Inflammation Research (2022) 71:1203–1212
https://doi.org/10.1007/s00011-022-01607-w

Inflammation Research

REVIEW

The role of adenosine A_1 receptor on immune cells

Lingyu Zhong[1] · Qiao Peng[1] · Xun Zeng[1]

Received: 28 May 2022 / Revised: 27 June 2022 / Accepted: 29 June 2022 / Published online: 5 September 2022

Abstract

Background Adenosine, acting as a regulator by mediating the activation of G protein-coupled adenosine receptor families (A_1, A_2A, A_2B, and A_3), plays an important role under physiological and pathological conditions. As the receptor with the highest affinity for adenosine, the role of adenosine A_1 receptor (A_1R)-mediated adenosine signaling pathway in the central nervous system has been well addressed. However, functions of A_1R on immune cells are less summarized. Considering that some immune cells express multiple types of adenosine receptors with distinct effects and varied density, exogenous adenosine of different concentrations may induce divergent immune cell functions.

Materials and methods The literatures about the expression of A_1R and its regulation on immune cells and how it regulates the function of immune cells were searched on PubMed and Google Scholar.

Conclusion In this review, we discussed the effects of A_1R on immune cells, including monocytes, macrophages, neutrophils, dendritic cells, and microglia, and focused on the role of A_1R in regulating immune cells in diseases, which may facilitate our understanding of the mechanisms by which adenosine affects immune cells through A_1R.

Keywords Adenosine A_1 receptor · Immune cells · Macrophage · Neutrophils · Dendritic cells · Microglia

Introduction

Adenosine is an endogenous small molecule that arises from the release of equilibrium transporters or from cell damage, but it is mainly produced by the hydrolysis of adenosine triphosphate through membrane-bound nucleotide enzymes: ectonucleoside triphosphate diphosphohydrolase-1 (CD39) and ecto-5′-nucleotidase (CD73) [1, 2]. Adenosine regulates cells and organs primarily through the downstream signals by its interaction with four G protein-coupled receptors (GPCRs), named A_1, A_2A, A_2B, and A_3 adenosine receptors, which are expressed in different cells and tissues in the body [3]. Under physiological conditions, the expression level of adenosine is low, usually in the range of 20–300 nM [4]. However, under ischemia and hypoxia as in the cases of necrosis and tumors, the concentration of adenosine in the tissue will reach micromolar level [5]. Under such condition, high concentrations of adenosine can regulate different immune cells by activating adenosine receptors, thereby affecting the function of immune cells under pathological conditions.

Adenosine has an impact on a variety of physiological aspects, such as neuronal activity, vascular function, and blood cell regulation [6]. The combination of adenosine with four different adenosine receptors and the different distribution of adenosine receptors on cells commonly indicate different regulatory functions [5]. A_1 and A_3 receptors inhibit the activity of adenylyl cyclase (AC) by coupling to the Gi protein, while A_1 receptor (A_1R) is mainly expressed in the central nervous system and A_3 receptor is widely expressed by a variety of primary cells and tissues. However, the A_2 receptors, including A_2A and A_2B receptors, are coupled to Gs proteins. The A_2A receptor, a high-affinity receptor, is expressed both centrally and peripherally, while A_2B receptor, a low-affinity receptor, is mainly expressed in the

✉ Qiao Peng
pengqiao@zju.edu.cn

✉ Xun Zeng
xunzeng@zju.edu.cn

[1] State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, People's Republic of China

peripheral area. Both of them activate AC mainly through the Gs protein, thereby promoting the production of cAMP [5, 7].

Different adenosine receptors have different affinities for adenosine. The A_1R shows the highest affinity for adenosine, which can reach 1–10 nM. The A_1R subtypes are expressed in large quantities in the central nervous system and are also abundant in other organs, such as the heart, kidneys, lungs, and livers, to regulate the functions of the organs themselves [8]. The A_1R in the kidneys is able to regulate proximal tubular sodium transport and fluid balance mediated by the tension of the afferent substance [9]. In allergic reactions, adenosine is able to cause bronchial contractions in humans by activating A_1R [10]. Studies related to the central nervous system have shown that the A_1R signaling has an effect on both sleep and the development of central nervous system [11]. The distribution of A_1R is also closely related to the main sites of cerebral infarction [12]. It is worth noting that the A_1R is also expressed on various immune cells, such as monocytes, macrophages, neutrophils, and dendritic cells, but not on T cells and NK cells [13]. The A_1R-mediated signaling plays an important regulatory role in the growth and development of immune cells and their functional differentiation, but there is no relevant literature summarizing this aspect of A_1R in immune cells. Based on this, this review mainly summarizes the effect of A_1R on different immune cells in the immune system and its latest research progress, which may provide reference for the future clinical application of A_1R-related treatments.

Adenosine A1 receptor

Structure

The A_1R is a glycoprotein with a molecular mass of ~ 36 kDa and contains a total of 326 amino acids [11, 14]. Similar to other adenosine receptors, the A_1R belongs to the G protein-coupled receptor family and contains a seven-fold transmembrane structure [15]. The seven transmembrane α-helix structures are connected by three extracellular domains and three intracellular domains, with the C-terminal remaining in the intracellular region [16]. The N-terminus and extracellular domains are responsible for ligand binding, while the C-terminal and intracellular domains bind to G proteins and then transduce the downstream signals [11]. The length of intracellular C-terminus in A_1R is shorter than other adenosine receptors, with only 36 amino acids [3, 17]. The sequence of the A_1R is more conserved among species [18]. A comparative study of rat, dogs, bovines, and humans shows that about 90% of the coding regions of the A_1R are similar [14].

Signaling pathways

The A_1R and the second messenger are coupled in a manner similar to A_3 receptor, which are different from the A_2A and A_2B receptors. After A_1R receives adenosine signal, the Pertussis toxin-sensitive Gi and/or Go proteins are activated, which results in the breakdown of G protein α and G protein β/γ isomers, and the GDP is converted to GTP after binding G protein α. G protein α-i inhibits the activity of AC, thus subsequent synthesis of cAMP, thereby restraining the weakening of the phosphorylation of cAMP-dependent protein kinase A (PKA) [19]. The G protein β/γ receptors bind to and activate phospholipase C-β (PLC-β), catalyzing PIP2 to form PI3. The PI3 then mobilizes internally stored calcium ions to activate the protein kinase C (PKC) protein, which plays an important role in the activation of the NF-κB pathway [20, 21]. At the same time, A_1R also causes activation of the ERK1/2 pathway by releasing the β/γ subunits of G protein (Fig. 1) [22, 23].

Agonists and antagonists

Most of the A_1R agonists are modification products of adenosine, which are mainly modified at three positions in adenosine [24]: N^6-position, C2 position, and 5′-position. CHA (N^6-cyclohexyladenosine) and CPA (N^6-cyclopentyladenosine) are just two examples of modification at the N^6-position [24, 25]. The use of hydrophobic cycloalkyl monosubstitution at the N^6-position of adenosine provides high selectivity for A_1R (Fig. 1) [25]. The introduction of chlorine atoms at the C2 position, such as CCPA, increases the selectivity of A_1R [1, 26]. Various agonists, such as NECA (5′-*N*-ethylcarboxamidoadenosine), MRS5595, and MRS5607, are generated by the addition of formamide derivatives at the 5′-position in the ribose unit of adenosine, which also confers special selectivity to A_1R [27].

Antagonists of A_1R are mainly divided into xanthine derivatives and non-xanthine. Most of the A_1R selective antagonists are mainly obtained by substitution of aromatic and cycloalkyl groups at C^8 position of the xanthine. Interestingly, substitution at the N^1, N^3, and N^7 positions can enhance the selectivity of A_1R [24]. Common xanthine derivative antagonists against A_1R mainly include DPCPX (8-cyclopentyl-1,3-dipropylxanthine) [28, 29] and rolofylline [30] (Fig. 1). In terms of non-xanthine antagonists, many heterozygous compounds have been found to be able to antagonize adenosine receptors, such as FK-453, a derivative of pyrazolo [1,5-a] pyridine, which has a high selectivity and antagonistic effect on A_1R [31, 32]. In addition, some derivatives of adenine have been continuously

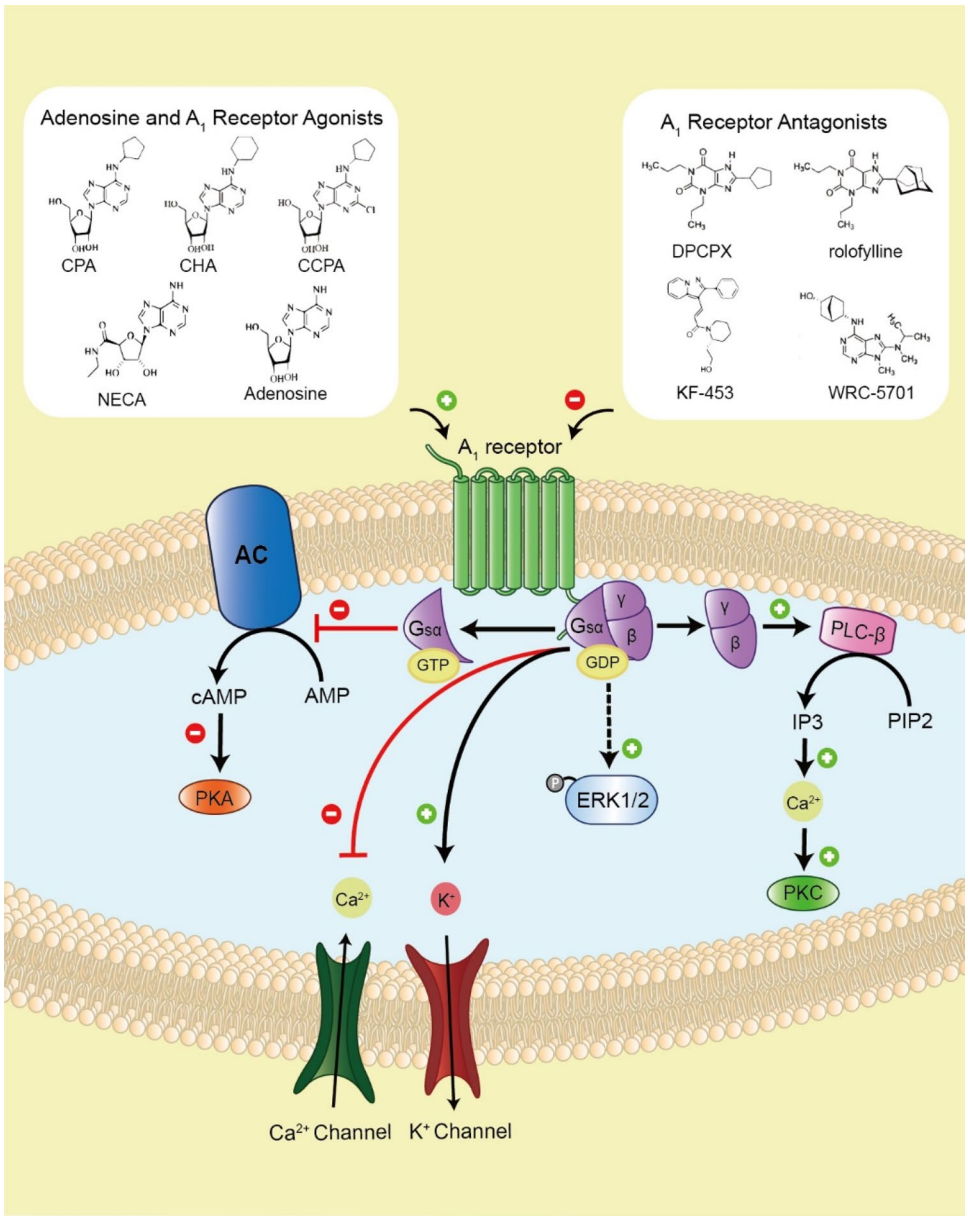

Fig. 1 Overview of A_1R signaling pathways. Stimulation of A_1R decreases adenylates cyclase (AC) activity and cAMP production, thus inhibiting protein kinase A (PKA), while it activates phospholipase C (PLC)-β to catalyze PIP2 to form PI3. The activation of A_1R also inhibits Ca^{2+} influx and promotes K^+ outflow [96]. Mitogen-activated protein kinases ERK1/2 phosphorylation is induced by A_1R activation

explored to act as antagonists of A_1R. The addition of isopropyl methylamine in the 8-position of adenine (WRC-0571) greatly increases its antagonism and water solubility [33].

Effect of A_1R on monocytes and macrophages

Differentiation

The A_1R plays an important role in the maturation and differentiation of monocytes. The expression level of A_1R on monocytes and macrophages is lower than that of A_2A and A_2B receptors [34, 35]. During bone growth and development, monocytes fuse into multinucleated giant cells and eventually differentiate into osteoclasts [36]. However, the activation of A_2A and A_2B receptors can inhibit the formation of osteoclasts [37]. In contrast, studies have shown that A_1R expressed on monocytes can be activated by changing the TRAF6/TAK1 signaling pathway, which promotes the monocytes by macrophage colony-stimulating factor (M-SCF) and receptor activator of nuclear factor-κB ligand (RANKL) to form multinucleated osteoclasts [38, 39]. After administering rolofylline, an A_1R antagonist, the number of monocytes differentiating into osteoclasts is significantly reduced. In addition, the intensity of this reduction is positively correlated with the increase of rolofylline concentration, suggesting that blocking A_1R can inhibit the differentiation of monocytes into osteoclasts [37, 40]. In accordance

with the in vitro results, studies in vivo also confirm the reduction of osteoclasts in bone resorption and bone loss after ovarian resection by knocking out adenosine A_1 receptor gene ($ADORA_1$) or using DPCPX as an antagonist to block the signal of A_1R [41]. Taken together, the stimulation of A_1R signaling is of great importance for the differentiation of monocytes into osteoclasts. Meanwhile, the A_1 receptor-selective agonist N^5-cyclopentyl adenosine (CPA) promotes, while the A_1 receptor antagonist 8-cyclopentyldipropylxanthine inhibits the formation of giant cells [42]. Landells et al. found that CPA inhibited the proliferation of monocytes in patients with asthma [35]. In summary, most of the results suggest that adenosine is able to promote the proliferation and differentiation of monocytes by activating A_1R.

Inflammatory response

Apart from modulating the differentiation of monocyte, the activation of A_1R can also regulate the cytokine production of monocytes and macrophages. Studies performed by Eudy and Sliva have demonstrated that the A_1R is required for the secretion of adenosine-stimulated interleukin (IL)-10 and IL-1β [43]. Only knocking out $ADORA_1$ in THP-1 macrophages can eliminate the secretion of IL-10 by exogenous adenosine [35]. Macrophages from $ADORA_1$ knockout (KO) mice show increased expression of the pro-inflammatory genes, IL-1, and matrix metalloproteinase (MMP)-12 after immune activation [44]. In CD73-deficient tumors, the stimulation by A_1R leads to significant downregulation of the pro-MI (classically activated macrophage) cytokine granulocyte macrophage colony-stimulating factor (GM-CSF), and of the pro-MII (alternatively activated macrophage) cytokines IL-10 and M-SCF [45]. Notably, both IL-10 and M-CSF are reported to affect the polarization and infiltration of macrophages [46]. Therefore, these results indicate that the exogenous adenosine can regulate the polarization and infiltration of macrophages through A_1R.

It has been shown that both A_1 and A_2 receptor agonists suppress the production of TNF-α by RAW 264.7 macrophage cell line or human monocytes [47]. However, it is still controversial about whether the production of nitric oxide (NO) by macrophages is affected under A_1R activation. Some studies have shown that the selective A_1R agonist CCPA can inhibit LPS-stimulated NO production in RAW264.7 macrophage cell line by activating A_1R [48], while others have reported that the activation of adenosine receptors with LPS stimulation may increase the expression of nitric oxide synthase (NOS) and NO [49, 50]. These controversial results illustrate that the distinct effector functions of monocytes induced by signaling through A_1R alone and through A_1R plus other adenosine receptors. Considering the fact that monocytes express both A_1 and A_2 receptors and these receptors can induce opposite cAMP-related signaling pathways, it is interesting to know whether different concentrations of adenosine have different effects on monocyte function by regulating the cAMP-related signaling pathways.

Notably, the expression of A_1R affects the function and inflammatory responses of macrophages. In a rat stroke model, A_1R is expressed on infiltrating macrophages. The reactivation and proliferation of both microglia and macrophages are reduced when A_1R is activated, which protects rats from ischemic injury after stroke [51]. In patients with ankylosing spondylitis, the mRNA level of A_1R on macrophage is 2.5-fold lower than normal macrophages, suggesting the involvement of A_1R in regulating the inflammatory response of macrophages [52]. In patients with multiple sclerosis, the expression level of A_1R, but not A_2 receptors, decreases in both mononuclear cells and macrophages in brain and blood, implying a reduced ability of adenosine to regulate macrophage-mediated inflammation through A_1R, thereby promoting the progression of multiple sclerosis [53]. In allergic reactions, the expression of A_1R on sputum macrophages has decreased, which also prevents adenosine from regulating inflammation in the airway/sputum, which illustrates the possibility that allergens cause inflammation and weakening of symptoms due to insufficient adenosine to regulate the inflammatory response [54]. Taken together, the decreased expression of A_1R increases the involvement of macrophage in inflammation, illustrating the importance of A_1R signaling in reducing macrophage-mediated inflammatory responses.

Effect of A_1R on neutrophils

Chemotaxis

Neutrophils are affected by the activation of A_1R in many aspects, such as chemotaxis, adhesion, and anti-inflammation. Previous results suggest that the migration of neutrophils to injured tissues is regulated through the involvement of A_2 receptors [55]. Later, by using different agonists, Cronstein et al. have demonstrated that the downstream G protein-linked receptor-mediated mechanism after A_1R activation and the involvement of intact microtubules were the main reasons for increased neutrophil migration [56]. Moreover, the migration of neutrophil is also related to adenosine concentration. When the concentration of adenosine is low, it mainly binds to A_1R to promote the migration of neutrophils to inflammatory tissues rather than healthy tissues. When the concentration of adenosine is high, it mainly binds to A_2 receptors to inhibit the production of toxic oxygen metabolites, thereby inhibiting the effect of activated neutrophils on damaged tissues to avoid further damage [56]. This feature may contribute to the distinct behavior of

adenosine-induced neutrophil chemotaxis in different disease models. For example, during bacterial infection, the migration of neutrophils is inhibited by LPS [57]. However, the activation of A_1R on neutrophils by reception of adenosine signaling can restore their migration ability. This restoration is caused by the downstream activation of p38MAPK pathway [57]. In this scenario, A_1R signaling can benefit neutrophil migration. However, in other cases, A_1R signaling inhibits neutrophil migration/infiltration. In a study of spinal cord adenosine receptors, intrathecal catheter injection of A_1R agonists significantly reduced neutrophil infiltration at sites of dermal inflammation [58]. In addition, neutrophil infiltration is a major feature of ischemia–reperfusion (IR) injury, but various studies have shown that activation of A_1R can alleviate this condition [59–64]. It is demonstrated that the ischemic intestinal injury is reduced by using adenosine to activate A_1R, because the activation of A_1R decreases the infiltration of neutrophils and increases the content of glutathione [59]. In a pulmonary IR model, treatment with A_1R agonist CCPA in mice reduced the expression of inflammatory cytokines and neutrophils infiltration, and neutrophils were absent in A_1R KO mice [60]. Myeloperoxidase (MPO) is considered as an indicator of neutrophil activation and infiltration into alveolar airspaces. The expression level of MPO in bronchoalveolar lavage fluid rises significantly after IR treatment, but decreases significantly in wild-type (WT) mice after activating the A_1R [60, 61]. In kidney and liver IR models, the activation of A_1R can reduce apoptosis, necrosis, neutrophil infiltration, and inflammatory cytokine production [62–64]. In contrast, studies by Forman et al. showed that the blockade of A_1R with A_1R antagonists attenuated myocardial IR injury, primarily by reducing the chemotaxis response of neutrophils to formyl-Met-Leu-Phe [65]. Taken together, these results suggest that the neutrophil chemotaxis in different disease models relies on the signaling of A_1R alone or A_1R along with other adenosine receptors.

Adhesion

Adenosine can promote the adhesion of neutrophils through A_1R, and this regulation may assist in neutrophil chemotaxis [66]. It is different from the occupation of A_2 receptor, which inhibits the adhesion of neutrophils [66]. A study showed that A_1R agonist COPA increased PMA-stimulated neutrophil-endothelial cell adhesion by 30% [67]. After entering the injured tissue, neutrophils can migrate to the vascular endothelium through the adhesion of endothelial cells and can be activated upon immune stimulation [68]. To be specific, this activation is mainly due to the activation of cell surface integrins during cell motility and the further binding of very late antigen 4 (VLA-4) to molecules on vascular endothelial cells [68]. However, Cronstein et al. proved that A_1R was able to increase human neutrophil adhesion to gelatin plates rather than to fibrinogen (a ligand for the beta 2 integrin CD11b/CD18), indicating that the enhancement of neutrophil-to-endothelial cell adhesion by A_1R is not through the traditional neutrophil integrins [66].

Inflammatory response

Activation of the A_1R also affects the inflammatory function of neutrophils. Bhalla et al. demonstrated that aged mice failed to efficiently eliminate *Streptococcus pneumococci* compared with young mice, which could be rescued by providing adenosine to aged mice. They further showed that the inhibition of A_1R impaired the ability of mouse polymorphonuclear cells to kill *Streptococcus pneumococci* [69]. The activation of A_1R using agonists restored the ability of polymorphonuclear cells in aged mice to kill engulfed *Streptococcus pneumoniae*. In addition, A_1R agonists can enhance Fcγ receptor-mediated phagocytosis and superoxide production of neutrophils [70, 71]. Meanwhile, plasma adenosine deaminase can enhance the release of toxic oxygen free radicals in neutrophils and promote the development of inflammation by stimulating the A_1R [72].

In summary, activation of A_1R enhances the inflammatory effect of neutrophils and promotes their migration to the inflammatory sites. However, in many IR models, activation of A_1R can reduce neutrophil infiltration and inflammation, which indicates the role of A_1R in adenosine therapy for relieving inflammation under organ transplantation.

Effect of A_1R on dendritic cells

Chemotaxis

Dendritic cells (DC) are highly differentiated antigen-presenting cells. DC cells are divided into three categories, namely, conventional dendritic cells (cDCs), plasmacytoid dendritic cells (pDCs), and monocyte-derived dendritic cells (moDCs) [73]. To be specific, the cDCs are determined according to their ontogenic development and phenotype. The pDCs can differentiate into DC-like antigen-presenting cells and can stimulate T cell responses, while producing a large amount of type I interferon [74, 75].The moDCs can share phenotypic markers with cDCs as antigen-presenting cells in tissues. It seems that different types of DCs manifest different expression tendency of adenosine receptors. For example, the human immature moDCs express A_1 and A_3 receptors, while immature pDCs express only A_1R [76]. Under physiological conditions, extracellular adenosine (nM to low μM) significantly increases intracellular calcium concentration by activating A_1R, promoting the migration of immature human pDCs to locations with high concentration of adenosine. Activation of A_1R can induce

a stronger calcium influx and actin recombination than the A_3 receptor, leading to the migration of immature moDCs [77]. After treatment with the A_1R agonist CHA, the drive-up effect of pDCs is enhanced, while this phenomenon is not present with the treatment of other adenosine receptor agonists. What is more, the chemotactic effect disappears after the inhibition of A_1R. During the maturation of pDCs stimulated with CD40L, the mRNA level of A_1R is reduced and chemotactic effect by adenosine is not found [76]. This suggests that A_1R is able to induce adenosine-dependent chemotaxis in immature pDCs, which may cause immature pDCs to migrate to the sites with high concentrations of adenosine, where they can induce an immune response and differentiate into mature pDCs.

Differentiation

moDCs are mainly differentiated from $CD14^+$ monocytes in peripheral blood in vitro. Under the stimulation of GM-CSF and IL-4, the monocytes will differentiate into immature $CD14^+CD1a^+$ MoDCs, and then moDCs will further maturate with the stimulation of LPS [77]. The mRNA level of A_1R on immature moDCs is higher than that on mature moDCs. However, when stimulated by LPS, the expression level of A2A and A2B receptor increases on DCs, while the expression level of A_1R decreases or is absent [34, 77]. Whether A_1R affects the differentiation of DCs is controversial. Novitskiy et al. showed that the activation of A_1R did not affect the differentiation of DCs, while Panther et al. showed that the increased expression of A_1R on moDCs and differentiation of immature moDCs were significantly correlated. Interestingly, Yasui et al. found that the activation of A_1 and A_2A receptors could alleviate theophylline, a substance that inhibits DCs differentiation, and then inhibit the monocyte differentiation into DCs, suggesting that the A_1R may cooperate with A_2A receptor in the differentiation and survival of DCs [78].

Inflammatory response

DCs show high sensitivity to adenosine in the inflammatory response. It has been reported that adenosine mainly blocks the inherent response of DCs through the A_1R signaling, then reduces the expression of inflammatory factors, including IL-2 and TNF-α, and finally inhibits the effect of DC-mediated inflammation [79]. In addition, adenosine exerts a strong inhibitory effect on vesicular MHC-I cross-presentation in resting DCs through A_1R [80], which may affect the immunomodulation in the surrounding T cell pools.

A_1R can sense low level of adenosine through its higher affinity for adenosine under physiological conditions, thereby regulating the migration and differentiation of immature monocytes and the expression of DC-secreted cytokines. In summary, A_1R might be a potential activator for modulating immature DCs.

Effect of A_1R on microglia

Microglia are main immune surveillance cells in brain, responding early to injury. After brain injury, microglia deform and metastasize to the damaged site, playing an important role in the neuroinflammatory responses [81, 82]. The mechanism of microglia migration is that a large amount of ATP and ADP are generated at the injury site, and the Gi/o-coupled P2Y receptors of microglia are activated to generate chemotaxis [83]. Compared with ATP, adenosine mainly affects the activation of microglia through A_1R.

A_1R is widely expressed on microglia, and the proportion of A_1R expressed on mouse microglia is more than 97% [84]. Primary-cultured microglia of rat highly express A_1R and A_3 receptors and lowly express A_2A receptor [85]. After nerve injury in the brain, the microglia migrate to the damaged site, secrete a variety of cytokines, phagocytose cell debris, and promote tissue repair and nerve regeneration [86]. It has been shown that activated A_1R by agonists can inhibit the microglia inflammatory response caused by TNF-α, IL-1β, and IFN-γ [87]. In multiple sclerosis model, increased expression of pro-inflammatory genes, decreased expression of anti-inflammatory genes, and enhanced activation of microglia/macrophages are observed in the spinal cord of $ADORA_1$ knockout mice compared to WT mice [44]. Moreover, mice with the $ADORA_1$ gene knocked out are more pronounced in demyelination deterioration and axonal damage [44]. Taken together, these results may shed light on future treatments for neuroinflammation-related diseases, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis [87].

In the central nervous system, the activation of A_1R is primarily responsible for negative excitatory transmission, while the activation of A_2A receptor promotes synaptic plasticity [88]. The activation of A_1R has an inhibitory effect on microglia in brain trauma mice [89]. To be specific, CX3CL1 mediates neuroprotective effects in different brain injury models through its inhibitory activity against microglia, but this regulation requires the presence and activation of A_1R [90, 91]. Moreover, these effects are eliminated in mice with A_1R deletion or after treatment with A_1R antagonists [90]. Selective stimulation of A_1R inhibits morphological activation of microglia, and microglia treated with A_1R agonists have reduced ability to promote nociceptive neurons [84]. Chronic treatment with another A_1R agonist, 5′-chloro-5′-deoxy-(±)-ENBA, is able to reduce neuropathic pain in mice by reducing activated microglia [92]. However, simultaneous stimulation of adenosine A_1 and A_2 receptors can promote the proliferation of microglia [93]. In summary,

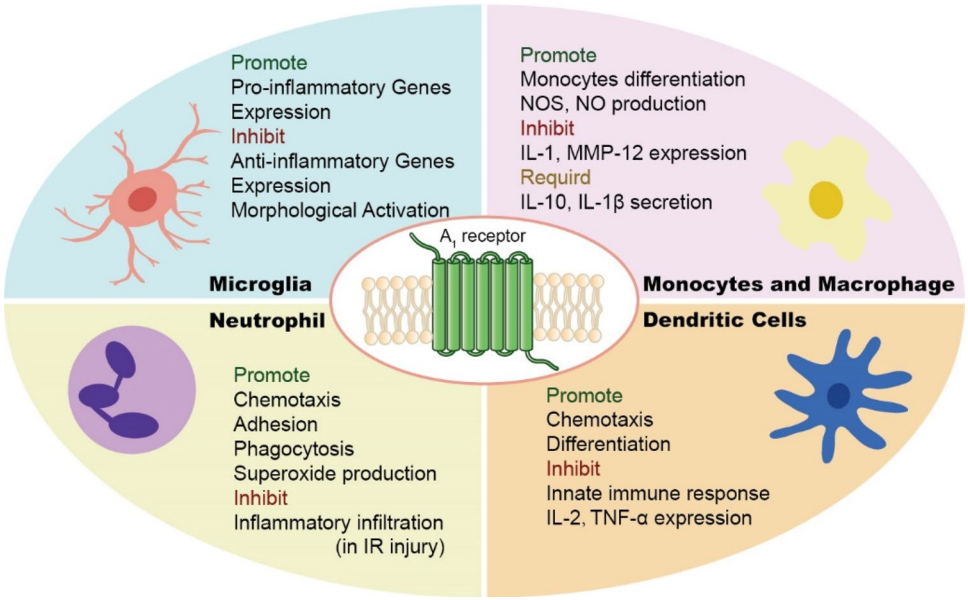

Fig. 2 Schematic diagram illustrating the role of A_1R on different types of immune cells. Activation of A_1R signaling pathway by adenosine can affect many immune cells, including monocytes, macrophage, dendritic cells, neutrophils, and microglia, resulting in various biological outcomes

A_1R mainly reduces inflammatory response by inhibiting the activity of microglia, regulates the immune balance at the brain injury site, and prevents excessive immune response.

Conclusion

A_1R, the receptor with the highest affinity with adenosine, has been shown to play an important role in inflammation and disease. The activation of A_1R can promote the differentiation and migration of some immune cells, as well as regulate the inflammatory response of immune cells after using A_1R activators (Fig. 2). This phenomenon suggests that A_1R may play a role in regulating the balance of immune cell activity in diseases, thereby preventing excessive immune responses at the site of inflammation. Apart from the above mentioned cell types, in vitro study also shows that activated B cells are able to express A_1R [94], and the A_1R-mediated autocrine signaling can regulate the function of B cells [95]. In conclusion, the activation of A_1R plays an important role in the growth and function of different types of immune cells, which may provide guidance for clinical application of agonists and antagonists of A_1R in the future.

Author contribution LZ drafted the main body of this manuscript and drew the figures. QP modified the manuscript. XZ takes primary responsibility for this paper as the corresponding author. All authors contributed to the article and approved the submitted version.

Funding This work was supported by the National Natural Science Foundation of China (31870899 and 32070899 to X.Z., 82103304 to Q.P.) and the Independent Task of State Key Laboratory for Diagnosis and Treatment of Infectious Diseases (2022zz07 to Q.P.).

Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

References

1. Jacobson KA, Gao ZG. Adenosine receptors as therapeutic targets. Nat Rev Drug Discov. 2006;5:247–64. https://doi.org/10.1038/nrd1983.
2. Stagg J, Smyth MJ. Extracellular adenosine triphosphate and adenosine in cancer. Oncogene. 2010;29:5346–58. https://doi.org/10.1038/onc.2010.292.
3. Fredholm BB, IJzerman AP, Jacobson KA, Linden J, Müller CE. International union of basic and clinical pharmacology. LXXXI. Nomenclature and classification of adenosine receptors—an update. Pharmacol Rev. 2011;63:1–34. https://doi.org/10.1124/pr.110.003285.
4. Allard B, Allard D, Buisseret L, Stagg J. The adenosine pathway in immuno-oncology. Nat Rev Clin Oncol. 2020;17:611–29. https://doi.org/10.1038/s41571-020-0382-2.
5. Borea PA, Gessi S, Merighi S, Vincenzi F, Varani K. Pharmacology of adenosine receptors: the state of the art. Physiol Rev. 2018;98:1591–625. https://doi.org/10.1152/physrev.00049.2017.
6. Borea PA, Gessi S, Merighi S, Vincenzi F, Varani K. Pathological overproduction: the bad side of adenosine. Br J Pharmacol. 2017;174:1945–60. https://doi.org/10.1111/bph.13763.
7. Franco R, Cordomí A, Llinas del Torrent C, Lillo A, Serrano-Marín J, Navarro G, Pardo L. Structure and function of adenosine receptor heteromers. Cell Mol Life Sci. 2021;78:3957–68. https://doi.org/10.1007/s00018-021-03761-6.
8. Chen JF, Eltzschig HK, Fredholm BB. Adenosine receptors as drug targets-what are the challenges? Nat Rev Drug Discov. 2013;12:265–86. https://doi.org/10.1038/nrd3955.
9. Modlinger PS, Welch WJ. Adenosine A1 receptor antagonists and the kidney. Curr Opin Nephrol Hypertens. 2003;12:497–502. https://doi.org/10.1097/00041552-200309000-00003.

10. Nadeem A, Obiefuna PCM, Wilson CN, Mustafa SJ. Adenosine A1 receptor antagonist versus montelukast on airway reactivity and inflammation. Eur J Pharmacol. 2006;551:116–24. https://doi.org/10.1016/j.ejphar.2006.08.059.
11. Kashfi S, Ghaedi K, Baharvand H, Nasr-Esfahani MH, Javan M. A1 adenosine receptor activation modulates central nervous system development and repair. Mol Neurobiol. 2017;54:8128–39. https://doi.org/10.1007/s12035-016-0292-6.
12. Liu YJ, Chen J, Li X, Zhou X, Hu YM, Chu SF, Peng Y, Chen NH. Research progress on adenosine in central nervous system diseases. CNS Neurosci Ther. 2019;25:899–910. https://doi.org/10.1111/cns.13190.
13. Bours MJL, Swennen ELR, Di Virgilio F, Cronstein BN, Dagnelie PC. Adenosine 5'-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. Pharmacol Ther. 2006;112:358–404. https://doi.org/10.1016/j.pharmthera.2005.04.013.
14. Ren H, Stiles GL. Characterization of the human A1 adenosine receptor gene. Evidence for alternative splicing. J Biol Chem. 1994;269:3104–10. https://doi.org/10.1016/s0021-9258(17)42054-0.
15. Glukhova A, Thal DM, Nguyen AT, Vecchio EA, Jörg M, Scammells PJ, May LT, Sexton PM, Christopoulos A. Structure of the adenosine A1 receptor reveals the basis for subtype selectivity. Cell. 2017;168:867-877.e13. https://doi.org/10.1016/j.cell.2017.01.042.
16. Jespers W, Schiedel AC, Heitman LH, Cooke RM, Kleene L, van Westen GJP, Gloriam DE, Müller CE, Sotelo E, Gutiérrez-de-Terán H. Structural mapping of adenosine receptor mutations: ligand binding and signaling mechanisms. Trends Pharmacol Sci. 2018;39:75–89. https://doi.org/10.1016/j.tips.2017.11.001.
17. Klinger M, Freissmuth M, Nanoff C. Adenosine receptors: G protein-mediated signalling and the role of accessory proteins. Cell Signal. 2002;14:99–108. https://doi.org/10.1016/S0898-6568(01)00235-2.
18. Effendi WI, Nagano T, Kobayashi K, Nishimura Y. Focusing on adenosine receptors as a potential targeted therapy in human diseases. Cells. 2020;9:1–36. https://doi.org/10.3390/cells9030785.
19. Defer N, Best-belpomme M, Hanoune J, Cre F, Best-belpomme M, Hanoune J, Sutherland E. Tissue specificity and physiological relevance of various isoforms of adenylyl cyclase. Am J Physiol Ren Physiol. 2000;279:400–16. https://doi.org/10.1152/ajprenal.2000.279.3.F400.
20. Liu AMF, Wong YH. G16-mediated activation of nuclear factor κB by the adenosine A1 receptor involves c-Src, protein kinase C, and ERK signaling*. J Biol Chem. 2004;279:53196–204. https://doi.org/10.1074/jbc.M410196200.
21. Schulte G, Fredholm BB. Human adenosine A1, A(2A), A(2B), and A3 receptors expressed in Chinese hamster ovary cells all mediate the phosphorylation of extracellular-regulated kinase 1/2. Mol Pharmacol. 2000;58:477–82. https://doi.org/10.1124/mol.58.3.477.
22. Faure M, Voyno-Yasenetskaya TA, Bourne HR. cAMP and βγ subunits of heterotrimeric G proteins stimulate the mitogen-activated protein kinase pathway in COS-7 cells. J Biol Chem. 1994;269:7851–4. https://doi.org/10.1016/s0021-9258(17)37127-2.
23. Schulte G, Fredholm BB. Signalling from adenosine receptors to mitogen-activated protein kinases. Cell Signal. 2003;15:813–27. https://doi.org/10.1016/S0898-6568(03)00058-5.
24. Deb PK, Deka S, Borah P, Abed SN, Klotz K-N. Medicinal chemistry and therapeutic potential of agonists, antagonists and allosteric modulators of A1 adenosine receptor: current status and perspectives. Curr Pharm Des. 2019;25:2697–715. https://doi.org/10.2174/1381612825666190716100509.
25. Yan L, Burbiel JC, Maaß A, Müller CE. Adenosine receptor agonists: from basic medicinal chemistry to clinical development. Expert Opin Emerg Drugs. 2003;8:537–76. https://doi.org/10.1517/14728214.8.2.537.
26. Klotz KN. Adenosine receptors and their ligands. Naunyn Schmiedebergs Arch Pharmacol. 2000;362:382–91. https://doi.org/10.1007/s002100000315.
27. Tosh DK, Phan K, Gao ZG, Gakh AA, Xu F, Deflorian F, Abagyan R, Stevens RC, Jacobson KA, Katritch V. Optimization of adenosine 5'-carboxamide derivatives as adenosine receptor agonists using structure-based ligand design and fragment screening. J Med Chem. 2012;55:4297–308. https://doi.org/10.1021/jm300095s.
28. Bogatko K, Poleszak E, Szopa A, Wyska E, Wlaź P, Świąder K, Wlaź A, Doboszewska U, Rojek K, Serefko A. The influence of selective A1 and A2A receptor antagonists on the antidepressant-like activity of moclobemide, venlafaxine and bupropion in mice. J Pharm Pharmacol. 2018;70:1200–8. https://doi.org/10.1111/jphp.12954.
29. Müller CE, Jacobson KA. Recent developments in adenosine receptor ligands and their potential as novel drugs. Biochim Biophys Acta - Biomembr. 1808;2011:1290–308. https://doi.org/10.1016/j.bbamem.2010.12.017.
30. Hocher B. Adenosine A1 receptor antagonists in clinical research and development. Kidney Int. 2010;78:438–45. https://doi.org/10.1038/ki.2010.204.
31. Moro S, Gao ZG, Jacobson KA, Spalluto G. Progress in the pursuit of therapeutic adenosine receptor antagonists. Med Res Rev. 2006;26:131–59. https://doi.org/10.1002/med.20048.
32. Scheiff AB, Yerande SG, El-Tayeb A, Li W, Inamdar GS, Vasu KK, Sudarsanam V, Müller CE. 2-Amino-5-benzoyl-4-phenylthiazoles: Development of potent and selective adenosine A1 receptor antagonists. Bioorganic Med Chem. 2010;18:2195–203. https://doi.org/10.1016/j.bmc.2010.01.072.
33. Muller CE. A1-adenosine receptor antagonists. Expert Opin Ther Pat. 1997;7:419–40. https://doi.org/10.1517/13543776.7.5.419.
34. Novitskiy SV, Ryzhov S, Zaynagetdinov R, Goldstein AE, Huang Y, Tikhomirov OY, Blackburn MR, Biaggioni I, Carbone DP, Feoktistov I, Dikov MM. Adenosine receptors in regulation of dendritic cell differentiation and function. Blood. 2008;112:1822–31. https://doi.org/10.1182/blood-2008-02-136325.
35. Haskó G, Pacher P. Regulation of macrophage function by adenosine. Arterioscler Thromb Vasc Biol. 2012;32:865–9. https://doi.org/10.1161/ATVBAHA.111.226852.
36. Boyce BF. Advances in the regulation of osteoclasts and osteoclast functions. J Dent Res. 2013;92:860–7. https://doi.org/10.1177/0022034513500306.
37. He W, Mazumder A, Wilder T, Cronstein BN. Adenosine regulates bone metabolism via A1, A2A, and A2B receptors in bone marrow cells from normal humans and patients with multiple myeloma. FASEB J. 2013;27:3446–54. https://doi.org/10.1096/fj.13-231233.
38. He W, Cronstein BN. Adenosine A1 receptor regulates osteoclast formation by altering TRAF6/TAK1 signaling. Purinergic Signal. 2012;8:327–37. https://doi.org/10.1007/s11302-012-9292-9.
39. Kara FM, Chitu V, Sloane J, Axelrod M, Fredholm BB, Stanley ER, Cronstein BN. Adenosine A1 receptors (A1Rs) play a critical role in osteoclast formation and function. FASEB J. 2010;24:2325–33. https://doi.org/10.1096/fj.09-147447.
40. He W, Wilder T, Cronstein BN. Rolofylline, an adenosine A1 receptor antagonist, inhibits osteoclast differentiation as an inverse agonist. Br J Pharmacol. 2013;170:1167–76. https://doi.org/10.1111/bph.12342.
41. Kara FM, Doty SB, Boskey A, Goldring S, Zaidi M, Fredholm BB, Cronstein BN. Adenosine A1 receptors regulate bone resorption in mice: Adenosine A1 receptor blockade or deletion

increases bone density and prevents ovariectomy-induced bone loss in adenosine A1 receptor-knockout mice. Arthritis Rheum. 2010;62:534–41. https://doi.org/10.1002/art.27219.
42. Merrill JT, Shen C, Schreibman D, Coffey D, Zakharenko O, Fisher R, Lahita RG, Salmon J, Cronstein BN. Adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes: a mechanism for methotrexate-induced nodulosis in rheumatoid arthritis. Arthritis Rheum. 1997;40:1308–15. https://doi.org/10.1002/art.16.
43. Eudy BJ, da Silva RP. Systematic deletion of adenosine receptors reveals novel roles in inflammation and pyroptosis in THP-1 macrophages. Mol Immunol. 2021;132:1–7. https://doi.org/10.1016/j.molimm.2021.01.018.
44. Tsutsui S, Schnermann J, Noorbakhsh F, Henry S, Yong VW, Winston BW, Warren K, Power C. A1 adenosine receptor upregulation and activation attenuates neuroinflammation and demyelination in a model of multiple sclerosis. J Neurosci. 2004;24:1521–9. https://doi.org/10.1523/JNEUROSCI.4271-03.2004.
45. Koszałka P, Gołuńska M, Urban A, Stasiłojć G, Stanisławowski M, Majewski M, Składanowski AC, Bigda J. Specific activation of A3, A2a and A1 adenosine receptors in CD73-knockout mice affects B16F10 melanoma growth, neovascularization, angiogenesis and macrophage infiltration. PLoS ONE. 2016;11:1–16. https://doi.org/10.1371/journal.pone.0151420.
46. Eljaszewicz A, Wiese M, Helmin-Basa A, Jankowski M, Gackowska L, Kubiszewska I, Kaszewski W, Michalkiewicz J, Zegarski W. Collaborating with the enemy: function of macrophages in the development of neoplastic disease. Mediators Inflamm. 2013. https://doi.org/10.1155/2013/831387.
47. Le Vraux V, Chen YL, Masson I, De Sousa M, Giroud JP, Florentin I, Chauvelot-Moachon L. Inhibition of human monocyte Tnf production by adenosine receptor agonists. Life Sci. 1993;52:1917–24. https://doi.org/10.1016/0024-3205(93)90632-d.
48. Haskó G, Szabó C, Németh ZH, Kvetan V, Pastores SM, Vizi ES. Adenosine receptor agonists differentially regulate IL-10, TNF-alpha, and nitric oxide production in RAW 264.7 macrophages and in endotoxemic mice. J Immunol. 1996;157:4634–40.
49. Hona W-M, Moochhala S, Khoo H-E. Adenosine and its receptor agonists potentiate nitric oxide synthase expression induced by lipopolysaccharide in RAW 264.7 murine macrophages. Life Sci. 1997;60:1327–35. https://doi.org/10.1016/s0024-3205(97)00078-7.
50. Zídek Z, Kmoníčková E, Holý A. Involvement of adenosine A 1 receptors in upregulation of nitric oxide by acyclic nucleotide analogues. Eur J Pharmacol. 2004;501:79–86. https://doi.org/10.1016/j.ejphar.2004.08.031.
51. Joya A, Ardaya M, Montilla A, Garbizu M, Plaza-García S, Gómez-Vallejo V, Padro D, Gutiérrez JJ, Rios X, Ramos-Cabrer P, Cossío U, Pulagam KR, Higuchi M, Domercq M, Cavaliere F, Matute C, Llop J, Martín A. In vivo multimodal imaging of adenosine A1 receptors in neuroinflammation after experimental stroke. Theranostics. 2020;11:410–25. https://doi.org/10.7150/thno.51046.
52. Akhtari M, Zargar SJ, Mahmoudi M, Vojdanian M, Rezaeimanesh A, Jamshidi A. Ankylosing spondylitis monocyte-derived macrophages express increased level of A2A adenosine receptor and decreased level of ectonucleoside triphosphate diphosphohydrolase-1 (CD39), A1 and A2B adenosine receptors. Clin Rheumatol. 2018;37:1589–95. https://doi.org/10.1007/s10067-018-4055-9.
53. Johnston JB, Silva C, Gonzalez G, Holden J, Warren KG, Metz LM, Power C. Diminished adenosine A1 receptor expression on macrophages in brain and blood of patients with multiple sclerosis. Ann Neurol. 2001;49:650–8. https://doi.org/10.1002/ana.1007.
54. Versluis M, Van Den Berge M, Timens W, Luijk B, Rutgers B, Lammers JWJ, Postma DS, Hylkema MN. Allergen inhalation decreases adenosine receptor expression in sputum and blood of asthma patients. Allergy. 2008;63:1186–94. https://doi.org/10.1111/j.1398-9995.2008.01735.x.
55. Roberta Rose F, Hirschhorn RE, Weissmann G, Cronstein BN. Adenosine promotes neutrophil chemotaxis. J Exp Med. 1988;167:1186–94. https://doi.org/10.1084/jem.167.3.1186.
56. Cronstein BN, Daguma L, Nichols D, Hutchison AJ, Williams M. The adenosine/neutrophil paradox resolved: human neutrophils possess both A1 and A2 receptors that promote chemotaxis and inhibit O-2 generation, respectively. J Clin Invest. 1990;85:1150–7. https://doi.org/10.1172/JCI114547.
57. Xu X, Zheng S, Xiong Y, Wang X, Qin W, Zhang H, Sun B. Adenosine effectively restores endotoxin-induced inhibition of human neutrophil chemotaxis via A1 receptor-p38 pathway. Inflamm Res. 2017;66:353–64. https://doi.org/10.1007/s00011-016-1021-3.
58. Bong GW, Rosengren S, Firestein GS. Spinal cord adenosine receptor stimulation in rats inhibits peripheral neutrophil accumulation: the Role of N-methyl-D-aspartate receptors. J Clin Invest. 1996;98:2779–85. https://doi.org/10.1172/JCI119104.
59. Ozacmak VH, Sayan H. Pretreatment with adenosine and adenosine A1 receptor agonist protects againts intestinal ischemia-reperfusion injury in rat. World J Gastroenterol. 2007;13:538–47. https://doi.org/10.3748/wjg.v13.i4.538.
60. Fernandez LG, Sharma AK, LaPar DJ, Kron IL, Laubach VE. Adenosine A1 receptor activation attenuates lung ischemia-reperfusion injury. J Thorac Cardiovasc Surg. 2013;145:1654–9. https://doi.org/10.1016/j.jtcvs.2013.01.006.Adenosine.
61. Gazoni LM, Walters DM, Unger EB, Linden J, Kron IL, Laubach VE. Activation of A1, A2A, or A3 adenosine receptors attenuates lung ischemia-reperfusion injury. J Thorac Cardiovasc Surg. 2010;140:440–6. https://doi.org/10.1016/j.jtcvs.2010.03.002.
62. Park SW, Kim JY, Ham A, Brown KM, Kim M, D'Agati VD, Lee HT. A1 adenosine receptor allosteric enhancer PD-81723 protects against renal ischemia-reperfusion injury. Am J Physiol-Ren Physiol. 2012. https://doi.org/10.1152/ajprenal.00157.2012.
63. Lee HT, Xu H, Nasr SH, Schnermann J, Emala CW. A1 adenosine receptor knockout mice exhibit increased renal injury following ischemia and reperfusion. Am J Physiol - Ren Physiol. 2004;286:298–306. https://doi.org/10.1152/ajprenal.00185.2003.
64. Kim J, Kim M, Song JH, Thomas Lee H. Endogenous A1 adenosine receptors protect against hepatic ischemia reperfusion injury in mice. Liver Transplant. 2007;14:845–54. https://doi.org/10.1002/lt.21432.
65. Forman MB, Vitola JV, Velasco CE, Murray JJ, Dubey RK, Jackson EK. Sustained reduction in myocardial reperfusion injury with an adenosine receptor antagonist: possible role of the neutrophil chemoattractant response. J Pharmacol Exp Ther. 2000;292:929–38.
66. Cronstein BN, Levin RI, Philips M, Hirschhorn R, Abramson SB, Weissmann G. Neutrophil adherence to endothelium is enhanced via adenosine A1 receptors and inhibited via adenosine A2 receptors. J Immunol. 1992;148:2201–6.
67. Felsch A, Stöcker K, Borchard U. Phorbol ester-stimulated adherence of neutrophils to endothelial cells is reduced by adenosine A2 receptor agonists. J Immunol. 1995;155:333–8.
68. Barletta KE, Ley K, Mehrad B. Regulation of neutrophil function by adenosine. Arterioscler Thromb Vasc Biol. 2012;32:856–64. https://doi.org/10.1161/ATVBAHA.111.226845.
69. Bhalla M, Simmons SR, Abamonte A, Herring SE, Roggensack SE, Bou Ghanem EN. Extracellular adenosine signaling reverses the age-driven decline in the ability of neutrophils to kill Streptococcus pneumoniae. Aging Cell. 2020;19:1–12. https://doi.org/10.1111/acel.13218.

70. Salmon JE, Cronstein BN. Fc gamma receptor-mediated functions in neutrophils are modulated by adenosine receptor occupancy. A1 receptors are stimulatory and A2 receptors are inhibitory. J Immunol. 1990;145:2235–40.
71. Zalavary S, Stendahl O. The role of cyclic AMP, calcium and filamentous actin in adenosine modulation of Fc receptor-mediated phagocytosis in human neutrophils. Biochim Biophys Acta. 1994;1222:249–56. https://doi.org/10.1016/0167-4889(94)90176-7.
72. Kälvegren H, Fridfeldt J, Bengtsson T. The role of plasma adenosine deaminase in chemoattractant-stimulated oxygen radical production in neutrophils. Eur J Cell Biol. 2010;89:462–7. https://doi.org/10.1016/j.ejcb.2009.12.004.
73. Gardner A, de Mingo Pulido Á, Ruffell B. Dendritic cells and their role in immunotherapy. Front Immunol. 2020;11:1–14. https://doi.org/10.3389/fimmu.2020.00924.
74. Reizis B. Plasmacytoid dendritic cells: development, regulation, and function. Immunity. 2019;50:37–50. https://doi.org/10.1016/j.immuni.2018.12.027.
75. Zhou B, Lawrence T, Liang Y. The role of plasmacytoid dendritic cells in cancers. Front Immunol. 2021;12:1–10. https://doi.org/10.3389/fimmu.2021.749190.
76. Schnurr M, Toy T, Shin A, Hartmann G, Rothenfusser S, Soellner J, Davis ID, Cebon J, Maraskovsky E. Role of adenosine receptors in regulating chemotaxis and cytokine production of plasmacytoid dendritic cells. Blood. 2004;103:1391–7. https://doi.org/10.1182/blood-2003-06-1959.
77. Panther E, Idzko M, Herouy Y, Rheinen H, Gebicke-HAERTER PJ, Mrowietz U, Dichmann S, Norgauer J. Expression and function of adenosine receptors in human dendritic cells. FASEB J. 2001;15:1963–70. https://doi.org/10.1096/fj.01-0169com.
78. Yasui K, Kondo Y, Wada T, Yashiro M, Tsuge M, Morishima T. Theophylline inhibits the differentiation of human monocyte into dendritic cell potentially via adenosine receptor antagonism. Clin Exp Allergy. 2009;39:1857–65. https://doi.org/10.1111/j.1365-2222.2009.03365.x.
79. Desrosiers MD, Cembrola KM, Fakir MJ, Stephens LA, Jama FM, Shameli A, Mehal WZ, Santamaria P, Shi Y. Adenosine deamination sustains dendritic cell activation in inflammation. J Immunol. 2007;179:1884–92. https://doi.org/10.4049/jimmunol.179.3.1884.
80. Chen L, Fredholm BB, Jondal M. Adenosine, through the A1 receptor, inhibits vesicular MHC class I cross-presentation by resting DC. Mol Immunol. 2008;45:2247–54. https://doi.org/10.1016/j.molimm.2007.11.016.
81. Prinz M, Jung S, Priller J. Microglia biology: one century of evolving concepts. Cell. 2019;179:292–311. https://doi.org/10.1016/j.cell.2019.08.053.
82. Ohsawa K, Kohsaka S. Dynamic motility of microglia: purinergic modulation of microglial movement in the normal and pathological brain. Glia. 2011;59:1793–9. https://doi.org/10.1002/glia.21238.
83. Nayak D, Roth TL, McGavern DB. Microglia development and function. Annu Rev Immunol. 2014;32:367–402. https://doi.org/10.1146/annurev-immunol-032713-120240.
84. Luongo L, Guida F, Imperatore R, Napolitano F, Gatta L, Cristino L, Giordano C, Siniscalco D, Di Marzo V, Bellini G, Petrelli R, Cappellacci L, Usiello A, de Novellis V, Rossi F, Maione S. The A1 adenosine receptor as a new player in microglia physiology. Glia. 2014;62:122–32. https://doi.org/10.1002/glia.22592.
85. Ohsawa K, Sanagi T, Nakamura Y, Suzuki E, Inoue K, Kohsaka S. Adenosine A3 receptor is involved in ADP-induced microglial process extension and migration. J Neurochem. 2012;121:217–27. https://doi.org/10.1111/j.1471-4159.2012.07693.x.
86. Wolf SA, Boddeke HWGM, Kettenmann H. Microglia in physiology and disease. Annu Rev Physiol. 2017;79:619–43. https://doi.org/10.1146/annurev-physiol-022516-034406.
87. Marucci G, Dal Ben D, Lambertucci C, Navia AM, Spinaci A, Volpini R, Buccioni M. Combined therapy of A1AR agonists and A2AAR antagonists in neuroinflammation. Molecules. 2021;26:1188. https://doi.org/10.3390/molecules26041188.
88. Gomes CV, Kaster MP, Tomé AR, Agostinho PM, Cunha RA. Adenosine receptors and brain diseases: neuroprotection and neurodegeneration. Biochim Biophys Acta - Biomembr. 1808;2011:1380–99. https://doi.org/10.1016/j.bbamem.2010.12.001.
89. Haselkorn ML, Shellington DK, Jackson EK, Vagni VA, Janesko-Feldman K, Dubey RK, Gillespie DG, Cheng D, Bell MJ, Jenkins LW, Homanics GE, Schnermann J, Kochanek PM. Adenosine A1 receptor activation as a brake on the microglial response after experimental traumatic brain injury in mice. J Neurotrauma. 2010;27:901–10. https://doi.org/10.1089/neu.2009.1075.
90. Cipriani R, Villa P, Chece G, Lauro C, Paladini A, Micotti E, Perego C, de Simoni MG, Fredholm BB, Eusebi F, Limatola C. CX3CL1 is neuroprotective in permanent focal cerebral ischemia in rodents. J Neurosci. 2011;31:16327–35. https://doi.org/10.1523/JNEUROSCI.3611-11.2011.
91. Catalano M, Lauro C, Cipriani R, Chece G, Ponzetta A, Di Angelantonio S, Ragozzino D, Limatola C. CX3CL1 protects neurons against excitotoxicity enhancing GLT-1 activity on astrocytes. J Neuroimmunol. 2013;263:75–82. https://doi.org/10.1016/j.jneuroim.2013.07.020.
92. Luongo L, Petrelli R, Gatta L, Giordano C, Guida F, Vita P, Franchetti P, Grifantini M, De Novellis V, Cappellacci L, Maione S. 5'-Chloro-5'-deoxy-(±)-ENBA, a potent and selective adenosine A1 receptor agonist, alleviates neuropathic pain in mice through functional glial and microglial changes without affecting motor or cardiovascular functions. Molecules. 2012;17:13712–26. https://doi.org/10.3390/molecules171213712.
93. Gebicke-Haerter PJ, Christoffel F, Timmer J, Northoff H, Berger M, Van Calker D. Both adenosine A1- and A2-receptors are required to stimulate microglial proliferation. Neurochem Int. 1996;29:37–42. https://doi.org/10.1016/0197-0186(95)00137-9.
94. Saze Z, Schuler PJ, Hong CS, Cheng D, Jackson EK, Whiteside TL. Adenosine production by human B cells and B cell-mediated suppression of activated T cells. Blood. 2013;122:9–18. https://doi.org/10.1182/blood-2013-02-482406.
95. Figueiró F, Muller L, Funk S, Jackson EK, Battastini AMO, Whiteside TL. Phenotypic and functional characteristics of CD39high human regulatory B cells (Breg). Oncoimmunology. 2016;5:e1082703. https://doi.org/10.1080/2162402X.2015.1082703.
96. Mei HF, Poonit N, Zhang YC, Ye CY, Cai HL, Yu CY, Zhou YH, Bei Wu B, Cai J, Cai XH. Activating adenosine A1 receptor accelerates PC12 cell injury via ADORA1/PKC/KATP pathway after intermittent hypoxia exposure. Mol Cell Biochem. 2018;446:161–70. https://doi.org/10.1007/s11010-018-3283-2.