J.; Choi, E.K.; Kim, K.; et al. CD226hiCD8⁺ T Cells Are a Prerequisite for Anti-TIGIT Immunotherapy. *Cancer Immunol. Res.* **2020**, *8*, 912–925. [[CrossRef](#)]
329. Arranz-Nicolás, J.; Martín-Salgado, M.; Rodríguez-Rodríguez, C.; Liébana, R.; Moreno-Ortiz, M.C.; Leitner, J.; Steinberger, P.; Ávila-Flores, A.; Merida, I. Diacylglycerol Kinase ζ Limits IL-2-Dependent Control of PD-1 Expression in Tumor-Infiltrating T Lymphocytes. *J. Immunother. Cancer* **2020**, *8*, e001521. [[CrossRef](#)] [[PubMed](#)]
330. Kawamura, A.; Kawamura, T.; Riddell, M.; Hikita, T.; Yanagi, T.; Umemura, H.; Nakayama, M. Regulation of Programmed Cell Death Ligand 1 Expression by Atypical Protein Kinase C Lambda/Iota in Cutaneous Angiosarcoma. *Cancer Sci.* **2019**, *110*, 1780–1789. [[CrossRef](#)]

331. Riddell, M.; Nakayama, A.; Hikita, T.; Mirzapourshafiyi, F.; Kawamura, T.; Pasha, A.; Li, M.; Masuzawa, M.; Looso, M.; Steinbacher, T.; et al. α PKC Controls Endothelial Growth by Modulating C-Myc via FoxO1 DNA-Binding Ability. *Nat. Commun.* **2018**, *9*, 5357–5370. [[CrossRef](#)]
332. Zhang, L.L.; Cao, F.F.; Wang, Y.; Meng, F.L.; Zhang, Y.; Zhong, D.S.; Zhou, Q.H. The protein kinase C (PKC) inhibitors combined with chemotherapy in the treatment of advanced non-small cell lung cancer: Meta-analysis of randomized controlled trials. *Clin. Transl. Oncol.* **2015**, *17*, 371–377. [[CrossRef](#)] [[PubMed](#)]
333. Tovell, H.; Newton, A.C. PHLPPing the balance: Restoration of protein kinase C in Cancer. *Biochem. J.* **2021**, *478*, 341–355. [[CrossRef](#)] [[PubMed](#)]
334. Newton, A.C. Protein kinase C as a tumor suppressor. *Semin. Cancer Biol.* **2018**, *48*, 18–26. [[CrossRef](#)]
335. Cooke, M.; Magimaidas, A.; Casado-Medrano, V.; Kazanietz, M.G. Protein kinase C in cancer: The top five unanswered questions. *Mol. Carcinog.* **2017**, *56*, 1531–1542. [[CrossRef](#)] [[PubMed](#)]
336. Sapon-Cousineau, V.; Sapon-Cousineau, S.; Assouline, S. PI3K inhibitors and their role as novel agents for targeted therapy in lymphoma. *Curr. Treat. Options Oncol.* **2020**, *21*, 51. [[CrossRef](#)] [[PubMed](#)]

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