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P2X4 receptors, immunity, and sepsis

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Abstract

Sepsis is life-threatening systemic dysfunction caused by a deregulated host response to an infectious insult. Currently, the treatment of sepsis is limited to the use of antibiotics, fluids, and cardiovascular/respiratory support. Despite these interventions, septic mortality remains high, with reduced life quality in survivors. For this reason, the identification of novel drug targets is a pressing task of modern pharmacology. Based on recent research, it appears that P2 purinergic receptors, which can regulate the host's response to infections, have been identified as potential targets for treatment of sepsis. Among P2 receptors, the $P2X_4$ receptor has recently captured the attention of the research community owing to its role in protecting against infections, inflammation, and organ injury. The present review provides an outline of the role played by $P2X_4$ receptors in the modulation of the host response to sepsis and the promise that targeting this receptor holds in the treatment of sepsis.'

Introduction

In 2016, the 3rd International Consensus Conference for Sepsis and Septic Shock defined sepsis as a life-threatening multiorgan dysfunction arising from a dysregulated host response to an infection, which has a high risk of death [1]. According to early estimates in this millennium, there are about 751,000 cases of sepsis (3.0 per 1,000 people) each year, resulting in over 200,000 deaths in the United States of America [2]. More recent studies indicate that sepsis causes, or contributes to, from one-third to one-half of all deaths occurring in hospitals in the United States, with the majority of patients presenting to hospital with sepsis rather than acquiring sepsis in hospital [3]. The overall sepsis-related health care cost in the US has been estimated to be $16-25 billion annually [4]. Taking into

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account the rapid expansion of the elderly population, which is affected disproportionately by sepsis due to physiologic frailty and immune senescence, the prevalence of sepsis and the associated health care costs are expected to rise significantly over the next two decades [5]

Several risk factors contribute to the development of sepsis, including chronic diseases impairing the immune system (e.g., acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, cancers) and treatment with immunosuppressive drugs [6]. In addition, age, sex, race and ethnic group are important determinants of sepsis prevalence, as it occurs more frequently in infants and elderly persons than in other age groups, at higher rates in males than in females, and at increased frequencies in African Americans as compared to Caucasians [7].

The clinical signs of sepsis are highly variable, depending on the initial site of infection, the pathogen, the pattern of acute organ dysfunction, as well as the underlying health status of the patient, and the interval before initiation of treatment [8]. Septic patients frequently display fever, shock, and respiratory failure [9]. Our understanding about the pathophysiological mechanisms underlying the onset and development of sepsis has evolved over the time. Initially, the development of sepsis was ascribed to a hyper-inflammatory condition characterized by an unrestrained immune response (systemic inflammatory response syndrome or SIRS) with a systemic cytokine storm, which is the result of an overproduction of several pro-inflammatory molecules including TNF-α, IL-1β, IL-2, IL-6, IL-8, and IFN-γ [9]. Subsequent hypotheses refined this original view, and proposed that sepsis develops through a sequential or parallel (SIRS)[10] and compensatory anti-inflammatory response syndrome (CARS), a condition with suppresses immunity and enhances the susceptibility to secondary infections[11].

Despite over 100 clinical trials conducted on sepsis, no FDA-approved treatment options exist that can improve sepsis survival [12]. For this reason, the identification of novel pharmacological approaches to manage sepsis is of extreme interest to the scientific community. Over the past two decades, increasing attention has been paid to the involvement of the purinergic system in the pathophysiology of sepsis [13-19]. The purine ATP is a well-recognized signaling molecule released at sites of infection, inflammation and cell injury. In this setting, extracellular ATP acts as a “danger” signal, which, through the activation of P2 receptors plays a critical role in immune cell migration, chemotaxis, and cytokine release [19-21].

In this brief review article, we have delineated the role of one of the P2 receptors, the $P2X_4$, in regulating immunity during infections, inflammation and sepsis.

Purinergic signalling: receptors, enzymes, transporters

Purinergic signaling is initiated by the release of nucleotides into the extracellular space through volume regulated anion channels, maxi-anion channels, transporters, connexins and pannexins [22], as well as exocytotic pathways and membrane damage (Fig. 1) [23]. Once released into the extracellular space, the nucleotides, which include ATP, ADP, UDP, and UDP-glucose, can trigger a series of cellular responses through the engagement of P2 receptors. These are classified into ionotropic P2X ($P2X_{1–7}$) and metabotropic P2Y

($P2Y_{1,2,4,6,11–14}$) receptors (Fig. 1) [23]. P2X receptors display a trimeric structure, where each monomer has two transmembrane domains. They are ion channels and gate primarily Na^+, K^+ and Ca^{2+}, and, in some cases, Cl^- [24]. The stimulation of $G_{q/11}$-coupled $P2Y_{1,2,4,6}$ and $P2Y_{11}$ receptors causes the activation of phospholipase C, leading to the downstream production of inositol-(1,4,5)-trisphosphate and diacylglycerol (DAG) [25]. Inositol-(1,4,5)-trisphosphate increases intracellular Ca^{2+} levels were DAG stimulates protein kinase C (PKC) [25]. Moreover, $P2Y_{11}$ receptor activation can stimulate whereas $P2Y_{12,13}$ receptor engagement can inhibit, adenylate cyclase [25]. As asserted above, in addition to ATP, UTP and its degradation product, UDP, can play important regulatory roles also in modulating the immune cell activities (i.e. neutrophil and monocyte chemotaxis, activation of granulocytes, dendritic cells, monocytes, neutrophils and lymphocytes)[26]. Indeed, UTP, UDP and UDP-glucose act as agonists on four P2Y receptor subtypes ($P2Y_2$, $P2Y_4$, $P2Y_6$ and $P2Y_{14}$), whereas no affinity has been observed for P2X receptors [26]. In general, the engagement of P2 receptors has been shown to facilitate immune cell function.

Following their release into the extracellular space, ATP and/or ADP are quickly converted by CD39 (ecto-nucleoside triphosphate diphosphohydrolase 1, E-NTPDase1) into AMP, and then, via CD73 (ecto-5'-nucleotidase) AMP is dephosphorylated into adenosine [27]. The latter is a purine nucleoside, which exerts its cellular actions through the engagement of specific G protein-coupled receptors classified as A_1, A_{2A}, A_{2B} and A_3. In particular, A_1 and A_3 receptors are coupled to G_i, G_q and G_o proteins, while the A_{2A} and A_{2B} receptors activate adenylyl cyclase via G_s or G_{olf} [28] (Fig. 1). The stimulation of A_{2B} receptors can trigger also phospholipase C via G_q [28,29]. In general adenosine exerts immunosuppressive effects [28,29]. Of note, since the CD39/CD73 enzyme axis is critical in the degradation of ATP, ADP, and AMP into adenosine, it can be considered as a an “immunological switch” which is able to shift an ATP-driven pro-inflammatory immune cell response toward an anti-inflammatory environment steered by adenosine [23] [27,30,31] (Fig. 1).

It is interesting to note that P1 and P2 purinergic receptors have distinct and divergent effects on immunity and inflammation regulation [32]. Whereas adenosine-mediated P1 purinergic receptor activation dampens inflammation and attenuate immune-mediated tissue injury overall [14,15,33], P2 purinergic receptor activation by ATP drives inflammasome activation and stimulates bacterial killing [34,35]. These divergent effects of P1 and P2 purinergic receptors on immunity and inflammation is clinically significant as sepsis is a disease characterized by initial hyper-inflammatory phase followed by hypo-immune state where the subject succumbs from immune paralysis [36]. Depending on the immune state of the septic subject, one can tailor therapy with either P1 (to dampen inflammation) or P2 (to promote immunity) purinergic receptors.

$P2X_4$ receptor: structure and molecular biology

P2X receptors are a family of non-selective trimeric ligand-gated channels, permitting Na^+, K^+ and Ca^{2+} ion fluxes upon binding extracellular ATP [37]. Seven subtypes of P2X receptors have been cloned and classified as $P2X_1$ to $P2X_7$, with functional channels assembled as homo- or heterotrimers [37]. Each monomer comprises two transmembrane domains linked by a large extracellular loop and intracellularly located N- and C-termini

[38]. The activity of P2X receptors is modified by several factors including the extracellular concentration of ions (Zn^{2+}, Cu^{2+}, Hg^{2+}, Ni^{2+}, Cd^{2+}), protons, lipids, steroids, and ethanol [39].

The $P2X_4$ receptor is one of the most sensitive purinergic receptors, as it is activated by nanomolar concentrations of extracellular ATP [39]. Of note, the Ca^{2+} permeability of $P2X_4$ is the highest among the P2X family [40].

Immunoprecipitation studies have revealed that the $P2X_4$ subtype can heteromerically assemble with other P2X members, including $P2X_1$, $P2X_2$ and $P2X_6$ [41,42]. In addition, structural interactions have been reported between $P2X_4$ and $P2X_7$ receptors [41,43]. In this regard, Schneider et al. [44] recently demonstrated that $P2X_4$ and $P2X_7$ subunits can form heterotrimeric $P2X_4/P2X_7$ receptors. Of note, the $P2X_4$ and $P2X_7$ subunit isoforms are widely co-expressed particularly on immune/inflammatory cells [45].

$P2X_4$ receptors are distributed throughout the body [46]. Indeed, they are widely expressed in central and peripheral neurons, microglia, and various glandular tissues such as pancreatic acinar cells and salivary glands as well as endothelial cells [47]. They are expressed also throughout the gastrointestinal tract, liver, lung, kidney and reproductive system [23][24]. At the cellular level, the $P2X_4$ receptor is located on plasma membrane, but also in intracellular compartments, such as lysosomes, vesicles, vacuoles and lamellar bodies[48].

Acute kidney injury and inflammation is a major complication of sepsis and has extremely high mortality (>70% in severe sepsis) [49]. Although several renal cells express $P2X_4$ purinergic receptor, the role for $P2X_4$ receptor in acute kidney injury and inflammation is unclear unlike the better-characterized pro-inflammatory role of $P2X_7$ receptor [50]. It appears that $P2X_4$ dampens renal fibrosis response during recovery from kidney injury as mice deficient in $P2X_4$ receptors have exacerbated renal fibrosis in a mouse model of chronic interstitial inflammation [51]. Furthermore, renal tubular $P2X_4$ receptor activation may promote kidney injury in early sepsis by promoting NOD-like receptor 3 inflammasome activation and facilitating IL-1β and IL-18 maturation [52].

$P2X_4$ receptor and immune system

All immune cells, whether from the myeloid or lymphoid lineage, express at least one P2X or P2Y receptor subtype (see Table 1) [53]. Consistently with this knowledge, an increasing body of evidence supports the critical role played by both P2X and P2Y receptors in immune cell biology [54-57]. In accordance with its wide distribution, the $P2X_4$ receptor has been shown to regulate a variety of pathophysiological processes, such as neuropathic pain and autoimmune diseases [39,58,59]. Many of these modulating roles are mediated by cells of the immune system.

Monocytes, and macrophages.—Monocytes and macrophages play a pivotal role in the immune response against micro-organisms and the pathogenesis of sepsis [60] [61]. These cells phagocyte and kill micro-organisms, release cytokines, and present pathogens to T cells, thus triggering both cellular and humoral immune responses [60]. All monocyte and macrophage cell types have been found to express P2X and P2Y receptors. In monocytes,

the most abundant P2X receptor transcripts are $P2X_4$, followed by transcripts for $P2X_7$ and $P2X_1$ [62], thus suggesting an important role for these receptor subtypes in monocyte functions.

Murine peritoneal macrophages express functionally active $P2X_4$ and $P2X_7$ receptors [63,64]. In particular, the exposure of these cells to low concentrations of ATP evoked a small $P2X_4$-driven ion current, while higher ATP concentrations evoked a large $P2X_7$-driven ion current [64]. However, the physiological role of the $P2X_4$ receptor-driven current was not explored in this study [64]. $P2X_4$ expression has been detected also on both human and rat alveolar macrophages [65], and the authors described a dynamic regulation of $P2X_4$ receptors during distinct phases of macrophage activation [65]. In resting macrophages, functional $P2X_4$ receptors as measured using ATP-evoked currents were maintained at very low levels, whereas they underwent a rapid up-regulation in response to phagocytosis [65]. By contrast, classical activation of macrophages elicited by their incubation with IFN- γ and TNF-α or IFN- γ and LPS, reduced the surface expression of $P2X_4$ receptors and decreased ATP-evoked currents without altering total $P2X_4$ receptor protein levels [65]. Of note, the alternative activation of these cells with IL- 4 or IL- 13 did not alter the total surface or the functional expression of these receptors [65]. Based on these observations, the authors hypothesized a scenario in which an initial bacterial or inflammatory stimulus elicits rapid trafficking of $P2X_4$ receptors to the macrophage cell surface causing increased Ca^{2+} influx, thus promoting their activity [65]. After the termination of macrophage activation, a feedback mechanism develops to curb $P2X_4$ receptor trafficking to the cell membrane and function, probably aimed at facilitating the resolution inflammation [65].

Recent observations highlighted molecular and functional interactions between $P2X_4$ and $P2X_7$ receptors on macrophages [66-68]. In particular, a physical protein–to protein interaction takes place between $P2X_4$ and $P2X_7$ receptors, where the two receptors are bridged by the C-terminus of $P2X_7$ receptor [66]. This physical interaction was facilitated by the presence of extracellular ATP [66]. Kawano et al. provided evidence about a role of $P2X_4$ receptor in modulating $P2X_7$ receptor-dependent inflammatory functions [67]. Indeed, by means of *in vitro* assay, it was observed that treatment of RAW264.7 cells with ATP elicited a $P2X_7$-dependent release of HMGB1 and IL-1β [67]. Of note, this event was blunted by the genetic ablation of $P2X_4$ receptor via short hairpin RNA transfection as well as by removing extracellular Ca^{2+}[67], thus confirming a functional interplay between $P2X_4$ and $P2X_7$ receptors, driven by a modulation of intracellular Ca^{2+} concentrations.

The $P2X_4$/$P2X_7$ linkage has been shown to hold a critical role also in eliciting macrophage death[68]. In particular, the recruitment of $P2X_7$ receptors in RAW264.7 cells with high concentrations of ATP determined an increase in Ca^{2+} influx, pore formation, and activation of ERK1/2 and p38MAPK, thus leading to cell death [68]. In this context, despite the activation of $P2X_4$ receptor alone did not induce cell death, the $P2X_4$ receptor-dependent acute-phase Ca^{2+} influx, elicited by the high levels of ATP, contributed to $P2X_7$ receptor-dependent cell death in activated macrophages [68].

Recently, our experiments revealed a role of ATP in regulating bacterial killing in macrophages via $P2X_4$ receptors [18]. We observed that the selective $P2X_4$ receptor

antagonist 5-BDBD and the shRNA-mediated receptor silencing, prevented the stimulant effect of ATP on *E. coli* killing by macrophages [18]. In addition, in macrophages isolated from $P2X_4$ receptor knockout mice, ATP failed to stimulate bacterial killing [18]. Thus, we concluded that $P2X_4$ receptors augment bacterial killing by macrophages. Mechanistically, we found that $P2X_4$ receptor activation specifically increased mitochondrial, but not cellular, ROS production, which was a likely mediator of the antibacterial effect of $P2X_4$ receptor activation [18].

In parallel, using the murine cecal ligation and puncture model, considered by several investigators as the “gold standard” mouse model of sepsis [69], we demonstrated also that macrophage $P2X_4$ receptors control bacterial spread and inflammation in sepsis [18]. That is, $P2X_4$ receptor knockout mice showed an increased bacterial load and a decreased survival in comparison with wild type animals [18], indicating that endogenous ATP released during sepsis, exerts a protective effect through $P2X_4$ receptor engagement [18]. Of note, we also provided evidence that protective effect of P2X4 receptor activation was mediated though $P2X_4$ receptor signaling on macrophages, as both adoptive transfer of $P2X_4^{-/-}$ receptor macrophages or myeloid-specific $P2X_4^{-/-}$ receptor mice emulated the deleterious phenotype of $P2X_4$ deficient animals.

Dendritic cells.—Dendritic cells (DCs) are the primary antigen-presenting cells in the body and therefore they are pivotal in linking innate and adaptive immunity [70]. Dendritic cell function is compromised during sepsis [71,72] and sepsis is associated with widespread dendritic cell depletion [73,74]. DCs are endowed with both P2Y receptors ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$ and $P2Y_{14}$) and P2X receptors ($P2X_1$, $P2X_4$, $P2X_7$) [75,76]. Our understanding of the role of P2X4 receptors in regulating dendritic cell function is in its infancy. Sakaki et al. demonstrated recently that $P2X_4$ receptor activation elicited a rapid and substantial initial Ca^{2+} influx in dendritic cells. This Ca^{2+} influx was required for optimal $P2X_7$-dependent IL-1β and IL-18 release from DCs [77]. Clearly, further studies are required to unravel the precise role of $P2X_4$ receptors in regulating DC function during immune responses and sepsis.

Neutrophils.—Neutrophils are professional phagocytes that play a central role in host defense against extracellular bacteria and fungi [78]. These cells are endowed with a unique capacity to very efficiently and rapidly engulf and thereby eliminate pathogens and cell debris [79]. Patients with sepsis display aberrant neutrophil activity, characterized by an impaired recruitment of these cells to sites of infection, abnormal longevity, and overproduction of toxic mediators leading to bystander organ injury [80].

A substantial body of evidence supports the notion that ATP regulates tightly several neutrophil functions, such as chemotaxis, rolling, adhesion, transmigration, phagocytosis, oxidative burst, extracellular trap formation, degranulation and apoptosis [56]. The role of $P2X_4$ receptors in neutrophils is incompletely understood. The only study dealing with this issue showed that $P2X_4$ knockout mice demonstrated reduced infiltration of neutrophils to the injury site in a murine spinal cord injury model [81]. It was however unclear from this study whether $P2X_4$ receptor signaling in neutrophils was required for optimal neutrophil infiltration or $P2X_4$ signaling indirectly affected neutrophil infiltration.

Considering our data, showing a stimulant role of $P2X_4$ receptors on macrophages in bacterial killing [18], it would be interesting to test whether $P2X_4$ receptors have a similar role in neutrophils.

T lymphocytes.—Sepsis results in a deluge of pro- and anti-inflammatory cytokines and immunosuppressive mediators, leading to $CD4^+$ and $CD8^+$ T cell dysfunction and death [82]. Although the precise mechanisms, underlying this condition of T cell suppression, are not well defined, several lines of evidence indicate that purinergic signaling may control T cells during sepsis in many different ways [20,83]. Indeed, the release of ATP via pannexin-1 pores during lymphocyte activation, enhances IL-2 release, in an autocrine manner, through the engagement of $P2X_1$, $P2X_4$ and $P2X_7$ receptors [84,85]. Mechanistically, ATP elicits Ca^{2+} influx through these receptors and stimulates the nuclear factor of activated T cells and MAPK signaling resulting in increased IL-2 production [84,86,87]. The accumulation of several purinergic components, including pannexin 1 channels, $P2X_1$ and $P2X_4$ receptors, at the immune synapse facilitates T cell–accessory cell communication, antigen recognition and T cell activation [87]. Mitochondria also translocate to the immune synapse where by directly providing the ATP to be released, fuel the autocrine purinergic signaling in the synaptic cleft [87]. $P2X_4$ receptors colocalize with mitochondria in clusters at the front of cells, facilitating the Ca^{2+} influx to maintain local mitochondrial ATP production at the levels needed for cell migration [88].

In patients with sepsis, purinergic signaling appears defective [89]. Indeed, resting cells from septic patients lack the autocrine purinergic feedback loops that maintain basal cytosolic Ca^{2+} levels and mitochondrial function thus, leading to a condition of cellular paralysis that impairs vigilance and precludes proper functional responses to T cell stimulation [89]. However, the suppression of purinergic signaling is not due to a reduction of P2X receptor expression, since the mRNA levels of these receptors appear unchanged ($P2X_4$ and $P2X_7$) or elevated ($P2X_1$) in patients with sepsis [89]. Further studies will be needed to unravel the precise role of purinergic signaling in T cells in sepsis.

Conclusions

Although antibiotic therapy still represents an irreplaceable part of sepsis management, this therapeutic approach is facing hard challenges due to the development of multi-resistant bacterial strains [90,91]. In addition, antibiotic treatment does not prevent the various immune abnormalities occurring during sepsis. For these reasons, it is necessary to foster an integrated approach in the treatment of sepsis, which might take advantage of our increasing understanding of the role of purinergic signaling is sepsis [92].

So far, in the arena of purinergic research much attention has been focused on $P2X_7$ receptors, as they have been shown to be involved in a plethora of inflammatory disorders (i.e. osteoarthritis, rheumatoid arthritis, chronic obstructive pulmonary disease, and Crohn’s disease), and thus they appear to be one of the most appealing potential drug target [93]. However, recently there has been also growing interest on the $P2X_4$ receptors. Indeed, this receptor subtype, which is widely investigated in the context of pain transmission [94,95], also has a role in mediating the effects of ATP in shaping immune/inflammatory responses.

For this reason, it is striking that the $P2X_4$ receptor, which is being widely expressed on cells of both the innate and adaptive arms of the immune system (see Table 1) remains poorly characterized in sepsis. Our pioneering preclinical studies demonstrated that $P2X_4$ receptor engagement is critical in limiting the dissemination of bacteria by enhancing killing of these pathogens[18]. This indicates that $P2X_4$ receptors are a potential target for antibacterial drug discovery. Unfortunately, the study of $P2X_4$ receptors has been seriously hindered by the lack of selective pharmacological tools. Indeed, for a long time, researchers had to rely on non-selective P2X receptor antagonists such as paroxetine, TNP-ATP, and BBG to characterize $P2X_4$ receptors (Fig. 2). We are hopeful that in the coming years medicinal chemists will generate selective and potent ligands for $P2X_4$ receptors

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Highlights

- Sepsis is an organ dysfunction caused by a deregulated immune response to an infection
- At present, no approved treatment options exist that can improve sepsis survival
- Increasing attention has been paid to the role of the purinergic system in sepsis pathophysiology

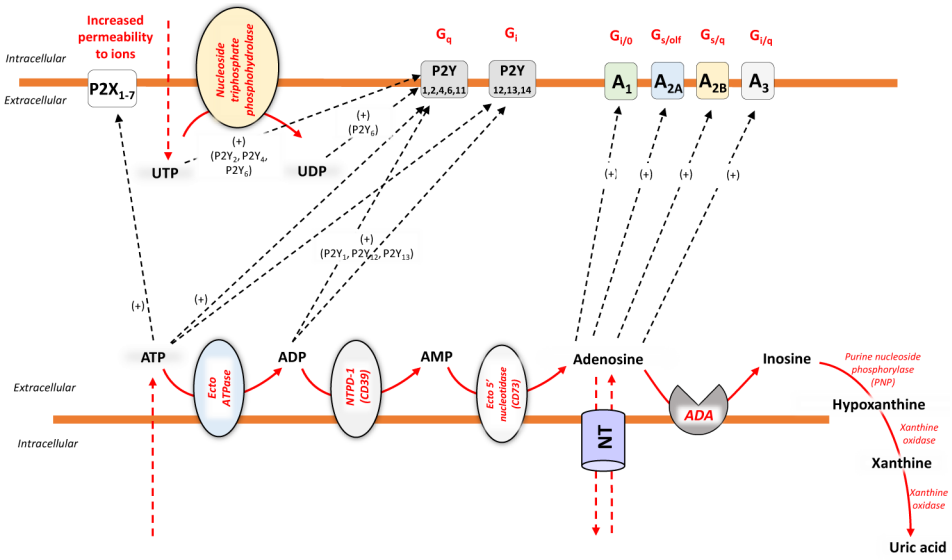

Figure 1.

Once released into the extracellular environment, through channels or other extrusion systems, ATP, ADP, AMP, and adenosine, are metabolized by a set of nucleotidases [nucleoside triphosphate diphosphohydrolases, ecto-ATPase, NTPD-1 (CD39), ecto-5'nucleotidase (CD73), purine nucleoside phosphorylase PNP), xanthine oxidase], leading to their sequential dephosphorylation and subsequent generation of other bioactive metabolites, which selectively interact with purinergic P1 (A_1, A_{2A}, A_{2B} and A_3) or P2 (P2X and P2Y) receptors. Several cell types are endowed with nucleoside transporters (NT), which operate the uptake of extracellular adenosine, thus actively participating to the careful regulation and termination of adenosine signaling.

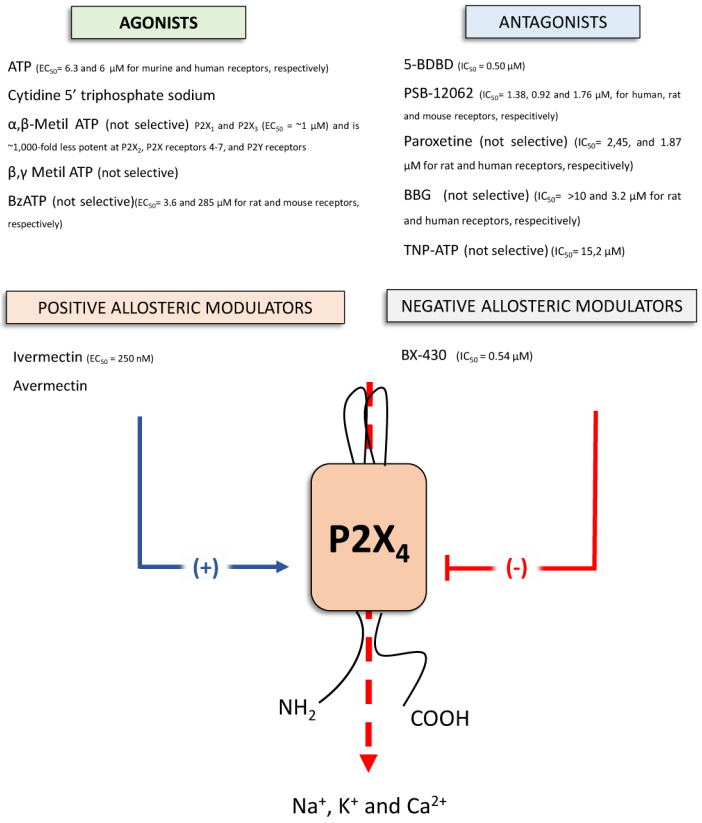

Figure 2.

Schematic structure of the $P2X_4$ receptor and the main commercially available ligands acting on this receptor subtype with indicated the IC_{50} and EC_{50} values.

Table 1.

Expression of P2 receptors on immune cells

Immune cell population	Purinergic receptors	References
Monocyte/macrophage	$P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$ $P2X_1$, $P2X_4$, $P2X_7$	[55,96]
Dendritic cells	$P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{14}$, $P2X_1$, $P2X_4$, $P2X_7$	[76,97]
Neutrophils	$P2Y_1$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$ $P2X_1$, $P2X_4$, $P2X_7$	[56]
Eosinophils	$P2Y_1$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{14}$, $P2X_1$, $P2X_4$, $P2X_7$	[98,99]
Mast cells	$P2Y_1$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$ $P2X_1$, $P2X_3$, $P2X_4$, $P2X_7$,	[100,101]
T lymphocytes	$P2Y_1$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$, $P2X_1$, $P2X_4$, $P2X_7$	[102]
B lymphocytes	$P2Y_1$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$ $P2X_1$, $P2X_4$, $P2X_7$	[57]
Natural killer cells	$P2Y_{11}$, $P2X_1$, $P2X_4$, $P2X_7$	[103]