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## Calcium regulates cell death in cancer: roles of the mitochondria and mitochondria-associated membranes (MAMs)

Alberto Danese<sup>1</sup>, Simone Patergnani<sup>1</sup>, Massimo Bonora<sup>1</sup>, Mariusz R. Wieckowski<sup>2</sup>, Maurizio Previati<sup>3</sup>, Carlotta Giorgi<sup>1\*</sup> and Paolo Pinton<sup>1\*</sup>

*<sup>1</sup>Dept. of Morphology, Surgery and Experimental Medicine, Section of Pathology, Oncology and Experimental Biology, Laboratory for Technologies of Advanced Therapies (LTTA), University of Ferrara, Ferrara, Italy*

*<sup>2</sup> Dept. of Biochemistry, Nencki Institute of Experimental Biology, Warsaw, Poland*

*<sup>3</sup>Department of Morphology, Surgery and Experimental Medicine, Section of Human Anatomy and Histology, Laboratory for Technologies of Advanced Therapies (LTTA), University of Ferrara, Ferrara, Italy*

\*Correspondence to:

Paolo Pinton, email: [paolo.pinton@unife.it](mailto:paolo.pinton@unife.it) or  
Carlotta Giorgi, email: [carlotta.giorgi@unife.it](mailto:carlotta.giorgi@unife.it)

**ABSTRACT**

Until 1972, the term 'apoptosis' was used to differentiate the programmed cell death that naturally occurs in organismal development from the acute tissue death referred to as necrosis.

Many studies on cell death and programmed cell death have been published and most are, at least to some degree, related to cancer. Some key proteins and molecular pathways implicated in cell death have been analyzed, whereas others are still being actively researched; therefore, an increasing number of cellular compartments and organelles are being implicated in cell death and cancer.

Here, we discuss the mitochondria and subdomains of the endoplasmic reticulum (ER) that interact with mitochondria, the mitochondria-associated membranes (MAMs), which have been identified as critical hubs in the regulation of cell death and tumor growth. MAMs-dependent calcium ( $\text{Ca}^{2+}$ ) release from the ER allows selective  $\text{Ca}^{2+}$  uptake by the mitochondria. The perturbation of  $\text{Ca}^{2+}$  homeostasis in cancer cells is correlated with sustained cell proliferation and the inhibition of cell death through the modulation of  $\text{Ca}^{2+}$  signaling.

## INTRODUCTION

Cell death is a crucial and essential aspect of life. Although this statement may be contradictory, cell death itself is directly connected to cell proliferation and cell survival [1].

Programmed cell death has been established as an anti-cancer defense mechanism; therefore, any modification to the related pathways leads to uncontrolled cell proliferation and oncogenesis.

Early classifications of cell death were based on morphological assays, and apoptosis was one of the first processes to be described. The initial morphological observations were described as the rounding-up of the cell, a reduction in cellular volume, chromatin condensation, cytoplasmic shrinkage, the retraction of pseudopods, nuclear fragmentation, and a particular boiling-like process termed blebbing [2].

Apoptosis is the most important and well-studied mechanism of cell death; approximately 10 million cells undergo the apoptotic process in an adult human under physiological conditions each day [3]. The primary proteins involved in apoptotic cell death and their respective activities will be discussed in the subsequent sections.

The apoptotic process is classified as type I cell death. Type II cell death is classified as autophagy, a pro-survival process that also acts as a pro-death pathway, as it is involved in several biological events, such as aging, development, protein turnover, neurodegeneration and cancer [4]. In addition to the canonical proteins mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK), the most well-studied proteins that act as initiation sensors, BECLIN1 and autophagy and BECLIN1 regulator 1 (AMBRA1) are also involved in the initial steps of autophagosome formation [5].

Necrosis is defined as type III cell death and has long been considered as an accidental and unscheduled form of cell death. Nonetheless, according to several

recent studies, the execution of the necrotic process may be regulated by a set of catabolic mechanisms and signal transduction pathways [6]. The Bcl-interacting protein 3 (BNIP3), Bcl-2-modifying factor (BMF) (pro-death proteins and members of the Bcl-2 family), NIP3-like protein X (Nix), the kinase receptor-interacting protein 1 (RIP1) and RIP3 proteins may be involved in this process, as they are speculated to be key signaling molecules involved in necrosis and, in turn, are regulated by caspases and ubiquitination [7-10].

The aforementioned cell death types are considered the main pathways involved in cell death. For a complete description, we must mention atypical cell death modalities, such as anoikis, a particular type of apoptosis induced by the loss of attachment to other cells or matrix. Anoikis involves Bid and Bim, which are activated following the detachment of cells from the extracellular matrix (ECM) and rapidly promote the assembly of Bax–Bak oligomers within the outer mitochondrial membrane (OMM) [11].

Pyroptosis is a cell death mechanism induced by caspase-1 activation, leading to interleukin (IL)-1 $\beta$  and IL-18 release. NLRP3-dependent caspase-1 activation plays a key role in this process. Indeed, mitochondria-associated adapter molecules, MAVS, are required for optimal NLRP3 inflammasome activity [12]. Paraptosis is a type of cell death triggered by the expression of the insulin-like growth factor receptor I [13]. Mitochondrial Ca<sup>2+</sup> has an extremely important role in hesperidin-induced paraptotic cell death [14].

Other cell death mechanisms that are not yet well characterized include cell death preceded by multinucleation and entosis (a phenomenon that occurs when a cell engulfs one of its live neighboring cells) [15].

All these cell death mechanisms are finely regulated by a complex network of proteins, whose transcription and degradation have profound effects on malignant cancer phenotypes. Some oncogenic mutations disrupt programmed cell death, leading to tumor initiation, progression or metastasis (e.g., mutations in the Bcl-2 protein family deregulate cell death).

Bcl-2 does not behave like a typical oncogene; it promotes cell survival by blocking programmed cell death (i.e., by having a direct effect on endoplasmic reticulum  $\text{Ca}^{2+}$  handling) instead of disrupting normal proliferation checkpoints [16]. Other examples include p53-like proteins, including TP53 itself, which was the first gene linked to apoptosis. p53 has tumor suppression properties, and this gene is mutated in the majority of human tumors [17]. Disruption of the Fas/CD95 receptor pathway, which regulates cell number in the immune system, leads to lymphoproliferative disorders and cancer [18]. Ras activation and phosphatase and tensin homologue (PTEN) loss are common in human tumors; phosphoinositide 3-kinase (PI3K) is activated by Ras and downregulated by the tumor suppressor PTEN.

These mechanisms are only some of the many mechanisms that regulate cell death, all of which induce different morphological phenotypes by regulating or directly controlling the involvement of downstream molecular pathways. In this review, we will focus on  $\text{Ca}^{2+}$ -dependent cell death mechanisms.  $\text{Ca}^{2+}$  transients have been implicated in most aspects of cell physiology and play important roles in regulating cell death [19]. In particular, we analyzed the ER and mitochondrial compartments and the intimate interactions that physically occur through the mitochondria-associated ER membranes (MAMs) that play important roles in cellular physiology and participate in the mechanism by which cancer cells resist apoptotic stimuli [20].

## **GENERAL CONCEPTS, FACTS, HYPOTHESIS AND CONTROVERSY RELATED TO $\text{Ca}^{2+}$**

The evolution of biological complexity arising from unicellular organisms to pluricellular structures was mediated by the development of dedicated messengers capable of synchronizing the activities of different cells and producing advantageous cooperation. These types of communication required cells to be able to produce an extracellular signal that bound a dedicated

receptor on the cell membrane. This messenger, in turn, allowed the transduction of information across the membrane to produce an intracellular second messenger that bound different intracellular ligands after traveling across the cytoplasm and stimulated multiple activities located in different cellular regions.

Considering its availability at the time the first multicellular organisms evolved and its chemical properties,  $\text{Ca}^{2+}$  became one of the most important (and most studied) intracellular second messengers.

Within cells, the average  $\text{Ca}^{2+}$  concentration is far above the  $\mu\text{M}$  range, but its heterogeneous distribution reflects the importance of its tight regulation. Indeed,  $\text{Ca}^{2+}$  is present at high concentrations in the so-called intracellular stores, mainly the endo/sarcoplasmic reticulum (ER/SR) and the Golgi apparatus, where its concentrations range between 300 and 1000  $\mu\text{M}$  [21, 22]. In contrast, very low  $\text{Ca}^{2+}$  concentrations are maintained in the cytoplasm, mitochondrial matrix and peroxisomal lumen, where it is expected to exert signaling effects (ranging from 100 to 500 nM) [23].

In non-excitabile cells, binding of an extracellular messenger to a specific G protein-coupled receptor allows the generation of intracellular inositol phosphate 3 (IP3), which binds the IP3 receptor (IP3R) located in the ER membrane. This receptor, an ion channel-linked receptor that opens after binding IP3, leads to the selective passage of  $\text{Ca}^{2+}$  from the ER lumen to the cytosol. Due to the dramatic difference in the  $\text{Ca}^{2+}$  concentrations between these two compartments, the opening of IP3R leads to a fast and dramatic increase in the cytosolic  $\text{Ca}^{2+}$  concentration ( $[\text{Ca}^{2+}]_c$ ), which easily reaches its targets and promotes events such as transcriptional regulation, protein synthesis, metabolic control, hormone secretion, cytoskeletal remodeling, and cell motility. In excitable cells, voltage-gated channels allow the generation of  $\text{Ca}^{2+}$  signals by importing extracellular  $\text{Ca}^{2+}$  (usually in the mM range) into the cytosol. These signals, which are reinforced by  $\text{Ca}^{2+}$ -induced cytoplasmic release of

intraluminal ER/SR  $\text{Ca}^{2+}$ , promote  $\text{Ca}^{2+}$ -mediated regulation of contractility and vesicle release, supporting the involvement of  $\text{Ca}^{2+}$  in a plethora of cellular functions [24].

A fascinating aspect of  $\text{Ca}^{2+}$  signaling that highlights its dramatic importance in the evolution of multicellular organisms is its capacity to regulate cell death. Indeed, multicellular organisms require tight control of the cellular  $\text{Ca}^{2+}$  concentrations to allow proper tissue homeostasis; loss of this control results in excess proliferation (which may lead to malignancies) or loss of tissue function (neurodegenerative pathologies).

One of the earliest contexts that allowed researchers to comprehend how  $\text{Ca}^{2+}$  regulates cell death was the activation of the T-cell receptor (TCR) on immature lymphocytes. TCR activation generates IP<sub>3</sub> and leads to IP<sub>3</sub>R opening. Short-term TCR activation has been proposed to lead to short and synchronized  $\text{Ca}^{2+}$  waves that activate nuclear factor of activated T cells (NFAT), subsequently stimulating IL-2 production and cell survival. In contrast, prolonged TCR activation induces wide and persistent elevation of the cytosolic free calcium concentrations ( $[\text{Ca}^{2+}]_c$ ), resulting in apoptosis. These results provide the foundation for the mechanism by which T cells undergo positive selection, which remains one of the prototypical examples of the duality of  $\text{Ca}^{2+}$  signaling [25].

Many other molecules have been proposed to induce elevated  $[\text{Ca}^{2+}]_c$  and subsequent apoptosis, including glucocorticoids in thymocytes, angiotensin II in cardiomyocytes, and testosterone in cardiomyocytes, T cells and neurons.

In addition, some pharmacological compounds yield the same result, including compounds that induce ER stress (e.g., thapsigargin [26]) and oxidative stress (e.g., hydrogen peroxide or menadione [27]), as well as prostaglandin intermediates, sphingolipids (e.g., arachidonic acid and c2-ceramide [28]), cisplatin and staurosporine. Indeed, all these compounds share the capacity to induce IP<sub>3</sub>R-mediated elevations of  $[\text{Ca}^{2+}]_c$  followed by apoptosis.



Furthermore, the involvement of IP3R in apoptosis has been reported in different cell types through IP3R isoform-specific silencing in response to several apoptotic stimuli [29].

Based on its messenger nature,  $\text{Ca}^{2+}$  is able to regulate the induction of apoptosis at different sites, presumably to maximize its effect or avoid the possibility that the alteration of one site would compromise message transmission.

Within the cytoplasm, elevated  $[\text{Ca}^{2+}]$  is able to activate a class of cysteine proteases called calpains. These enzymes are capable of inducing proteolytic activation of caspase-12 that, in turn, induces the cascade activation of caspase-9 and -3, resulting in the execution of the apoptotic program. This program has primarily been associated with ER stress and cisplatin exposure and depends on IP3R [30].

One of the most well-studied  $\text{Ca}^{2+}$ -induced cell death pathways is the cross-talk between the ER and mitochondria. These compartments communicate through selective signals in regions called MAMs (see following chapter). At these sites,  $\text{Ca}^{2+}$  released from the ER is directly taken up by the mitochondria through specialized microdomains. The main physiological role of  $\text{Ca}^{2+}$  uptake involves the control of mitochondrial metabolic activity, as revealed by the ATP production rate. Indeed, the  $\text{Ca}^{2+}$ -sensitive mitochondrial dehydrogenases (i.e., pyruvate-,  $\alpha$ -ketoglutarate- and isocitrate-dehydrogenases) are activated by  $\text{Ca}^{2+}$ . These three enzymes represent the rate-limiting steps of the Krebs cycle and thus control the supply of electrons into the respiratory chain and the generation of the proton gradient across the inner membrane, which is necessary for  $\text{Ca}^{2+}$  uptake and ATP production.

In contrast to these physiological parameters, prolonged accumulation of mitochondrial  $\text{Ca}^{2+}$  may lead to a phenomenon known as the mitochondrial permeability transition (MPT).

Induction of the MPT leads to the loss of inner mitochondrial membrane (IMM) permeability, with a rapid breakdown of mitochondrial membrane potential

( $\Delta\Psi_{mt}$ ), loss of ATP, osmotic shock to the organelle and rupture of the OMM [2]. Loss of ATP then decreases ion homeostasis and cell integrity, ultimately resulting in necrosis [31].

This mechanism has been widely investigated in pathological cell death, particularly in cell death associated with ischemia and reperfusion injury.

Most of the current literature is consistent with the notion that the  $Ca^{2+}$ -induced MPT is primarily related to necrotic cell death.

Nonetheless, some reports have proposed that the MPT is involved in the regulation of apoptosis. Indeed, the rupture of the OMM during mitochondrial swelling can lead to the release of mitochondrial pro-apoptotic factors, including cytochrome C, apoptosis-inducing factor (AIF), SMAC/DIABLO and EndoG, which are required for the intrinsic apoptosis pathway. Isolated mitochondria exposed to MPT-inducing stimuli are able to induce apoptotic-like morphological rearrangements when mixed with isolated nuclei. In addition, the pro-apoptotic protein Bax can induce the loss of  $\Delta\Psi_{mt}$  through a pathway distinct from the  $Ca^{2+}$ -inducible, cyclosporin A-sensitive PTP pathway.

Because ATP is a critical component of apoptosis, one could argue that the loss of mitochondrial ATP synthesis due to the MPT would not be permissive to MPT-induced apoptosis. Thus, the MPT may not involve the entire mitochondrial network within the cell, but instead it may appear as “flickering” at the level of a single mitochondrion. This flickering could generate localized and multi-phasic release of pro-apoptotic factors from the mitochondria, leading to apoptosis.

ER-to-mitochondria  $Ca^{2+}$  transfer has also been recently linked to type II programmed cell death [32]. Autophagy is usually activated during metabolic energy stress, a condition in which the process promotes the recycling of intracellular contents to produce metabolic intermediates [33]. As mentioned above, mitochondrial  $Ca^{2+}$  uptake stimulates ATP production, and blocking this signaling by IP3R knockdown or pharmacological inhibition (i.e., using xestospongins) stimulates autophagy [34]. This stimulation is mediated by the

activation of AMPK, an energy sensor that is activated during nutrient deprivation to inhibit the activity of the mTOR, a negative regulator of autophagy [35]. Recently, contradictory reports have highlighted the complex role of  $\text{Ca}^{2+}$  in the activation of autophagy. Reports from both Missiroli et al. [36] and Cardenas et al. [37] were focused on the role of autophagy in tumor progression, the former by knockout of the master oncosuppressor PML (promyelocytic leukemia protein) and the latter by pharmacological inhibition and siRNAs targeting the  $\text{Ca}^{2+}$  machinery. Both reports confirmed the inhibition of ER-to-mitochondria  $\text{Ca}^{2+}$  transfer, although the authors reported contrasting outcomes related to cell survival. The report from Missiroli et al. [36] proposed that inhibition of  $\text{Ca}^{2+}$  transfer, a mechanism typical of several pro-tumor conditions (see the following chapters), stimulates pro-survival autophagy, which is only shifted to pro-cell death autophagy when cells were further stressed (i.e., by the administration of chemotherapeutics and pro-autophagic compounds). In contrast, the report from Cardenas et al. indicated that the induction of autophagy was not sufficient to compensate for the energetic crisis in cancer cells, leading to cell death. [38] Several explanations may justify these different observations, including the differences in experimental procedures, but the most likely explanation is the extent to which  $\text{Ca}^{2+}$  signaling was inhibited. Indeed, the former report observed a milder  $\text{Ca}^{2+}$  transfer inhibition that could have resulted in milder autophagic stimulation, leading to a pro-survival state compared with that of the latter report.

Overall, in addition to the many regulatory aspects that should be further investigated,  $\text{Ca}^{2+}$  is clearly an important intracellular messenger that participates in a complex system of cell functions, with cell death being one of the most relevant functions.

**EFFECTOR SYSTEM FOR ELEVATED  $\text{Ca}^{2+}$  CONCENTRATIONS**

A plethora of stimuli influence the increase in the cytosolic  $\text{Ca}^{2+}$  concentrations ( $[\text{Ca}^{2+}]_i$ ) and the release of  $\text{Ca}^{2+}$  from the ER; therefore, cells are constantly working to maintain the correct concentration gradient.

Under physiological conditions, stimuli generally promote low and transient increases in  $[\text{Ca}^{2+}]_i$ ; in contrast, under pathological conditions, variations in  $[\text{Ca}^{2+}]_i$  induced by these stimuli are pronounced and sustained. In particular, during programmed cell death, especially apoptosis,  $[\text{Ca}^{2+}]_i$  is dramatically increased. Consequently, the mitochondria take up large amounts of  $\text{Ca}^{2+}$ , leading to the induction of apoptosis.

These stimuli, termed apoptotic inducers, are physiological (e.g., corticosteroids or nitric oxide enzymes, NOS) or pharmacological (e.g., chemodrugs, such as cisplatin) stimuli. Corticosteroids are widely used to treat cancer and other diseases, such as autoimmunity, by counteracting TCR activation. Interestingly,  $\text{Ca}^{2+}$  has been shown to be an indispensable factor for T lymphocyte activation and proliferation; moreover, short-term corticosteroid treatments attenuate the TCR-mediated  $\text{Ca}^{2+}$  elevations necessary for T-cell activation. Prolonged treatments cause thymocyte apoptosis mediated by persistently elevated cytosolic  $\text{Ca}^{2+}$  levels. However, the exact mechanism of corticosteroid action on  $\text{Ca}^{2+}$  handling is not well understood. The primary hypothesis is that these hormones inhibit the Src family kinase Lck, which normally regulates IP3R activity [39].

The relationship between  $\text{Ca}^{2+}$  and hormones is not only restricted to autoimmunity and cancer but is also involved in heart disease. For example, angiotensin activates the apoptotic program by modulating  $\text{Ca}^{2+}$  signaling. In particular, angiotensin, which is released in response to glucocorticoids and estrogens, generates IP3 and diacylglycerol (DAG) by binding to AT-1 receptor (AT-1R), a G-protein-coupled receptor that activates phospholipase C [40]. As a

result, overall  $\text{Ca}^{2+}$  signaling is activated and apoptosis may be triggered. Interestingly, angiotensin may also function by opening the L-type voltage-dependent  $\text{Ca}^{2+}$  channel (L-VDCC). In fact, administration of an L-type  $\text{Ca}^{2+}$  channel blocker inhibits angiotensin-induced apoptosis [41].

Other factors have been shown to be involved in heart disease following alterations in  $\text{Ca}^{2+}$  signaling. Nitric oxide synthase (NOS) enzymes widely regulate  $\text{Ca}^{2+}$  homeostasis by inhibiting L-type channel activity and  $\text{Ca}^{2+}$ -release from the SR. As a result, the apoptotic program is blocked due to a reduction in mitochondrial  $\text{Ca}^{2+}$  uptake, which prevents mitochondrial fragmentation and cytochrome C release. Overall, the NOS family seems to exert beneficial effects that counteract some pathologies, including ischemia and reperfusion injury. In fact, these enzymes have also been described as the primary causes of several pathologies, particularly cancer. First, alterations in the expression of NOS enzymes have been observed in several human cancers [42]. High NO levels were sufficient to activate anti-apoptotic proteins, such as Akt, Bcl-2 and Ras [43, 44]. Interestingly, all these proteins are important mediators of apoptosis, as they regulate  $\text{Ca}^{2+}$  signaling.

Finally, intracellular  $\text{Ca}^{2+}$  homeostasis and  $\text{Ca}^{2+}$  release from the ER may be modulated by various cytotoxic agents. Generally, these compounds are used to promote apoptotic cell death by disrupting  $\text{Ca}^{2+}$  homeostasis. Notably, most of these compounds are widely used as anti-cancer treatments. For example, cisplatin, one of the most widely used chemotherapeutic agents, induces  $\text{Ca}^{2+}$  leakage from the ER, causing a subsequent increase in intracellular  $\text{Ca}^{2+}$  levels and apoptosis [45].

## THE MITOCHONDRIAL CALCIUM UNIPORTER (MCU) COMPLEX AND THE ROLE OF ITS COMPONENTS IN TUMORIGENESIS

As described above,  $\text{Ca}^{2+}$  homeostasis is responsible for controlling a vast number of cellular functions. Mitochondrial  $\text{Ca}^{2+}$  uptake plays an essential role in the maintenance of homeostasis and participates in cellular metabolism, cytosolic  $\text{Ca}^{2+}$  buffering, secretory functions, cell survival, proliferation, migration and cell death [46]. For many years, mitochondrial  $\text{Ca}^{2+}$  uptake was ascribed to a single transport mechanism mediated by an individual protein that functions as a uniporter; however, the uniporter was recently shown to be a macromolecular complex consisting of pore-forming and regulatory subunits, rather than a single protein [47].

The pore is physically formed by oligomers of MCU, a protein located in the IMM. MCU has two putative transmembrane domains, with C- and N-terminal domains spanning the mitochondrial matrix [48].

Mitochondrial calcium uptake protein 1 (MICU1) is an important regulatory subunit of the complex; its discovery preceded the identification of MCU [49]. MICU1 performs a gatekeeping function, stabilizing the closed state of the MCU complex and cooperating to allow  $\text{Ca}^{2+}$  to accumulate inside the mitochondria [50].

MICU2 shares 25% sequence identity with MICU1 and interacts with both MICU1 and MCU. The structure and function of this protein are still subjects of debate [51].

A 10-kDa single-pass membrane protein named efflux-multidrug resistance protein (EMRE) interacts with MICU1 and MCU oligomers. Thus, EMRE acts as a bridge between MICU1 activity and the channel properties of MCU; its loss drives the reduction of mitochondrial  $\text{Ca}^{2+}$  uptake to the same extent as MCU depletion [52].

MCUb is an MCU paralogue/isogene that acts as an endogenous dominant-

negative isoform [53].

Mitochondrial  $\text{Ca}^{2+}$  overload has been associated with apoptosis and necrosis in many pathological conditions [17], and as a mitochondrial  $\text{Ca}^{2+}$  uniporter, MCU has many pathophysiological implications. When a pro-apoptotic stimulus occurs, MCU-expressing cells display an enhanced sensitivity to apoptosis [54]. Moreover, inhibition of the pathway that activates the MCU complex by phosphorylating the uniporter through  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (CaMKII) and protein tyrosine kinase 2 beta (Pyk2) prevents  $\text{Ca}^{2+}$  overload in mitochondria, reactive oxygen species (ROS) production, and cell death [55]. Therefore, modulation of the expression of MCU complex subunits could improve our understanding of the possible pathogenic role of the uniporter. Below, we discuss its potential tumorigenic, apoptosis-modulating functions.

As shown in our previous study, microRNA-25 (miR-25) is up-regulated in human prostate and colon cancers and targets the MCU gene. miR-25 decreases MCU expression and, consequently, reduces mitochondrial  $\text{Ca}^{2+}$  uptake and resistance to  $\text{Ca}^{2+}$ -dependent apoptotic death [56].

Elevated mitochondrial  $[\text{Ca}^{2+}]$  and ROS accumulation via MCU activity may induce cell death by increasing OMM permeability and the opening of the mitochondrial permeability transition pore (mPTP) [31]. MCU overexpression increases mitochondrial ROS generation and accumulation and, conversely, silences MCU or inhibits its activity through the introduction of the dominant-negative subunit MCUb, decreasing mitochondrial ROS generation induced by various stimuli [57].

MICU1 knockout cells lose their MCU complex gatekeeping function and are highly susceptible to apoptotic cell death under stress conditions because of the increased basal ROS levels during mitochondrial  $\text{Ca}^{2+}$  uptake [58].

A recent study from the University of Padua highlights a possible role of MCU in the regulation of breast cancer progression via hypoxia inducible factor-1 $\alpha$

(HIF-1 $\alpha$ ). MCU and HIF-1 $\alpha$  expression are suggested to be directly related; moreover, HIF-1 $\alpha$ -regulated genes are expressed in human breast cancer samples, which is sufficient to consider MCU as a novel marker of cancer progression [59].

## **ROLES OF OTHER MITOCHONDRIAL PROTEINS INVOLVED IN MITOCHONDRIAL Ca<sup>2+</sup> HOMEOSTASIS IN TUMORIGENESIS**

To date, a consensus supports the theory that the MCU complex is responsible for mitochondrial Ca<sup>2+</sup> influx. However, other proteins have been proposed to promote mitochondrial Ca<sup>2+</sup> uptake. The most relevant of these proteins is the leucine zipper-EF hand-containing transmembrane protein 1 channel (LETM1), which seems to function as an electrogenic Ca<sup>2+</sup>/H<sup>+</sup> exchanger with a dual role [60]. Indeed, at high mitochondrial [Ca<sup>2+</sup>] or at low cytosolic pH, LETM1 functions through an extrusion mechanism. In the presence of low mitochondrial [Ca<sup>2+</sup>], it regulates the entry of this cation [61]. Nevertheless, the true role of LETM1 is not well understood. In fact, many research groups have proposed that LETM1 acts as a mitochondrial K<sup>+</sup>/H<sup>+</sup> exchanger [62]. As shown in the study by the Demarex group using LETM1 and NCLX overexpression and the redox-sensitive probe roGFP, NCLX, but not LETM1, mediates Ca<sup>2+</sup> extrusion from mitochondria [63]. However, this channel seems to be involved in tumorigenesis. For instance, changes in LETM1 expression have been detected in human malignancies, including triple-negative breast cancer (TNBC) and head and neck squamous cell carcinoma [64, 65].

Under physiological conditions, mitochondrial Ca<sup>2+</sup> influx must be equal to mitochondrial Ca<sup>2+</sup> efflux. This action is principally achieved by the Na<sup>+</sup>-Ca<sup>2+</sup>-Li<sup>+</sup> exchanger (NCLX), which exchanges 3 Na<sup>+</sup> ions for 1 Ca<sup>2+</sup> ion [66]. This flux is primarily achieved because the mitochondrial Na<sup>+</sup> concentration is less than the cytosolic Na<sup>+</sup> concentration. This Na<sup>+</sup> gradient, coupled with the large negative



mitochondrial membrane potential, provides a huge driving force for  $\text{Ca}^{2+}$  extrusion. Despite its importance in  $\text{Ca}^{2+}$  extrusion, the actual link between this exchanger and tumorigenesis has not been well described. Nevertheless, the mitochondrial  $\text{Ca}^{2+}$  levels have been increased with the benzodiazepine CGP37157, a specific inhibitor of NCLX, to promote subsequent mitochondrial damage and to induce apoptosis [67]; interestingly, these effects have also been observed in a prostate cancer cell line [68].

As reported above, mitochondrial  $\text{Ca}^{2+}$  is primarily transported into the matrix by MCU. However,  $\text{Ca}^{2+}$  must pass through the OMM. The voltage-dependent anion channel (VDAC) exerts this function. VDAC is a large channel (2.5–3 nm) that represents the primary permeability pathway through which solutes enter the OMM [69]. The VDAC channel has often been referred to as a “general diffusion pore,” although this appellation is not accurate. In fact, VDAC finely regulates several cellular processes, particularly apoptosis, due to its capacity to allow the “passage” of  $\text{Ca}^{2+}$  and thus to amplify or diminish the apoptotic response. In the 2012 study by the Van Remmen group, mitochondrial superoxide release occurred through VDAC [70].

Because the absence of apoptosis is recognized as one of the hallmarks of cancer, the mPTP may play a pivotal role in cancer.

Accordingly, the role of the mPTP in cell death has been investigated in several cancer types, including colon cancer, osteosarcomas and leukemia. However, despite the great potential of this target as a cancer treatment, the use of mPTP modulators during tumorigenesis has not shown great efficacy, likely because the molecular structure of mPTP is not well understood and not all of its components have been identified. The C subunit of mitochondrial F1/FO ATP synthase was recently shown to be a fundamental regulator of mPTP activity [71-73]. Indeed, upon its pharmacological inhibition, the induction of the MPT by  $\text{Ca}^{2+}$  is inhibited. Thus, this mPTP member may be a novel target for promising new anti-cancer therapies [74].

## ONCOGENE- AND ONCOSUPPRESSOR-MEDIATED MODULATION OF MITOCHONDRIAL Ca<sup>2+</sup> HOMEOSTASIS

As reported above, only a few proteins regulate the proper influx and efflux of Ca<sup>2+</sup> from the mitochondria. In contrast, several proteins regulate Ca<sup>2+</sup> flux towards this organelle with the ultimate purpose of activating/inhibiting apoptosis. Not surprisingly, most of these proteins are oncogenes and tumor suppressors.

Historically, the proto-oncogene Bcl-2 was the first protein to be identified as an anti-apoptotic protein capable of preventing apoptosis in a Ca<sup>2+</sup>-dependent manner [28, 75]. For example, alterations of Bcl-2 function have been identified in several leukemias and carcinomas [76]. Bcl-2 is a member of the large Bcl-2-protein family, which contains numerous anti-apoptotic and pro-apoptotic members [77]. Notably, the anti-apoptotic protein Bcl-XL, which is deregulated in several cancer types, blocks the apoptosis pathway by neutralizing pro-apoptotic Bcl-2 members, such as Bak, Bax, Bid and Bim [78]. In addition, Bcl-XL exerts its anti-apoptotic functions by regulating the activity of Ca<sup>2+</sup> channels, including IP3Rs and VDAC isoforms [79].

Furthermore, the protein kinase B (PKB)/Akt protein regulates Ca<sup>2+</sup> flux inside the mitochondria. In fact, this well-known oncogene reduces Ca<sup>2+</sup> release from the ER by modulating IP3R activity, thus protecting cells from apoptotic stimuli [80]. Furthermore, the PKB/Akt signaling pathway is regulated by PTEN [81]. Notably, PTEN is a tumor suppressor whose expression is lost in a plethora of human malignancies (e.g., breast and prostate cancer). A lack of PTEN increases PKB/Akt activity, which in turn regulates the reduction of mitochondrial Ca<sup>2+</sup> accumulation due to a decrease in Ca<sup>2+</sup> release from the ER and interferes with the apoptotic machinery [82].

In addition to its transcriptional role, the tumor suppressor p53 modulates apoptosis by controlling Ca<sup>2+</sup> flux into the mitochondria. In fact, p53 was shown

to cooperate with sarco/endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase (SERCA) pumps at the ER-MAM compartment [17]. As a result, the activity of these pumps increases to increase the amount of  $\text{Ca}^{2+}$  released from the ER. Thus, mitochondria are overloaded with  $\text{Ca}^{2+}$ , and the apoptotic program is triggered. However, p53 not only cooperates with SERCA pumps at the MAM level but also acts as a bridge to maintain the correct PML localization at ER-mitochondria sites [36]. Notably, the oncosuppressor PML, which is deregulated in several human cancers [83, 84], regulates  $\text{Ca}^{2+}$ -dependent apoptosis [85]. In the absence of p53, PML is no longer localized at the juxtapositions between mitochondria and MAMs, and its pro-apoptotic functions are lost. In addition, as shown in the study by Missiroli et al. [36], PML-p53-dependent regulation of mitochondrial homeostasis is also a crucial element in the autophagic pathway, thus highlighting the possibility of creating pioneering therapeutic strategies against malignancies characterized by the absence/mutations of PML and p53. Likewise, p66Shc and the putative oncogene protein kinase C- $\beta$  (PKC- $\beta$ ) cooperate to preserve the physiological levels of apoptosis and autophagy. Indeed, upon activation by PKC- $\beta$ , p66Shc becomes localized to the mitochondrial compartment, where it influences apoptosis and autophagy by regulating the mitochondrial  $\text{Ca}^{2+}$  levels and bioenergetics [86, 87].  $\text{Ca}^{2+}$ -dependent apoptosis may also be regulated by at least two members of the Ras family. In fact, altered expression of K- and H-Ras is sufficient to reduce  $\text{Ca}^{2+}$  transfer from the ER to the mitochondria, thus blocking the apoptotic program [88]. Remarkably, this oncogene is mutated in 33% of cancers, including pancreatic, colorectal and lung cancers [89].

## MAMs: STRUCTURE AND COMPOSITION

Specific organization of the intracellular organelles enables direct communication between various compartments within the cell. Among the different direct interactions or “close contacts” between cellular organelles, MAMs have recently attracted the attention of many researchers, as represented by the growing number of publications describing the important roles of MAMs in physiology and pathology. MAMs consist of regions of the ER involved in direct interactions with the mitochondria. However, proteins from other cellular compartments have also been found in MAMs, suggesting that MAMs also form close contacts with other intracellular structures in addition to the ER. For instance, plasma membrane (PM) proteins are observed in MAMs, indicating the presence of close contacts between the mitochondria and the PM [90]. According to numerous studies, mitochondria-ER contact sites are dynamic structures. However, because we are able to isolate these structures, the interactions between these membranes are strong, and they are not destroyed during isolation procedures. Plasma membrane-associated membranes (PAMs) [91] and ER-mitochondria encounter structures (ERMES) [92] are other examples of the physical and functional contacts that are isolated during cellular subfractionation.

Most researchers believe that the first evidence showing that the mitochondria and ER are closely positioned at some regions comes from the early 1970s in the studies by Franke and Kartenbeck [93] and Morre et al. [94]. However, the first reports on the direct association between the mitochondria and ER date back to as early as the late 1950s [95]. Almost simultaneously with the aforementioned observations from the 1970s, Lewis and Tata [96] observed that a fraction of the ER was observed in low-speed centrifugation pellets containing the mitochondrial fraction during subfractionation of rat liver homogenates. Based on this observation, we acknowledge this paper as the first report to describe a

MAM isolation procedure. Almost twenty years later, in the early 1990s, the Vance group made great progress in the MAM field by presenting a detailed protocol describing the isolation of pure MAM fractions in a series of articles published in *J. Biol. Chem.* [97], which was improved upon by Meier et al. [98] ten years later. Over the years, the MAM isolation method was improved and optimized to enable the isolation of MAMs from different animal tissues and cell cultures [99]. The existence of the MAM fraction is not an exclusive characteristic of mammalian cells; close interactions between mitochondria and the ER have also been described in yeast [100]. Interestingly, similar contacts between mitochondria and the ER have been described for chloroplasts and the ER in plants [101].

In addition to the development of more refined protocols for isolating pure MAM fractions, the list of proteins present at mitochondria-ER contact sites increases every year. Although many proteins localized at the MAM have been identified, we have not determined which proteins can be used as universal MAM markers because some MAM proteins are only present in certain organs, tissues or cell types. Another problem is the observation that no protein is exclusively localized to the MAM fraction. Instead, the localization of a specific protein at the MAM is only appropriately termed as enriched because these proteins are also present in other cellular compartments. Regarding the molecular composition of the MAM fraction, an article by Poston et al. [90] presents a detailed proteomic analysis of the MAM. These authors detected and classified approximately 1200 proteins from the MAM fraction isolated from a mouse brain and confirmed that the MAM fraction contains proteins characteristic of the PM and the Golgi apparatus (24% and 6%, respectively, of the total proteins detected in MAMs) [90]. Detailed, systematic lists of proteins present in the MAM fraction grouped based on their function have been presented by several groups, including Schon and Area-Gomez [102], Poston et al. [90], Vance [103], Marchi et al. [104], Patergnani et al. [105], Raturi and Simmen [106], and Giorgi et al. [20]. Based on

the long list of proteins found in the MAM fraction or that translocate to the MAMs under certain conditions, MAMs seem to play important roles in various processes. Originally, the MAM fraction was considered important for lipid synthesis and trafficking (long-chain fatty acid coenzyme A ligase-1 (FACL-1) and -4, phosphatidylserine synthase-1 (PSS-1) and -2, serine active site containing 1 (SERAC1), fatty acid transport protein 4 (FATP4), acyl-CoA desaturase, phosphatidylethanolamine N-methyltransferase 2 (PEMT2) and many other proteins present in MAM involved in this process are reviewed in [102]) and  $\text{Ca}^{2+}$  handling (e.g., IP3R, ryanodine receptor, sigma-1 receptor (SIG1R), and promyelocytic leukemia protein (PML)). MAMs were later linked to the modulation of mitochondrial morphology (mitochondria-shaping proteins and chaperone proteins (MFN-1 and -2)), apoptosis (Bcl-2, hematopoietic cell-specific Lyn substrate1 (HCLS1)-binding protein 3 (HS1BP3)), mitochondrial contact site formation (VDAC and adenine nucleotide translocase (ANT)), protein folding (calnexin (CNX)) and sorting (phosphofurin acidic cluster sorting protein 2 (PACS-2)), ER stress (glucose-regulated protein 75-kDa (GRP75) and endoplasmic reticulum resident protein 44 (ERp44)), inflammation (inflammasome components: NALP3, adaptor ASC and thioredoxin interacting protein (TXNIP)), autophagy (pre-autophagosome/autophagosome markers (ATG14 and ATG5), and p66Shc) and the cellular response to oxidative stress (p66Shc protein, an Ero1 $\alpha$ ). The presence of these important proteins involved in crucial cellular processes explains why alterations in MAM composition are related to the pathogenesis of different disorders [106], including type-2 diabetes (mTOR complex 2 (mTORC2) and MAM-associated Akt), and several neuronal-based diseases, such as Parkinson's disease and Huntington's disease, and neurodegenerative diseases, such as schizophrenia, dementia and seizures. Moreover, MAMs have been proposed to be involved in familial Alzheimer's disease (FAD) [107, 108] and GM1-gangliosidosis [109].

## MAM PROTEINS MODULATE $\text{Ca}^{2+}$ HOMEOSTASIS, CELL DEATH AND TUMORIGENESIS

The ER and mitochondrial networks control different aspects of cellular metabolism, and, through their both dynamic and close interactions, are also involved in the transmission of physiological and pathological  $\text{Ca}^{2+}$  and ROS signals directly from the ER to the mitochondria.

Thus, their contact sites are considered specialized microdomains for the transfer of  $\text{Ca}^{2+}$  signals.  $\text{Ca}^{2+}$  ions released from the ER by IP3Rs cross the OMM [2], which is freely permeable through VDACS, move to the IMM and accumulate in the matrix via the MCU complex in a process mediated by local  $\text{Ca}^{2+}$  sites of accumulation, which overcome the apparent low  $\text{Ca}^{2+}$  affinity of the MCU [110]. Nevertheless, if excessive  $\text{Ca}^{2+}$  influx occurs, pro-apoptotic factors, such SMAC/DIABLO, cytochrome C, and AIF may be released into the cytosol, resulting in apoptosis triggered by the opening of the mPTP [111, 112].

MAMs represent platforms for the anchoring of many pro- and anti-apoptotic factors involved in tumor regulation.

This role was previously defined for the serine/threonine kinase Akt [113], which is physically and functionally linked to both the ER and mitochondria. Akt phosphorylates numerous proteins, including members of the Bcl-2 family (i.e., Bad and Bax), to activate its anti-apoptotic function, and hexokinase 2 (HK2), which phosphorylates VDAC1 to prevent  $\text{Ca}^{2+}$ -dependent opening of the mPTP and the release of pro-apoptotic proteins [114].

Bcl-2 is an oncoprotein that has a central role in the regulation of apoptosis because of its capacity to delay or block the programmed death pathway in different cell types. Bcl-2 overexpression reduces the steady state  $\text{Ca}^{2+}$  levels within the ER, resulting in reduced mitochondrial fragmentation and the initiation of apoptosis [28]. Bax and Bak are members of the Bcl-2 family that

control apoptosis from the ER and mitochondria in response to  $\text{Ca}^{2+}$  stimulation [115].

As shown in a recent study by our group, myeloid cell leukemia protein 1-long isoform (Mcl-1L) is highly expressed in human malignancies and is localized to the mitochondrial membrane. This localization is consistent with its role in the control of key mitochondrial events during apoptosis to counteract the activity of the pro-apoptotic proteins Bak and Bax [116].

The tumor suppressor PTEN, one of the most commonly lost or mutated tumor suppressor genes in human cancers, also localizes to MAMs. PTEN is a dual-specific phosphatase for lipids and proteins that exhibits enhanced ER localization during  $\text{Ca}^{2+}$ -dependent apoptosis. In this case, PTEN interacts with IP3R3 to counteract Akt-mediated phosphorylation of the receptors and induce a subsequent increase in  $\text{Ca}^{2+}$  transfer from the ER to the mitochondria to trigger apoptosis in a protein phosphatase-dependent manner [82].

IP3R3 is the favorite target of another important tumor suppressor, PML, which is localized to the nucleus and cytosol and is associated with the ER and MAMs [85]. Indeed, PML forms a multiprotein complex with IP3R3, Akt and the protein phosphatase PP2a to modulate the apoptotic pathway triggered by  $\text{Ca}^{2+}$  accumulation in the matrix. The suppression of this protein blocks PP2a localization at MAMs, which in turn does not prevent Akt-mediated IP3R3 phosphorylation. Therefore, IP3R3 hyperphosphorylation inhibits  $\text{Ca}^{2+}$  transfer from the ER to the mitochondria, thereby inhibiting apoptosis [117].

Based on recent studies, fetal and adult testis expressed 1 (FATE1), a cancer-testis antigen that has a role in regulating the ER-mitochondria distance and  $\text{Ca}^{2+}$  uptake by the mitochondria, [118] inhibits pro-apoptotic signaling in many cancer cell lines by destabilizing BIK, a pro-apoptotic protein [119].

The interactions between the mitochondria and the ER are modulated by different proteins, including the mitochondria-shaping proteins MFN-1/-2 (mitofusin-1/-2). In particular, the absence of MFN-2 changes the morphology of



the ER and decreases the interactions between the mitochondria and ER by 40%, causing altered transfer of  $\text{Ca}^{2+}$  signals to the mitochondria [120].

Moreover, the mitochondria and the ER are the major sites of ROS production, and many regulators of the oxidative state of the cell are localized at the MAM [121]. p66Shc plays a key role in this process, as it is a cytosolic protein involved in the cellular response to oxidative stress and tumorigenicity that has recently been identified at mitochondria-ER association sites. The increase in p66Shc induced by elevated intracellular ROS levels is, in turn, triggered by steroid-induced signaling, which promotes cell proliferation in prostate cancer cells [122]. Instead, the oxidative cellular environment promotes the phosphorylation of p66Shc at Ser36 that migrates to the mitochondrial matrix after being recognized by the prolyl-isomerase Pin1 and dephosphorylated by phosphatase 2A. Here, the protein perturbs mitochondrial function that ultimately leads to apoptosis [86]. Based on other data from the Lebedzinska group, a significant portion of p66Shc is also present in MAM fractions and its levels increase in an age-dependent manner [123].

Moreover, according to the recent findings by Anelli et al. [124], Ero1 $\alpha$ , a quality controller of oxidative protein folding in the ER, is enriched in MAMs and regulates  $\text{Ca}^{2+}$  flux. The levels of redox-active Ero1 $\alpha$  impact  $\text{Ca}^{2+}$  storage and IP3R-dependent flux. Its silencing inhibits  $\text{Ca}^{2+}$  re-uptake by the mitochondria, likely by modifying MCU activity. The overexpression of redox-active Ero1 $\alpha$  increases passive  $\text{Ca}^{2+}$  efflux from the ER, thus reducing the  $[\text{Ca}^{2+}]_{\text{ER}}$  and mitochondrial  $\text{Ca}^{2+}$  fluxes in response to IP3 agonists.

All these proteins cooperate to define a complex picture where mitochondrial  $\text{Ca}^{2+}$  signals are crucial initiators of apoptosis.

## CONCLUSIONS

Ca<sup>2+</sup> plays a pivotal role in many biological systems and is of great interest for its potential implications in human malignancies. The interaction between the mitochondria and the ER Ca<sup>2+</sup> store plays an essential role in allowing these organelles to effectively and rapidly respond to cellular Ca<sup>2+</sup> signals. ER-mitochondria contact sites, also known as MAMs, are involved in Ca<sup>2+</sup> homeostasis and participate in cholesterol and phospholipid metabolism and other mitochondrial functions and dynamics. Since the role of MAMs has been revealed, their relevance in disease has become apparent. Altered mitochondrial-ER contacts can deregulate Ca<sup>2+</sup> signaling, which results in alterations in metabolism and cell death. The study of Ca<sup>2+</sup> homeostasis and these functional domains has become critical, particularly in relation to cell death and cancer onset and regulation. All these findings highlight the fundamental activity of MAMs, which act as hotspot domains in cancer onset and progression, although their roles in regulating cell death are only partially understood. Therefore, we must expand our knowledge about the composition, function, and regulation of MAMs and how protein networks cooperate to control communication within this organelle to search for new cancer treatments..

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ACCEPTED MANUSCRIPT

**Conflict of Interest Statement**

To whom it may concern

With the present letter I officially declare that do not exist any conflict of interests.

Sincerely yours,  
Paolo Pinton

ACCEPTED MANUSCRIPT

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 Lanzi, P. Lapaquette, L.R. Lapierre, J. Laporte, J. Laukkarinen, G.W. Laurie, S.  
 Lavandero, L. Lavie, M.J. LaVoie, B.Y. Law, H.K. Law, K.B. Law, R. Layfield, P.A.  
 Lazo, L. Le Cam, K.G. Le Roch, H. Le Stunff, V. Leardkamolkarn, M. Lecuit, B.H.  
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 Q.Y. Lei, D.A. Leib, G. Leibowitz, I. Lekli, S.D. Lemaire, J.J. Lemasters, M.K.  
 Lemberg, A. Lemoine, S. Leng, G. Lenz, P. Lenzi, L.O. Lerman, D. Lettieri Barbato,  
 J.I. Leu, H.Y. Leung, B. Levine, P.A. Lewis, F. Lezoualc'h, C. Li, F. Li, F.J. Li, J. Li, K. Li,  
 L. Li, M. Li, M. Li, Q. Li, R. Li, S. Li, W. Li, W. Li, X. Li, Y. Li, J. Lian, C. Liang, Q. Liang,  
 Y. Liao, J. Liberal, P.P. Liberski, P. Lie, A.P. Lieberman, H.J. Lim, K.L. Lim, K. Lim,  
 R.T. Lima, C.S. Lin, C.F. Lin, F. Lin, F. Lin, F.C. Lin, K. Lin, K.H. Lin, P.H. Lin, T. Lin,  
 W.W. Lin, Y.S. Lin, Y. Lin, R. Linden, D. Lindholm, L.M. Lindqvist, P. Lingor, A.  
 Linkermann, L.A. Liotta, M.M. Lipinski, V.A. Lira, M.P. Lisanti, P.B. Liton, B. Liu, C.  
 Liu, C.F. Liu, F. Liu, H.J. Liu, J. Liu, J.J. Liu, J.L. Liu, K. Liu, L. Liu, L. Liu, Q. Liu, R.Y.  
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 Z. Liu, Z. Liu, J.P. Liuzzi, G. Lizard, M. Ljubic, I.J. Lodhi, S.E. Logue, B.L. Lokeshwar,  
 Y.C. Long, S. Lonial, B. Loos, C. Lopez-Otin, C. Lopez-Vicario, M. Lorente, P.L.  
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## Figures

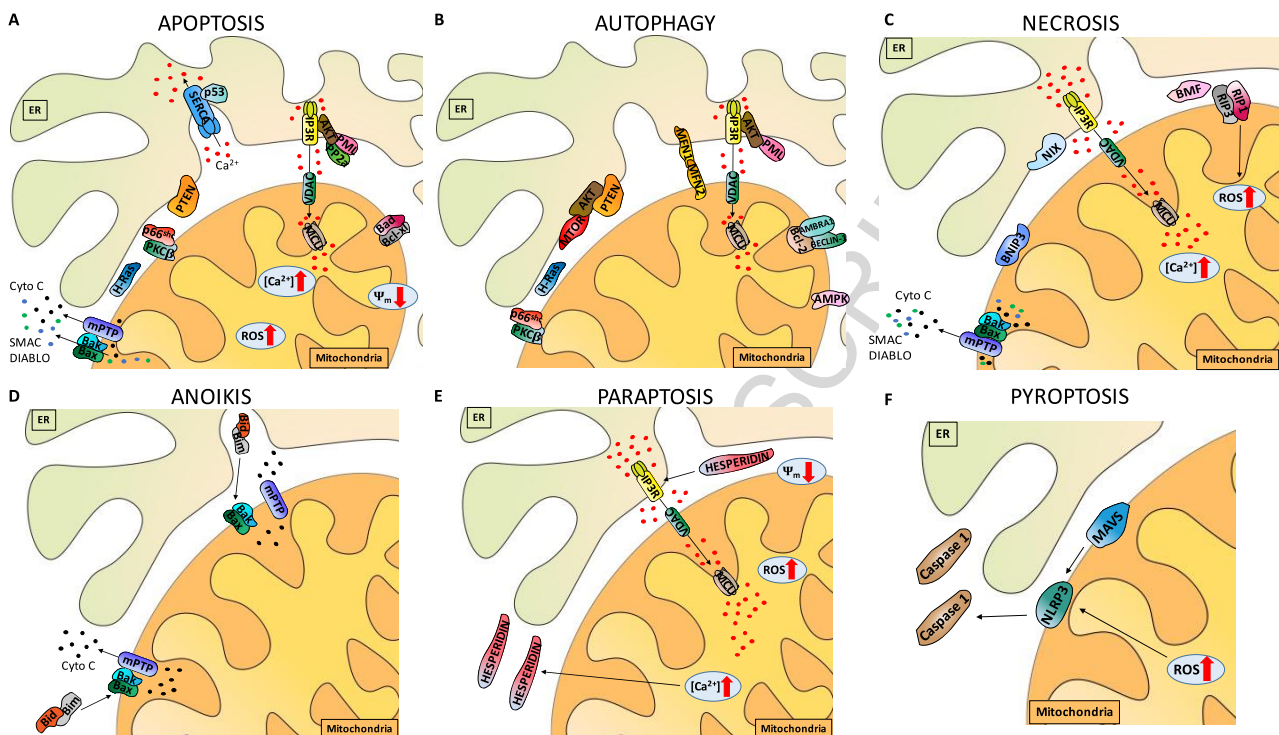


Figure 1. **Summary of the mitochondrial, ER and MAM proteins involved in primary cell death mechanisms.** Representation of proteins at the mitochondria-ER interface that play active roles in cell death. Proteins that prevent or promote cell death affect intracellular  $\text{Ca}^{2+}$  dynamics and homeostasis by binding  $\text{Ca}^{2+}$  and modulating intracellular  $\text{Ca}^{2+}$  uptake and release mechanisms.  $\text{Ca}^{2+}$  overload-induced mitochondrial damage and ROS production display a cause-effect relationship, resulting in a decreased mitochondrial membrane potential ( $\Psi_m$ ). Calcium channels play essential roles in  $\text{Ca}^{2+}$  homeostasis, and modifications in their activities are potentially fatal to the cell.

SERCA is a  $\text{Ca}^{2+}$  ATPase that transfers  $\text{Ca}^{2+}$  from the cytosol to the ER lumen at the expense of ATP hydrolysis. IP3R consists of 4 subunits of approximately 310 kDa each and is essential for efficient  $\text{Ca}^{2+}$  transfer between the ER and mitochondria. VDAC is the major permeability pathway in the OMM;  $\text{Ca}^{2+}$  flux across the outer membrane occurs mainly through VDAC. The MCU allows the passage of calcium ions into the mitochondrial matrix.

**A)** MAM proteins involved in apoptosis. The Bcl-2-protein family includes numerous anti-apoptotic (i.e., Bcl-XL) and pro-apoptotic (i.e., Bak, Bax, and Bad) members. H-Ras reduces  $\text{Ca}^{2+}$  transfer from the ER to mitochondria and blocks the apoptotic program. The oncosuppressor PML regulates  $\text{Ca}^{2+}$ -dependent apoptosis. PTEN interacts with IP3R to prevent Akt from phosphorylating the receptors. p53 modulates apoptosis by controlling  $\text{Ca}^{2+}$

flux into the mitochondria. np66Shc and the putative oncogene PKC- $\beta$  cooperate to preserve the physiological levels of apoptosis and **B)** autophagy.

Autophagy is a self-degradative process that recruits a double membrane-bound vesicle, termed the autophagosome, which then fuses with a lysosome to form an autolysosome.

BECLIN1 and AMBRA1 are involved in the initial steps of autophagosome formation. AMPK is an energy sensor that is activated during nutrient deprivation to inhibit the activity of mTOR, a negative regulator of autophagy. The mitochondria-shaping proteins MFN-1/-2 modulate interactions between the mitochondria and ER; their ubiquitination precedes the removal of damaged mitochondria and thus is an early event in autophagy. Concerning necrosis **C)**, recent evidence has implicated Bax, Bmf, BNIP3, and Nix as part of the necrotic program. The kinases RIP1 and RIP3 are key signaling molecules in necrosis and are regulated by caspases and ubiquitination.

Anoikis **D)** involves Bid and Bim, which are activated by the detachment of cells from the ECM and rapidly promote the assembly of Bax-Bak oligomers within the OMM. Hesperidin **E)** induces paraptosis-like cell death by activating ERK1/2. Pyroptosis **F)** is induced by NLRP3-dependent caspase-1 activation; MAVS is required for optimal NLRP3 inflammasome activity.

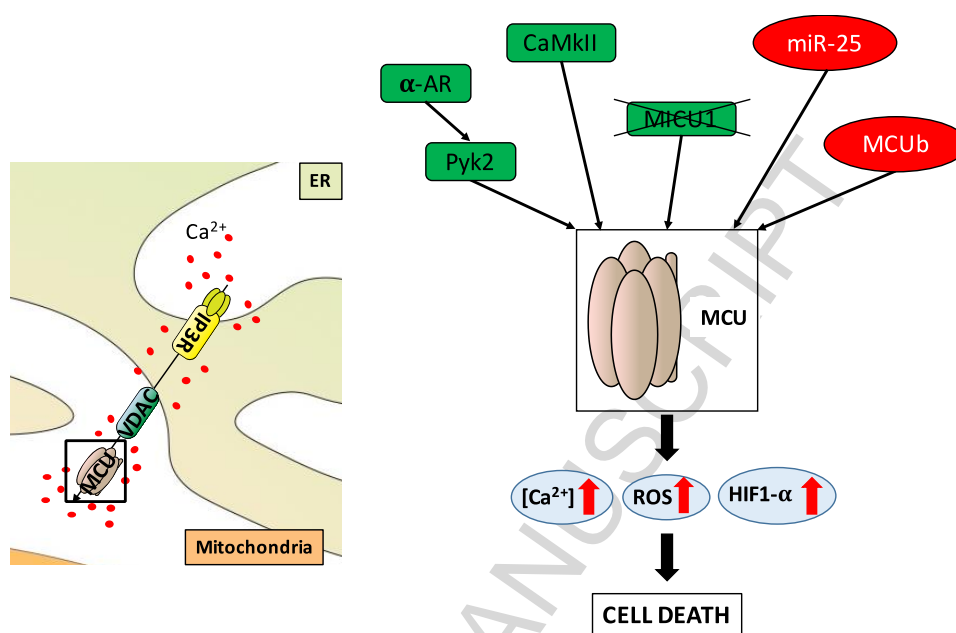


Figure 2. **Proteins that modulate the activity of the MCU complex and cell death.** The MCU located in the IMM is responsible for  $\text{Ca}^{2+}$  uptake. Modulation of MCU complex subunits and function could increase the probability that cells will undergo apoptotic cell death under stress conditions because of the increased basal ROS levels present during mitochondrial  $\text{Ca}^{2+}$  uptake.

Proteins that promote  $\text{Ca}^{2+}$  entry into the mitochondria are shown in green, and proteins that decrease mitochondrial  $\text{Ca}^{2+}$  uptake and ROS generation are shown in red.

The pathway that activates the MCU complex is inhibited by CaMKII-dependent phosphorylation of the uniporter, and Pyk2 prevents  $\text{Ca}^{2+}$  overload in the mitochondria, ROS production and subsequent cell death, which are important in tumor progression. MICU1 knockout cells have increased basal ROS levels during mitochondrial  $\text{Ca}^{2+}$  uptake, leading to apoptotic cell death under stress conditions. In contrast, miR-25 (which decreases MCU expression) and MCUb (which acts as an endogenous dominant-negative isoform of MCU) reduce mitochondrial  $\text{Ca}^{2+}$  uptake and, consequently, drive resistance to  $\text{Ca}^{2+}$ -dependent apoptotic death.

<b>Protein</b>	<b>Gene Expression in Cancer</b>	<b>Relation to Ca<sup>2+</sup></b>	<b>References</b>
<b>Akt</b>	Pancreas (A, D), Breast (M), Prostate (A)	Inhibition of Ca <sup>2+</sup> release from the ER	[80, 125]
<b>AMBRA1</b>	Breast (A), Prostate (A, M)	Involved in regulating TPC-dependent calcium release	[5]
<b>AMPK</b>	Skin (M), Prostate (A), Pancreas (A, D)	Chronic calcium exposure decreases AMPK activity	[35]
<b>Bad</b>	Prostate (A), Pancreas (A, D), Uterus (A, D)	Sensitizes the mitochondria to Ca <sup>2+</sup> , making them more susceptible to Ca <sup>2+</sup> release from the ER	[126]
<b>Bak</b>	Breast (A), Prostate (A), Skin (A, M)	Regulate calcium leakage from the endoplasmic reticulum	[127]
<b>Bax</b>	Prostate (A), Pancreas (A, D), Breast (A), Stomach (M)	Regulate calcium leakage from the endoplasmic reticulum	[127]
<b>Bcl-XL</b>	Uterus (A, M), Breast (A), Prostate (A), Colon (A), Nervous System (D, M)	Acts on Bax inhibitor-1 (BI-1) to increase Ca <sup>2+</sup> leakage from the ER, with BI-1 acting as a Ca <sup>2+</sup> channel or as an IP3R sensitizer	[75, 128]
<b>Bcl-2</b>	B-cell (M), Central Nervous System (A, M), Pancreas (D), Breast (A)	Induction of Ca <sup>2+</sup> release from the ER	[75]
<b>Bid</b>	Prostate (A), Nervous System (A)	Regulates calcium concentrations and homeostasis in the ER	[75]
<b>Bim</b>	Prostate (A, M, D), Breast (A, M), Uterus (M, A)	Bim-deficient cells exhibit severe defects in calcium release	[8, 76, 129]
<b>BECLIN1</b>	Prostate (A), Breast (A)	Activated by increased [Ca <sup>2+</sup> ] <sub>i</sub> and may induce autophagy	[5]
<b>BMF</b>	Uterus (B, M, A), Prostate (A)	Supports Bim in some cell death processes	[8]
<b>BNIP3</b>	Prostate (A, D), Pancreas (A, D)	Induces atypical cell death with features of both apoptosis and necrosis	[7]
<b>MAVS</b>	Breast (A), Prostate (A), Ovary (A, D), Stomach (M, A)	Lead to defects in mitochondrial calcium	[12]
<b>MFN-1</b>	Lung (A, M), Ovary (A), Esophagus (A, M), Breast (A), Head (A, M)	Important as a mediator of mitochondrial fusion	[130, 131]
<b>MFN-2</b>	Pancreas (A, D), Esophagus (M, A, D), Prostate (M, A, D)	Facilitates calcium cross-talk between the ER and mitochondria	[130, 131]
<b>mTOR</b>	Skin (M), Uterus (M, A), Prostate (M, A, D)	Intracellular Ca <sup>2+</sup> signaling is a crucial component in the canonical mTOR-dependent autophagy pathway	[33, 35]

<b>NIX</b>	Prostate (D), Ovary (D, A)	Increase ER/SR calcium stores in cardiac myocytes	[9]
<b>NLRP3</b>	Breast (A), Prostate (A), Skin (M), Lung (M, A)	Localization of PML at ER/MAM contact sites is required for its pro-apoptotic activity via a calcium (Ca <sup>2+</sup> )-mediated pathway	[12]
<b>PKC-β</b>	Breast (A), Prostate (A), Lung (M), Skin (M)	Binds Ca <sup>2+</sup> through its C2 domain	[132]
<b>PML</b>	Prostate (M), Colon (M), Breast (A), Lung (M, A), Uterus (A, M)	Regulates apoptosis in the ER by modulating calcium release, negative regulator of Akt	[36, 84, 85]
<b>PP2a</b>	Prostate (A), Central Nervous System (M), Pancreas (A, D)	Regulates calcium transients in cardiomyocytes	[107, 133]
<b>PTEN</b>	Uterus (M), Prostate (M, D), Head (M, D), Stomach (M), Breast (A, M), Pancreas (M)	Regulates Ca <sup>2+</sup> release via IP3R3	[81, 82]
<b>p53</b>	Almost all	Interacts with the C-terminal portion of the SERCA pump, increasing ER Ca <sup>2+</sup> loading	[17, 19, 35]
<b>p66</b>	Prostate (A), Breast (A), Esophagus (A, M, D)	Involved in the cellular response to oxidative stress	[86, 122]
<b>HRAS</b>	Pancreas (A, D), Breast (A), Urinary Tract (M), Head (M)	Regulation of Ca <sup>2+</sup> signaling	[88]
<b>RIP1</b>	Skin (A), Prostate (A), Breast (A)	Phosphorylated by increased cytoplasmic calcium concentrations	[134]
<b>RIP3</b>	Skin (M), Prostate (A)	Mediates oxidative stress through CaMKII	[10]

**Table 1: MAM proteins involved in tumorigenesis and tumor progression.** A = amplification; M = mutation; D = deletion.

## Highlights

Mitochondria-associated membranes (MAMs) as critical hubs in signal transduction

MAMs act as hotspot domains in cancer onset and progression

Perturbation of  $\text{Ca}^{2+}$  homeostasis at the MAMs in cancer cells is correlated with sustained cell proliferation and the inhibition of cell death

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