

P2X receptors in immune cells: key regulators of inflammation and immune function

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ABSTRACT

P2X receptors are a family of ATP-gated ion channels comprising seven subtypes (P2X1–P2X7). These receptors mediate rapid cation fluxes and downstream signaling events that regulate inflammation, synaptic transmission, and cell death. P2X receptors are widely expressed in immune cells of both myeloid and lymphoid lineages, including macrophages, microglia, dendritic cells, neutrophils, eosinophils, natural killer cells, myeloid-derived suppressor cells, T, B, and innate lymphocytes. Through these diverse populations, P2X receptors influence cytokine secretion, chemotaxis, phagocytosis, antigen presentation, and the balance between immune activation and suppression. Beyond initiating inflammatory responses to infectious or sterile insults, P2X signaling contributes to immune tolerance and homeostasis. This review summarizes current and emerging insights into the immunomodulatory roles of P2X receptors across innate and adaptive compartments, highlighting mechanistic pathways and translational relevance. Collectively, P2X receptors act as central integrators of metabolic and inflammatory cues, representing promising therapeutic targets for inflammatory, autoimmune, and neuro-immune diseases, as well as cancer.

1. Introduction

Extracellular ATP (eATP) and its degradation products, including ADP, AMP, and adenosine, exert multiple regulatory functions within the immune system through the coordinated activity of purinergic receptors and ectonucleotidases. eATP acts as a damage-associated molecular signal, modulating both innate and adaptive immune responses via purinergic signaling pathways. These mechanisms have been extensively reviewed in recent literature, to which the reader is referred for a comprehensive overview (Antonioli et al., 2019; Giuliani et al., 2020; Rueschpler and Schloer, 2025). Here, we give an overview of recent advances concerning the role of P2X receptors, a family of ligand-gated ion channels activated by eATP, which are key mediators of inflammatory signaling and immune cell function. They play critical roles in various physiopathological processes, including synaptic transmission, inflammation, pain perception, and immune responses (North, 2016). Structurally, P2X receptors are trimeric, with each subunit spanning the membrane twice and forming a central ion-conducting pore (Sheng and Hattori, 2022). Upon ATP binding, the receptor

undergoes a conformational change that enables the influx of cations, such as sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+) efflux, leading to depolarization of the cell membrane and subsequent downstream signaling (Surprenant and North, 2009). There are seven known subtypes of P2X receptors (P2X1–P2X7), each with distinct tissue distributions and functional properties. Notably, P2X7 has been extensively studied for its role in immune cell activation and cell death, making it a target of interest in inflammatory and neurodegenerative diseases (Di Virgilio et al., 2017; Adinolfi et al., 2018). P2X receptors are expressed in a wide variety of cell types across multiple tissues, reflecting their diverse physiological roles. In the nervous system, they are found on neurons and glial cells, where they contribute to neurotransmission, pain signaling, and neuroinflammation (Burnstock and Kennedy, 2011). Microglia, the resident immune cells of the central nervous system, prominently express P2X4 and P2X7 receptors, which are involved in cytokine release and inflammatory responses (Calovi et al., 2019). Additionally, epithelial and endothelial cells express P2X receptors, where they help regulate vascular tone, barrier function, and responses to mechanical stress (Ralevic, 2015; Jorgensen, 2019; Platania et al.,

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2025). P2X receptors are implicated in numerous pathophysiological processes across various organs and systems, with their function in immune cells playing a central role in most of these processes (Fig. 1). Here, we will provide an overview of the role of P2X receptors in different cells of both the innate and adaptive immune systems, aiming to summarize the original literature on the topic alongside more recent studies.

2. P2X receptors in cells of the innate immune system

2.1. Monocytes and macrophages

Monocyte/macrophage-derived cell lineages, including dendritic cells and osteoclasts, likely exhibit the greatest diversity of P2X receptor expression and represent the most extensively studied immune cell populations in terms of P2X receptor functional characterization. Since P2X receptors function and variants often differ between species, we will separately cover the data obtained in human and murine experimental models (Schafer et al., 2022; Sluyter et al., 2023; Pegoraro et al., 2024). Moreover, we will dedicate a paragraph to the role of macrophage P2X in the response to infectious agents.

2.2. P2X receptors in human monocytes and macrophages

Human macrophages exhibit a heterogeneous expression of P2X receptors, including P2X1, P2X4, P2X5, and P2X7 (Gu et al., 2000; Stokes and Surprenant, 2009; Hazleton et al., 2012; Janks et al., 2019). THP-1 monocytes express all P2X receptors at the mRNA level, except for P2X2,

whereas THP-1-derived macrophages lack both P2X2 and P2X3, and exhibit diminished ATP-evoked P2X1-mediated calcium response (Layhadi and Fountain, 2017). Functional studies using patch-clamp recordings confirm distinct receptor kinetics: P2X1 generates rapidly desensitizing currents inhibited by pyridoxalphosphate-6-azophenyl-2', 4'-disulfonic acid (PPADS); P2X4 produces slowly desensitizing currents potentiated by ivermectin; and P2X7 mediates slow, non-desensitizing currents sensitive to selective antagonists (Vargas-Martinez et al., 2020).

Macrophage differentiation and polarization further modulate P2X receptor expression. Peripheral monocyte-to-macrophage differentiation reduces P2X1 and its splice variant, P2X1del. Similarly, P2X7 predominates in primary cells and M1 macrophages (Pelegrin and Surprenant, 2009), while P2X4 is mainly expressed in THP-1-differentiated cells (Layhadi and Fountain, 2017; Vargas-Martinez et al., 2020; Ruiz-Rodriguez et al., 2023). From a functional perspective, P2X7 has been known for decades to play a central role in macrophage biology. Di Virgilio and collaborators demonstrated that exposure of macrophages to eATP caused cell blebbing and interleukin-1 β (IL-1 β) secretion at the end of the last century (Chiozzi et al., 1996; Ferrari et al., 1997). Since then, many papers have appeared in the literature showing that P2X7 is important for priming, production, maturation, and secretion of IL-1 β family members, mainly through NLRP3 inflammasome activation. These studies have been extensively covered by us and others in other reviews, to which we refer readers for a more complete overview of the subject (Di Virgilio et al., 2017; Orioli et al., 2017; Pelegrin, 2021). More recently, various studies have also implicated P2X4 in macrophage-mediated inflammatory processes (Trang and Salter, 2012; Peikert et al., 2022; Schneider et al., 2022;

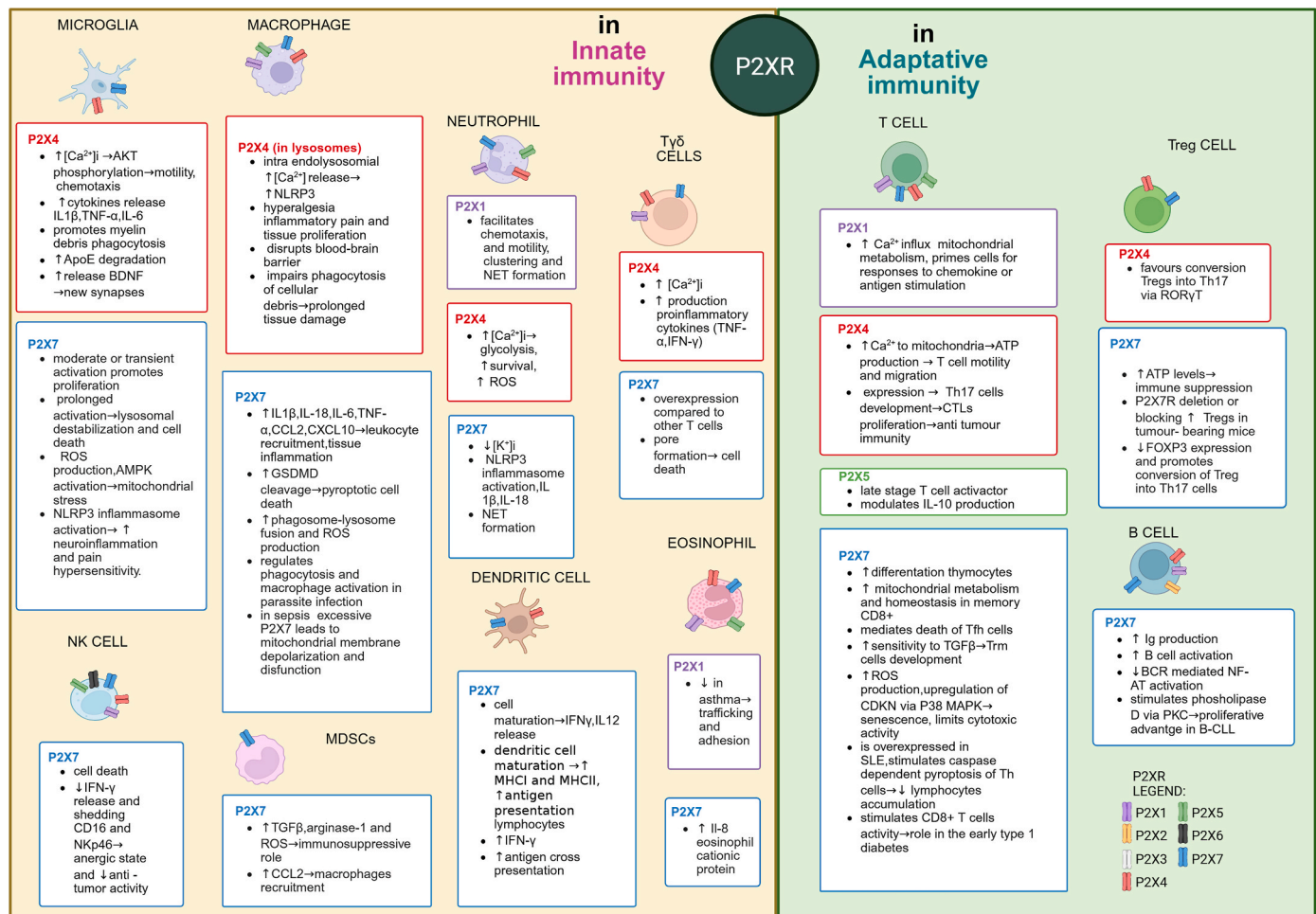


Fig. 1. P2X receptors role in cells of the innate and adaptive immune system.

Gamiotea-Turro et al., 2024). Pharmacological inhibition of P2X4 with 5-(3-Bromophenyl)-1,3-dihydro-2H-benzofuro[2-e]-1,4-diazepin-2-one (5-BDBD) in human macrophages reduces IL-1 β , tumor necrosis factor- α (TNF α), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6) production. Furthermore, P2X4-deficient cells display reduced P2X7 expression, suggesting that P2X4 may modulate P2X7 in macrophages (Schneider et al., 2022).

2.3. P2X receptors in monocytes and macrophages from murine pathological models

Similar to what demonstrated in humans, several studies in murine models show that monocyte/macrophage P2X4 and P2X7 play a central role in cytokine and chemokine production and release, as well as in phagocytosis. For example, Merz and colleagues showed that lipopolysaccharide (LPS) stimulation increases P2X4 and P2X7 expression in monocytes, indicating an inflammatory response without differentiation towards macrophages (Merz et al., 2021). Bone marrow-derived macrophages from P2X4-null mice show reduced ATP-mediated release of chemokines and acute inflammation's cytokines, leading to decreased phlogosis and a higher proportion of anti-inflammatory monocytes (Peikert et al., 2022). Accordingly, macrophage P2X4 contributes to the transition from acute to persistent inflammatory muscle hyperalgesia (Oliveira-Fusaro et al., 2020) by driving p38 MAPK phosphorylation, PPAR γ activation, M1 polarization, and gene expression of inflammatory mediators (Schneider et al., 2022; de Azambuja et al., 2025). In accordance with these data, IL-4 treatment suppresses P2X4 expression (Gordon and Martinez, 2010; de Azambuja et al., 2025). Similarly, in experimental endometriosis models, P2X4 signaling promotes macrophage infiltration and the expression of IL-33, cyclooxygenase 2 (COX-2), and prostaglandin E2 (PGE2), thereby driving tissue proliferation (Ulmann et al., 2010; de Rivero Vaccari et al., 2012; Xie et al., 2014; Nagata et al., 2025). In line with these data, receptor blockade reduces macrophage infiltration and pain sensitivity, suggesting P2X4 as a potential new therapeutic target for this highly prevalent pathology, which still lacks therapeutic options (Nagata et al., 2025). P2X4 also has a key role in macrophage phagocytosis. Following ischemic stroke, ATP-mediated P2X4 activation enhances pro-inflammatory cytokine production, disrupts the blood brain barrier, and impairs cellular debris clearance, prolonging tissue damage. Accordingly, P2X4 inhibition or deficiency reduces inflammation, enhances phagocytosis, and increases CD36 expression in brain macrophages (Gamiotea-Turro et al., 2024). Even if P2X4 plays an important role in these cells, P2X7 remains the main purinergic receptor associated with macrophage biology, where, beyond inflammasome activation, it also orchestrates other signalling pathways. These include metabolic reprogramming and transcriptional responses, driven by calcium-dependent activation of nuclear factors and kinases (Brautigam et al., 2005; Li et al., 2018), thereby enhancing leukocyte recruitment and peripheral sites (Shieh et al., 2014; Almeida-da-Silva et al., 2019). Furthermore, P2X7 promotes phagosome-lysosome fusion, reactive oxygen/nitrogen species (ROS/RNS) production (Lenertz et al., 2009; Zhu et al., 2014), and upregulation of MHC-II and co-stimulatory molecules (CD80, CD86), thus linking innate sensing with antigen presentation and T-cell activation (Lioi et al., 2015; Furuta et al., 2023; Acuna-Castillo et al., 2024). Macrophage P2X7 also contributes to autoimmune pathologies. For example, in experimental autoimmune uveitis, macrophage-specific P2X7 expression drives retinal inflammation via Th17 cells induction, while deletion reduces disease severity and inflammasome-related gene expression (Dechelle-Marquet et al., 2025).

2.4. Macrophage P2X7 in response to infection

Since the discovery of P2X7 expression in macrophages, the receptor has been attributed a central role in responses to infection, which vary depending on pathogen and inflammatory context. For example, during

Mycobacterium tuberculosis infection, P2X7 enhances antimicrobial functions by promoting inflammasome activation, IL-1 β release, and bacterial killing. However, its prolonged or excessive stimulation can cause necrosis, pyroptosis, and tissue damage (Santiago-Carvalho et al., 2021; Lecuyer et al., 2023). In *Leishmania amazonensis* infection, P2X7 promotes macrophage activation through nitric oxide (NO) release, IL-1 β secretion, and parasite clearance (Chaves et al., 2009). During schistosomiasis, which causes immune suppression, P2X7 activity is impaired due to elevated ATP hydrolysis and increased A2B receptor expression, leading to reduced phagocytosis (Thorstenberg et al., 2024). Similarly, in response to *Trypanosoma cruzi*, P2X7 induces the release of the TLR4 cofactor CD14 inside extracellular vesicles, sustaining LPS signalling, and regulating monocyte function (Fracasso et al., 2021). Finally, P2X7 regulates mitochondrial integrity and immune function in sepsis, where excessive P2X7 activation in monocytes leads to mitochondrial membrane depolarization and dysfunction, which, in turn, impairs NLRP3 inflammasome activation and contributes to immune suppression mediated by HIF-1 α upregulation and increased mortality (Martinez-Garcia et al., 2019). Immune responses to viral infections are also associated to P2X7, for example, in COVID-19, elevated P2X7 and NLRP3 expression in alveolar macrophages correlates with hyperinflammation, lung injury, and poor clinical outcomes (Lecuyer et al., 2023). Consistent with these data, soluble P2X7 plasma levels in COVID-19 patients are associated with increased C-reactive protein (CRP), IL-6, disease severity, and mortality (Garcia-Villalba et al., 2022; Vultaggio-Poma et al., 2023). Accordingly, a gain-of-function single-nucleotide polymorphism of P2X7 (rs208294) is associated with severe SARS-CoV-2 infection, highlighting its potential as a genetic biomarker and therapeutic target (Lindo et al., 2024).

2.5. Microglial P2X receptors

Microglia are the primary immune cells of the central nervous system and act as a first line of defense against infection and injury. They are often compared to resident macrophages in peripheral tissues (Calovi et al., 2019; Trinh et al., 2022). Given this role, it is not surprising that P2X4 and P2X7 receptors are key regulators of microglial function. Maneu and Garcia provide a detailed overview of P2X receptors in neuroinflammation in this issue; we refer the reader to their article for further information (Maneu and Garcia, 2026). Here, we focus on the main signaling pathways and functions mediated by P2X4 and P2X7 in microglia.

P2X4 supports several core microglial activities, including cell movement, chemotaxis, phagocytosis, and cytokine release (Ohsawa et al., 2007; Horvath and DeLeo, 2009; Ohsawa and Kohsaka, 2011; Gofman et al., 2014; Franco-Bocanegra et al., 2019; Illes et al., 2020). Its role in cell survival remains unclear, as some studies suggest it is important for microglial viability, whereas others report little effect in its absence (Vazquez-Villoldo et al., 2014; Paola et al., 2024). Under stress conditions such as hypoxia or neuropathic pain, P2X4 contributes to the release of pro-inflammatory cytokines (Li et al., 2011; Zhang et al., 2025). At the intracellular level, P2X4 activates signaling pathways such as MAPK/ERK, PKA/PKC, and AKT, which can converge on the NLRP3 inflammasome, leading to increased production of IL-1 β , IL-6, and TNF- α (He et al., 2022; Li et al., 2024; Zhou et al., 2024).

Besides its inflammatory role, P2X4 aids in clearing myelin debris and stimulates the release of brain-derived neurotrophic factor (BDNF), supporting synaptic plasticity under normal conditions (Trang et al., 2009; Parkhurst et al., 2013). However, in disease states such as neuropathic pain or inflammation-induced depression, excessive BDNF release driven by P2X4 contributes to synaptic dysfunction and neuronal hyperexcitability (Inoue and Tsuda, 2018; Wei et al., 2024). The P2X4-BDNF-Tropomyosin receptor kinase B (TrkB)-Potassium Chloride cotransporter 2 (KCC2) pathway has also been implicated in pain hypersensitivity, including morphine-induced hyperalgesia (Kohno and Tsuda, 2021; Gilabert et al., 2023). P2X4 also promotes apolipoprotein E

degradation and has been linked to memory impairment in Alzheimer's disease (Hua et al., 2023).

P2X7 plays a central role in microglial-mediated phlogosis responses by promoting inflammasome activation, mitochondrial stress, cytokine release, and cell death. Inhibition of P2X7 reduces the production of IL-1 β , IL-6, and TNF- α , as well as the expression of interferon regulatory factors such as IRF5 and IRF8, and decreases the number of interferon-responsive microglial cells (He et al., 2017; Chiozzi et al., 2019; Imraish et al., 2023; Dechelle-Marquet et al., 2025). Given that P2X4 and P2X7 both contribute to microglia-driven inflammation, it is not surprising that combined inhibition of these receptors enhances anti-inflammatory effects (Imraish et al., 2023). P2X7 activity is linked to microglial proliferation and death as moderate activation can support proliferation, whereas strong or prolonged activation induces ROS production, mitochondrial fragmentation, and apoptosis (Tao et al., 2022; Bedetta et al., 2025). In Alzheimer's disease, P2X7 activation promotes IL-18 release and sustains a pro-inflammatory environment, contributing to microglial overactivation, synaptic dysfunction, and the progression of amyloid- β and tau pathology (Heavener et al., 2025; Maurya et al., 2025). These findings highlight the P2X7/IL-18 axis as a potential marker of disease progression and a promising therapeutic target, suggesting that P2X7 inhibition may help reduce neuroinflammation and slow disease progression (Ronning et al., 2023). In neuropathic pain models, P2X7 receptors detect eATP released from damaged nerves, promoting a pro-inflammatory microglial phenotype and activating the NLRP3 inflammasome, which increases IL-1 β production and worsens pain sensitivity. Pharmacological inhibition of P2X7 reduces microglial activation, promotes a shift toward an anti-inflammatory phenotype, and alleviates pain (Zhang et al., 2024a). Of interest, we recently demonstrated that P2X7 activation in microglial cells induces the release of mitochondria-enriched microparticles that can be transferred to and integrated into recipient cells. This process enhances cellular metabolism and promotes a pro-inflammatory state, underscoring the role of P2X7 as a central mediator of intercellular organelle and microparticle transfer in these immune cells (Falzoni et al., 2024).

2.6. P2X receptors in dendritic cells

Dendritic cells (DCs) are professional antigen-presenting cells central to initiating and regulating adaptive immune responses. They express four subtypes of P2X receptors (P2X1, P2X4, P2X5, and P2X7) that are involved in DC maturation, migration, and function (Ferrari et al., 2000b). While P2X1 and P2X5 remain relatively understudied, we know that P2X7 and P2X4 play regulatory roles in DCs, with evidence suggesting that their functions are interdependent as one receptor can influence or regulate the activity of the other (Zech et al., 2016). The demonstration of the importance of the P2X7 receptor in modulating DCs responses, including IL-1 β secretion and maturation, as well as MHC-II antigen presentation, dates back more than 20 years (Mutini et al., 1999; Pizzirani et al., 2007). In recent years, the importance of P2X7 in DC maturation and function has been supported by various studies. For example, Li and colleagues demonstrated that in allergic airway inflammation, P2X7 activation on DCs promotes NLRP3 recruitment, leading to the release of IL-1 β and IL-18, together with the nuclear protein HMGB1. HMGB1 acts as a potent DAMP in combination with eATP, amplifying inflammatory signals and inducing Th2/Th17 immune polarization (Li et al., 2018). The role of P2X7 in DCs maturation and, consequently, in their antigen-presenting capacity via both MHC-I and II pathways has been demonstrated in numerous recent studies. For instance, Saez and colleagues demonstrated that P2X7-dependent activation of pannexin-1 promotes DC migration to lymph nodes, thereby facilitating antigen presentation to T cells (Saez et al., 2017). In line with these findings, Yu et al. showed that both protein and mRNA expression of P2X7 increase during DCs maturation, leading to the release of IFN γ and IL-12 via the NF- κ B pathway (Yu et al., 2025). Consistent with these data, ATP-stimulated DCs upregulate

MHC-I and MHC-II, along with CD86 and CD80, without altering the expression levels of co-inhibitory molecules, in a P2X7-dependent manner. Once these ATP-stimulated DCs present the antigen to CD4⁺ T cells, they induce the release of high amounts of IFN γ (Furuta et al., 2023). As for DC-dependent antigen presentation, recent studies demonstrate an important role for P2X7 in cross-presentation. Antigen cross-presentation, or cross-dressing, is a non-traditional mechanism in which DCs present non-self cytosolic antigens acquired from a donor cell that are already complexed with MHC-I. Recent findings have identified P2X7 as a key mediator of cross-dressing between apoptotic cells and DCs, as its expression on both the donor apoptotic cell and the receiving DC is required for the process and for the consequent maturation of CD8⁺ lymphocytes (Barrera-Avalos et al., 2021). Consistent with these findings, P2X7 is also enhancing viral antigen cross-presentation (Longo et al., 2024). Of interest in this case, P2X7 on donor cells activates the release of particles carrying MHC-I/antigen complexes (Longo et al., 2024). The vesicles released by DCs following P2X7 activation possess a complex cargo that includes MHC-II molecules, components of the NLRP3 inflammasome, mature IL-1 β , tissue factor, and the P2X7 receptor itself (Baroni et al., 2007; Pizzirani et al., 2007). These P2X7-associated extracellular vesicles (P2X7-EVs), which were first identified in macrophages (MacKenzie et al., 2001) and dendritic cells (Pizzirani et al., 2007), have since been extensively investigated in various other immune (Falzoni et al., 2024), neuronal (D'Arrigo et al., 2021), and cancer (Pegoraro et al., 2021, 2025; Vultaggio-Poma et al., 2022) cell types. These studies have demonstrated their important role in profoundly altering pro-inflammatory or tumor microenvironments by modulating eATP levels and thereby shaping immune responses (Adinolfi et al., 2023).

2.7. P2X receptors in neutrophils

Neutrophils are the most abundant leukocytes in blood and serve as the first responders to infection and sterile inflammation. eATP acts on neutrophils as a find-me signal for their recruitment to the wound/infection site, helping these cells to localize bacteria and tissue damage (Therkildsen et al., 2019). Neutrophil P2X1 plays a significant role in the response to chemotactic stimuli, a process involving Rho kinase-dependent actomyosin-mediated contraction at the cell rear (Lecut et al., 2009). Deficiency of the P2X1 receptor in a mouse model of LPS-induced endotoxemia reduced mortality and systemic inflammation, tissue damage, and coagulopathy. The main way P2X1 participated in endotoxemia was through its role in neutrophil emigration from venules (Maitre et al., 2015). Therefore, P2X1 receptors represent a potential therapeutic target for mitigating neutrophil-mediated tissue damage. However, developing selective P2X1 antagonists has been challenging. Although small-molecule P2X1 inhibitors have only recently become available, further biological validation is required to confirm their selectivity and pharmacological suitability for use in preclinical disease models (Bennetts et al., 2022). P2X4 expression in neutrophils has been reported in some pathological conditions (Sluyter et al., 2024) and in specific neutrophil subpopulations (Maynard et al., 2022).

In a murine model of colitis, increased luminal ATP levels in the colon of *Entpd8* $-/-$ mice promoted glycolysis in neutrophils through P2X4 receptor-dependent Ca^{2+} influx, which is linked to prolonged survival and elevated ROS production in these cells (Tani et al., 2021).

Human and murine neutrophils express functional P2X7 receptors, which play a pivotal role in clearance of infective bacteria (Karmakar et al., 2016). Neutrophils are key mediators in abacavir-induced thrombosis via their P2X7 receptors. Abacavir, a nucleoside reverse transcriptase inhibitor used in HIV-1 therapy, promotes platelet-leukocyte interactions by activating neutrophils, which facilitates binding between platelet P-selectin and neutrophil P-selectin glycoprotein ligand-1 (PSGL-1). Notably, neutrophil activation via P2X7 leads to the release of soluble lectin-like oxidized low-density lipoprotein

receptor-1 (sLOX-1), which subsequently activates platelets. This mechanism likely underlies the elevated cardiovascular risk observed in patients receiving abacavir. (Blanch-Ruiz et al., 2023).

Different P2X receptors have also been associated with NETosis, a specialized form of neutrophil cell death characterized by the release of neutrophil extracellular traps (NETs). NETs represent an efficient innate immune mechanism against apicomplexan parasites, including *Besnoitia besnoiti*, enhanced by eATP via P2X1 receptor (Espinosa et al., 2023). NET release from neutrophils is also increased by oleic acid (OA) and linoleic acid (LA) via pannexin-1-dependent ATP release and P2X1 activation (Alarcon et al., 2020). Neutrophil P2X7 activation was also found to enhance NET formation driven by TLR3 ligands in psoriasis (Zhang et al., 2024b). Nitrogen-containing bisphosphonates (N-BPs) trigger ATP-dependent P2X7 activation, leading to IL-1 β release from innate immune cells and promoting NETs, which contribute to sustained inflammation associated with N-BP treatment, potentially explaining their inflammatory side effects despite potent anti-resorptive efficacy (Bando et al., 2021).

2.8. Eosinophils' P2X receptors

Eosinophils are traditionally associated with allergy and parasitic defence (Berek, 2016; Siddiqui et al., 2023). These cells express P2X1, P2X4, and P2X7 (Ferrari et al., 2000a), all of which have been implicated in the aethiogenesis of eosinophil-mediated asthmatic reactions. Bronchoalveolar lavage fluids of asthmatic patients show high ATP concentrations (Idzko et al., 2007), which have been shown to affect P2X1 responses in eosinophils (Wright et al., 2016). Indeed, in eosinophils from healthy donors, activation of P2X1 increases adhesion, a phenotype that is lost in eosinophils from asthmatic patients and can be restored by apyrase pretreatment, suggesting receptor desensitization due to elevated eATP levels in the asthmatic microenvironment. These findings highlight a functional defect in P2X1 signalling in asthma, which may contribute to altered eosinophil trafficking and inflammation (Wright et al., 2016). As far as P2X4 is concerned, we know that in human peripheral blood mononuclear cells (PBMCs), eosinophils are the leukocytes expressing the highest levels of the receptor, both in healthy controls and in allergic patients (Paalme et al., 2019; Sluyter et al., 2024). However, so far, little is known about the receptor's role in allergic reactions.

P2X7 expression is elevated during acute and chronic asthma-related airway inflammation in both humans and mice (Li et al., 2018; Ren et al., 2023). Reduced P2X7 activity has been linked to lower asthma prevalence, while its activation on eosinophils, regulated by IFN γ , promotes the release of IL-8 and eosinophil cationic protein (Ferrari et al., 2000a; Mohanty et al., 2001; Idzko et al., 2003; Alberto et al., 2016). These data collectively indicate that P2X7 plays a regulatory role in asthma susceptibility and airway inflammation and are consistent with the finding that the P2X7 ligand LL37 exacerbates eosinophil activation in a receptor-mediated manner (Jiao et al., 2017).

2.9. P2X responses in natural killer cells

Natural killer (NK) cells are key effectors of innate immunity against tumours and viral infections, acting independently of prior antigen sensitization (Bryceson and Ljunggren, 2011). Although NK cells express multiple P2X receptor subtypes, including P2X1, P2X4, P2X5, P2X6, and P2X7 (Gorini et al., 2010), the specific roles of these receptors remain incompletely defined. The P2X7 receptor is highly expressed and functional in invariant NK T (iNKT) cells (Yu et al., 2018; Adhikary et al., 2019; Liu and Kim, 2019; Elhage et al., 2025), yet its immunomodulatory function has been unclear. Recent findings by Baroja-Mazo et al. revealed that ATP-induced P2X7 activation in human NK cells leads to an anergic phenotype, characterized by reduced cytotoxicity against cancer cells and diminished IFN γ production. These effects were reversed by P2X7 antagonism or cytokine priming with IL-2 or IL-15,

while P2X7 knockdown enhanced NK cell-mediated killing of tumour target cells, indicating that P2X7 signaling negatively regulates NK cell antitumour activity (Baroja-Mazo et al., 2023). These data are consistent with the antitumoral effects of P2X7 antagonist administration in murine cancer models, which also lead to increased levels of IFN γ (Adinolfi et al., 2012; Amoroso et al., 2015; De Marchi et al., 2019, 2022). In line with these data, NK-P2X7 was shown to be important in tumor restraining therapeutic approaches based on the blockade of ectonucleotidases CD39 and CD73 (Yan et al., 2020; Parra-Tello et al., 2025). Loss of P2X7 receptor in a murine model of α -sarcoglycan muscular dystrophy led to a decrease in muscle-infiltrating NK cells (Astigiano et al., 2025). These data are consistent with the capacity of a P2X7-blocking antibody to reduce iNK levels via complement-dependent cytotoxicity (Elhage et al., 2025).

2.10. P2X receptors in myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells with immunosuppressive properties, reducing T and NK cells' response. Little is known about the role of P2X receptors in these cells. A recent study identified P2X7 expression in human MDSCs and reported a consistent cell-surface presence in early, granulocytic, and monocytic MDSCs (Elhage et al., 2025). Of interest, when treating human PBMCs with a P2X7-blocking monoclonal antibody in the presence of complement, MDSC numbers could be significantly reduced via complement-dependent cytotoxicity (Elhage et al., 2025). Previous studies identified P2X7 in murine MDSCs, showing that it is highly expressed and promotes the production of TGF- β , arginase-1 (Arg-1), and ROS, thereby sustaining MDSC immunosuppression in a neuroblastoma model (Bianchi et al., 2014). Furthermore, P2X7 is uncoupled from cytotoxic activity in MDSCs (Bianchi et al., 2014), suggesting that, even at the high ATP levels present in the tumor microenvironment (De Marchi et al., 2020), MDSCs will not undergo P2X7-dependent cell death. Finally, a recent paper confirmed a role for P2X7 in activating MDSC immunosuppressive activity by increasing the production of Arg-1, indoleamine 2,3-dioxygenase1 (IDO-1), and IL-10. The same study also demonstrated that administration of a P2X7-targeting drug, together with a NLRP3 blocker and an anti-PD-L1 antibody, substantially reduces *in vivo* melanoma growth, leading to a significant decrease in tumor-infiltrating MDSCs (Ando et al., 2025).

2.11. P2X receptors in innate lymphocytes

Innate-like immune cells, including mucosal-associated invariant T (MAIT) cells and $\gamma\delta$ T cells, represent a unique interface between the adaptive and innate immune systems. These cells are distinguished by their ability to mount rapid effector responses upon stimulation, while retaining features of antigen-specific T lymphocytes. MAIT cells reside mainly in mucosal tissues and play a critical role in microbial defence, while $\gamma\delta$ T cells and other innate lymphoid cells (ILCs) contribute to tissue surveillance and inflammation (Van Kaer et al., 2022). Recent findings have underscored the importance of purinergic signalling in the regulation of these cell subsets. Using a P2X7-specific nanobody, it has been demonstrated that both MAIT and $\gamma\delta$ T cells express markedly higher levels of P2X7 than conventional T cells. ATP-dependent P2X7 activation induces an increased calcium influx, pore formation, and $\gamma\delta$ T cell death, suggesting that P2X7 functions as a regulatory checkpoint that constrains innate-like T cell activity under inflammatory conditions (Winzer et al., 2022). In addition to P2X7, $\gamma\delta$ T cells also express P2X1 and P2X4. Stimulation with CD3/CD28-coated beads and isopentenyl pyrophosphate (IPP), activates P2X4, leading to increased calcium influx and enhanced production of pro-inflammatory cytokines, such as TNF- α and IFN- γ . Interestingly, the P2X4 antagonist 2',3'-O-(2,4,6-trinitrophenyl) adenosine triphosphate (TNP-ATP) significantly suppressed cytokine release but did not affect CD69 expression, suggesting a selective regulatory role for P2X4 in cytokine release (Manohar et al.,

2012).

Notably, TCR-mediated differentiation between $\alpha\beta$ and $\gamma\delta$ T cells is influenced by MAPK signaling, which can be potentiated by eATP via P2X receptor engagement. Consistent with this, genetic deletion or pharmacological blockade of P2X7 decreases ERK phosphorylation, influencing differentiation toward the $\alpha\beta$ T lineage (West et al., 2012).

3. P2X receptor role in cells of the adaptive immune system

3.1. P2X receptors in T lymphocytes

T cells are central effectors of the adaptive immune response, orchestrating immune defense through a variety of specialized subsets. Each subset performs a distinct role that, together, ensures effective yet tightly controlled immune protection. CD4⁺ T helper (Th) cells, classified into Th1, Th2, and Th17, coordinate immune responses by releasing cytokines that activate other leukocytes. CD8⁺ cytotoxic T cells eliminate infected or malignant cells, and T follicular helper (Tfh) cells promote B cell differentiation and antibody production within germinal centers. CD4⁺ or CD8⁺ memory T cells persist long after the initial immune challenge, enabling rapid responses upon re-exposure to familiar antigens (Murphy et al., 2012). Purinergic P2X receptors have emerged as crucial regulators of T cell-mediated signaling.

Human T cells express several P2X receptor subtypes, specifically P2X1, P2X4, P2X5, and P2X7 (Jacob et al., 2013), each contributing distinctively to T cell physiology. P2X1 facilitates calcium influx in quiescent CD4⁺ T cells, maintaining basal mitochondrial calcium levels that support oxidative metabolism and prime cells for rapid responses to antigenic or chemokine stimulation (Campello et al., 2006). P2X4 localizes at immune synapses, where it regulates mitochondrial calcium uptake and ATP production during T cell activation (Woehrlé et al., 2010) and contributes to T cell motility and migration (Ledderose et al., 2018). P2X5, in its truncated form, functions as a late-stage activator that modulates IL-10 production, influencing the resolution phase of immune responses (Abramowski et al., 2014). P2X7 exhibits the most diverse and profound impact on T cell physiology. In the thymus, ATP-driven P2X7 signaling modulates calcium fluxes that guide thymocyte differentiation and selection (Ross et al., 1997). In mature T cells, P2X7 shapes cellular fate and effector functions. Its activation supports mitochondrial metabolism in memory CD8⁺ T cells via AMP-activated protein kinase signaling (Borges da Silva et al., 2018), and facilitates tissue-resident memory T cell formation by increasing sensitivity to TGF- β (Borges da Silva et al., 2020). Conversely, sustained P2X7 activation induces oxidative stress and cellular senescence in tumor-infiltrating lymphocytes via p38 MAPK and upregulation of CDK inhibitor 1a, ultimately limiting cytotoxic activity (Romagnani et al., 2020). At high eATP concentrations, P2X7 enhances antigen presentation by increasing MHC-I, MHC-II, and costimulatory molecule expression (Furuta et al., 2023). However, excessive eATP can be deleterious, triggering pyroptosis in Tfh cells (Faliti et al., 2019) or promoting self-killing of tissue-resident CXCR6⁺ CD8⁺ T cells (Dudek et al., 2021).

The intestinal immune system exemplifies how P2X receptor signaling influences immune balance. In the lamina propria, T cells coexist with a rich and active microbial community. Here, eATP released from commensal bacteria or damaged epithelial cells serves as a powerful signaling molecule (Perruzza et al., 2017). Maintaining intestinal homeostasis involves a delicate balance between pro-inflammatory and regulatory forces. Commensal-derived ATP serves as both a signal and a safeguard, shaping T cell subset dynamics via P2X7-mediated communication between the microbiota and the host immune system (Grassi and Marino, 2024). In the gut mucosa, CD8⁺ and invariant natural killer T (iNKT) cells express high levels of P2X7 and are especially vulnerable to ATP-induced cell death, a process believed to prevent excessive local inflammation (Heiss et al., 2008). Microbial ATP that disperses into Peyer's patches can also limit Tfh cell activity via P2X7, thereby regulating secretory IgA (sIgA) production and shaping

microbial composition (Proietti et al., 2014). Conversely, lower intestinal ATP levels enhance IgA responses, impacting systemic metabolism (Perruzza et al., 2022). Other microbial metabolites, such as propionate, further influence immunity by suppressing IL-17 production in $\gamma\delta$ T cells (Dupraz et al., 2021). To prevent ATP toxicity, Tfh cells downregulate P2X7 expression (Piconese et al., 2009), and commensal-specific IgA responses are suppressed (Proietti et al., 2019). The role of P2X7 extends beyond the gut, influencing systemic autoimmunity and neuro-inflammation. In systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), P2X7 expression is increased in Th1 and Th17 cells, correlating with disease progression (Li et al., 2020). However, P2X7 also plays protective roles: in SLE, it triggers caspase-dependent pyroptosis in Tfh cells, thereby limiting lymphocyte accumulation (Mellouk et al., 2022). In RA, loss of P2X7 in Tfh cells leads to increased pathogenic antibody production (Felix et al., 2019). Similar dual functions are observed in other diseases, such as experimental autoimmune encephalitis, where P2X7 is expressed on gut-derived Th cells that migrate to inflamed regions of the brain and spinal cord (Hiltensperger et al., 2021). Similarly, in early-stage type 1 diabetes, P2X7 enhances CD8⁺ T cell activity against pancreatic targets (Tezza et al., 2018).

3.2. P2X receptors in regulatory T cells

Regulatory T cells (Tregs) are a specialized subset of CD4⁺ T cells, characterized by the expression of forkhead box P3 (FOXP3), high CD25 expression, and low CD127 expression, that maintain immune tolerance and suppress excessive inflammation (Grover et al., 2021). Impaired Treg function is associated with many autoimmune diseases (Buckner, 2010). Tregs differ from other T lymphocytes in their response to eATP as low levels of the nucleotide do not affect cell proliferation and survival, whereas high eATP concentrations activate immune suppression rather than cell death (Trabanelli et al., 2012). During inflammation or epithelial damage, Tregs contribute to reducing eATP via CD39/CD73, which degrade ATP into adenosine and are considered positive fitness markers for these cells (Schenk et al., 2011; Ohta and Sitkovsky, 2014; Valentini et al., 2023). P2X receptors seem to favor the conversion of Tregs into Th17 cells. Indeed, activation of P2X4 on CD70-high CD11c-low DCs drives Th17 cell differentiation by promoting ROR γ T expression, the key transcription factor for Th17 lineage commitment (Hamoudi et al., 2022). These Th17 cells support anti-tumor immunity by stimulating the growth of cytotoxic T lymphocytes (Yamamoto et al., 2021). Similarly, P2X7 activation diminishes FOXP3 expression and drives the conversion of Tregs into pro-inflammatory Th17 cells in inflammatory bowel disease models (Figliuolo et al., 2017; Ruo et al., 2026). These data are consistent with the finding that blockade of P2X7 in both healthy controls and colon carcinoma-bearing mice induces a significant decrease in IL-17 and IL-23, (Pegoraro et al., 2025). Similar data were also obtained in rheumatoid arthritis (Ardissone et al., 2011), graft-versus-host disease (Cuthbertson et al., 2024; Elhage et al., 2025a), and autoimmune uveitis (Cao et al., 2026) models, suggesting an important role for the receptor in Th17-mediated responses. Moreover, genetic deletion of P2X7 led to accumulation of Tregs in tumor-bearing mice, increasing TGF- β levels (De Marchi et al., 2019, 2022). Interestingly, levels of the same Treg-signature growth factor were also reduced following administration of P2X7 antagonists in melanoma-bearing mice (Grignolo et al., 2026).

3.3. P2X receptors in B lymphocytes

In B cells, eATP serves as a key signal for maturation and antibody secretion (Yu et al., 2025). These effects are mediated primarily through P2X receptors. While T lymphocytes have long been at the center of immunological research on P2X receptors, B lymphocytes, equally vital to adaptive immunity, have received comparatively less attention in recent years, with few studies. Most P2X receptor subtypes are expressed in B cells, with P2X3 and P2X7 typically at lower levels under

physiological conditions. Interestingly, immortalization of human B cells by Epstein-Barr virus, which generates lymphoblastoid cell lines widely used in immunology and genetics, markedly increases P2X4, P2X5, and P2X7 expression, likely reflecting shifts in ATP metabolism (Lee et al., 2006). Among all P2X receptors, P2X7 has emerged as a central regulator of B cell physiology. Although B cells from healthy individuals express relatively low levels of P2X7 compared to other lymphocyte subsets (Winzer et al., 2022), activation of this receptor triggers a cascade of downstream effects increasing B cell survival, activation, and antibody production (Sakowicz-Burkiewicz et al., 2013b). Under metabolic stress, such as high-glucose conditions mimicking diabetes, P2X7-mediated functions are impaired, resulting in reduced immunoglobulin release and increased susceptibility to apoptosis (Solini et al., 2004; Sakowicz-Burkiewicz et al., 2013a, 2013b). Beyond its role in antibody synthesis, P2X7 activation induces rapid shedding of membrane molecules such as CD23, CD21, and L-selectin via matrix metalloproteinases (Sengstake et al., 2006). This process impacts B cell activation, migration, and IgE regulation (Przybyla et al., 2018). CD23, a low-affinity IgE receptor, is cleaved by ADAM10 upon P2X7 activation in both human (Gu et al., 1998) and murine (Pupovac et al., 2015) B lymphocytes, likely marking an early step in P2X7-driven apoptosis (Pupovac et al., 2015). CD21, which forms a complex with CD19 and CD81 to fine-tune BCR signaling, can bind soluble CD23 to suppress IgE secretion (Cherukuri et al., 2001). Once released, CD21 can bind CD23, further inhibiting IgE secretion (Fremaux-Bacchi et al., 1998). L-selectin, essential for lymphocyte trafficking (Venturi et al., 2003), is similarly lost upon P2X7 activation, further influencing B cell migration. Mechanistically, P2X7 activation in B cells also modulates intracellular calcium dynamics and transcriptional signaling. Pippel et al. observed that P2X7 engagement paradoxically inhibits calcium influx and nuclear factor of activated T cells (NFAT) activation, possibly due to altered ion fluxes or membrane depolarization, ultimately leading to suppressed B cell function (Pippel et al., 2015).

In pathological settings, P2X7 expression is frequently dysregulated. Elevated levels have been reported in B cells from patients with chronic kidney disease (Lajdova et al., 2017) and B-chronic lymphocytic leukemia (B-CLL) (Adinolfi et al., 2002), where P2X7 confers a proliferative advantage (Baricordi et al., 1999). In B-CLL, P2X7 activation stimulates phospholipase D through protein kinase C signaling (Shemon et al., 2007), while elevated soluble CD23 and L-selectin in patient sera correlate with disease activity and prognosis (Jamieson et al., 1996). Similarly, during sepsis, P2X7 expression increases transiently in CD19⁺ B cells, normalizing upon recovery, a phenomenon likely driven by CD4⁺ T cell activation (Martinez-Banaclocha et al., 2023). P2X7 is a promising but underexplored therapeutic target in B cells. Its blockade reduces calcium influx and co-stimulatory molecule expression and may affect BCR and cytokine signaling, while *in vivo* inhibition improves kidney allograft survival by limiting immature and memory B cells (Ding et al., 2020; Yu et al., 2025).

4. Conclusions

P2X receptors have emerged as promising therapeutic targets for modulating immune-driven pathology across inflammatory and neuro-immune disorders. Their ability to translate eATP signaling into cytokine release, antigen presentation, and regulated cell death situates them at the crossroads of immune activation and resolution. Among these receptors, P2X4 and P2X7 are attractive drug targets due to their defined roles in inflammasome activation, macrophage polarization, and lymphocyte function. Pharmacological modulation of P2X activity offers the potential to restore immune balance, limit tissue damage, and ameliorate chronic inflammation in conditions such as neurodegenerative diseases. Continued translational research integrating immunopharmacology, structural biology, and *in vivo* disease modeling will be essential to harness the therapeutic potential of P2X receptor signaling

for precision immunotherapy.

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CRediT authorship contribution statement

Elena Adinolfi: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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