Immunology Letters 205 (2019) 9–15

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Adenosine signaling and the immune system: When a lot could be too much

Luca Antonioli[a,c,*], Matteo Fornai[a], Corrado Blandizzi[a], Pál Pacher[b], György Haskó[c]

[a] Department of Clinical and Experimental Medicine, University of Pisa, 56126, Pisa, Italy
[b] National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, 20892, USA
[c] Department of Anesthesiology, Columbia University, New York, NY, 10032, USA

ARTICLE INFO

Keywords:
Adenosine
Adenosine receptors
Immune cells
Inflammation
Cancer

ABSTRACT

Adenosine is increasingly recognized as a key mediator of the immune response. Signals delivered by extracellular adenosine are detected and transduced by G-protein-coupled cell-surface receptors, classified into four subtypes: A_1, A_{2A}, A_{2B} and A_3. These receptors, expressed virtually on all immune cells, modulate all aspects of immune/inflammatory responses. These immunoregulatory effects, which are mostly anti-inflammatory, contribute to the general tissue protective effects of adenosine and its receptors. In some instances, however, the effect of adenosine on the immune system is deleterious, as prolonged adenosine signaling can hinder anti-tumor and antibacterial immunity, thereby promoting cancer development and progression and sepsis, respectively.

1. Introduction

Inflammatory response is the result of a complex interaction between immune cells and several soluble factors, aimed at protecting the host from invasion by microorganisms and eliminate debris at sites of tissue injury in order to maintain tissue homeostasis [1,2]. However, an exuberant immune/inflammatory response, not adequately balanced by endogenous mechanisms of homeostatic control, can lead to persistent and abnormal forms of collateral tissue damage [1,2].

In this regard, adenosine, a purine nucleoside that accumulates in the extracellular space at sites of tissue damaged is a pivotal player in the modulation of immune responses and in restraining inflammatory tissue damage [1]. Indeed, over the years, a number of studies have identified extracellular adenosine as a 'retaliatory metabolite', which indicates that it is generated as a result of cellular injury or stress, and that through interacting with specific G protein-coupled receptors, it regulates the immune/inflammatory cell functions[3–5] to protect tissues from injury and stress [5–11]. However, chronic exposure to adenosine may under some conditions may be harmful, as adenosine can create an immunosuppressed niche, which is necessary for the onset and development of neoplasia and infection [12–16] [17].

Pioneering studies on the immunomodulatory role of adenosine date back to the early '70 s of last century (Fig. 1), when the critical role of this nucleoside in shaping the development and the activity of several immune cell populations was first established [18–22]. This then lead to the identication of a direct correlation between defective adenosine metabolism and the onset of adenosine deaminase deficiency, a congenital, severe, combined immunodeficiency (ADA-SCID) [23–26]. Subsequently, seminal studies demonstrated a role for adenosine in human lymphocyte maturation and proliferation [21,27] [28–32] as well as in the regulation of lymphocyte activity [22,33,34]. In this context, consistent data also supported the involvement of the adenosine system in mediating the pharmacological effects of several anti-inflammatory and immunomodulating drugs (i.e. methotrexate, salicylates) that are widely used in the clinical practice to manage chronic inflammatory disorders [8,35–43]. The idea of targeting the adenosine system was then advanced by introducing specific novel pharmacological entities for the management of several immune-mediated disorders [44,45]. At present, some of these drugs are under preclinical evaluation with encouraging results [44], while others have already entered the phase of clinical development for the treatment of rheumatoid arthritis [46] or as novel anticancer immunotherapies [12,47].

2. The adenosine machinery: enzymes, transporters and receptors

Under physiological conditions, intracellular adenosine derives mainly from S-adenosylhomocysteine via S-adenosylhomocysteine hydrolase (Fig. 2) [48]. Once synthesized, adenosine is extruded into the extracellular space via nucleoside transporters [48]. Nucleoside transporters can be divided into two categories based on their molecular and functional features: *1)* the concentrative nucleoside transporters (CNTs) including CNT1, CNT2 and CNT3, which normally mediate the intracellular influx of nucleosides against their concentration gradient but can also transport adenosine to the extracellular space [49]; and *2)* the equilibrative nucleoside transporters (ENT1, ENT2, ENT3 and ENT4), which facilitate nucleoside passage across cell membranes in either

* Corresponding author at: Department of Clinical and Experimental Medicine, University of Pisa, Via Roma 55, 56126–Pisa, Italy.
E-mail address: luca.antonioli@medmcs.unipi.it (L. Antonioli).

https://doi.org/10.1016/j.imlet.2018.04.006
Received 5 April 2018; Accepted 23 April 2018
Available online 24 April 2018

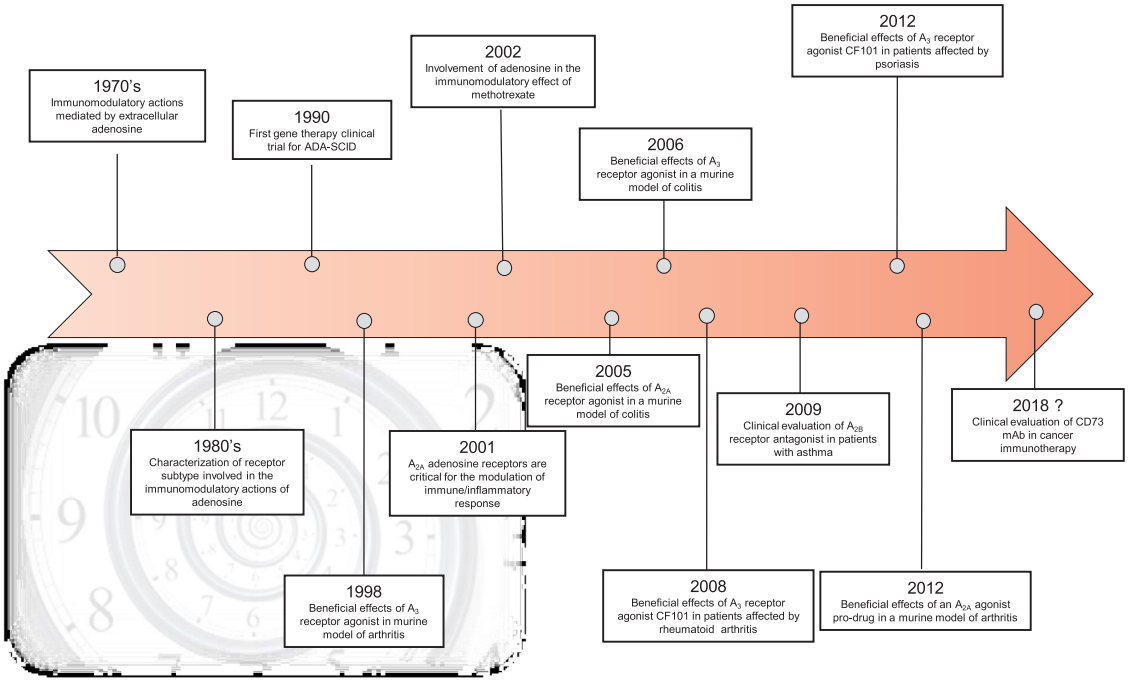

Fig. 1. Timeline of the main selected events regarding the immunomodulatory role of adenosine.

direction based on their concentration gradients [50].

In the presence of detrimental conditions, such as inflammation, hypoxia, ischemia trauma or neoplastic *milieu*, the extracellular levels of adenosine increase massively, reaching micromolar range [51,52]. In these pathological contexts, adenosine accumulation stems from increased extracellular dephosphorylation of ATP, which is mediated by in a sequential manner by ecto- nucleotide triphosphate diphosphohydrolase-1 (also named CD39) and by ecto-5′-nucleotidase (CD73) (Fig. 2) [9]. A number of studies have identified CD73 as a critical check point in regulating the duration and the magnitude, of the "adenosine halo" surrounding immune cells [47]. In addition to the CD39-CD73 axis, adenosine can be generated through an alternative catabolic pathway (Fig. 2), which is initiated by the nicotinamide adenine dinucleotide (NAD^+) glycohydrolases/CD38 enzyme axis that converts extracellular NAD^+ into adenosine diphosphate ribose (ADPR) [53]. ADPR is then processed by CD203a into AMP, which is subsequently metabolized by CD73 to adenosine [53].

Once released into the extracellular space, adenosine concentration is fine-tuned by re-uptake into the cells through the nucleoside transporters, as well as through its conversion into inosine by adenosine deaminase both inside and outside the cell [1,45,54], which ultimately leads to the generation of the stable end product uric acid by xanthine oxidase (Fig. 2) [55].

The biological actions of extracellular adenosine are mediated by G protein-coupled cell-surface receptors, distinguished into four subtypes: A_1, A_{2A}, A_{2B} and A_3 (Fig. 2) [5]. A_1 and A_3 receptors are coupled to G_i, G_q and G_o proteins [5]. Their stimulation can also elicit the release of calcium ions from intracellular stores [5]. A_{2A} and A_{2B} receptors, which are linked to G_s or G_{olf}, stimulate adenylyl cyclase [5]. A_{2B} receptors can also cause phospholipase C activation through G_q [5]. In addition, all adenosine receptors are coupled to mitogen activated protein kinase (MAPK) pathways, such as extracellular signal-regulated kinase 1 (ERK1), ERK2, p38 MAPK and JUN N terminal kinase [5].

3. Adenosine receptors and innate immunity

Monocytes and macrophages. All four adenosine receptor subtypes are expressed on monocytes and macrophages, and their levels and function undergo significant changes during the maturation of macrophages from monocytes. Indeed, quiescent monocytes are characterized by a low expression of A_1, A_{2A} and A_3 receptors, while their density increases during differentiation into macrophages [56]. Receptor expression is regulated by the several pro-inflammatory cytokines. In particular, interleukin-1 (IL-1) and tumor necrosis factor (TNF) induce increases in A_{2A} receptor expression on human monocytes. In addition, these cytokines, through inhibiting A_{2A} receptor desensitization by preventing G-protein coupled receptor kinase 2 (GRK2) and β-arrestin association, enhance receptor function [57]. By contrast, the IFN-γ reduces the expression of A_{2A} receptors [38]. Adenosine itself can regulate receptor expression: adenosine induces heme oxygenase-1 (HO-1) via A_{2A} receptor engagement, and the resultant increased HO-1 enzymatic activity in turn selectively increases the expression of the A_{2A} via the generation of carbon monoxide [58]. In this context, the increase in the A_{2A} receptor expression increases the sensitivity of macrophages toward the anti-inflammatory effect of adenosine [58]. Pro-inflammatory stimuli also regulate macrophage A_{2B} receptors expression [59]. In particular, A_{2B} receptors expression increases following TLR stimulation, leading to the generation of a macrophage phenotype characterized by an increased sensitivity to the immunosuppressive extracellular adenosine [59]. By contrast, IFN-γ inhibited A_{2B} expression, thus mitigating macrophage sensitivity to adenosine and preventing macrophage transition towards an immunoregulatory/immunosuppressive phenotype [59].

Several studies indicate that adenosine, by activating A_{2A}, A_{2B} and A_3 receptors, restrains the macrophage production of several pro-inflammatory mediators such as TNF, IL-6, IL-12, nitric oxide (NO) and macrophage inflammatory protein (MIP)-1α [4,36,60–66]. In parallel, extracellular adenosine promotes the release of the anti-inflammatory cytokine IL-10 by monocytes and macrophages via A_{2A} and A_{2B} receptors [10,35,38,67]. A_3 receptors can also modulation macrophage migration towards apoptotic cells. In this regard, Joós et al. [68] demonstrated that the autocrine ATP release and its subsequent conversion into adenosine is essential to preserve the velocity and direction of macrophages towards apoptotic thymocytes. In this context, the deletion of A_3 gene delayed the kinetics of apoptotic cell clearance, thus highlighting the relevance for this receptor subtype in this context.

In the past few years, several experimental findings have demonstrated a pivotal involvement of adenosine also in driving the

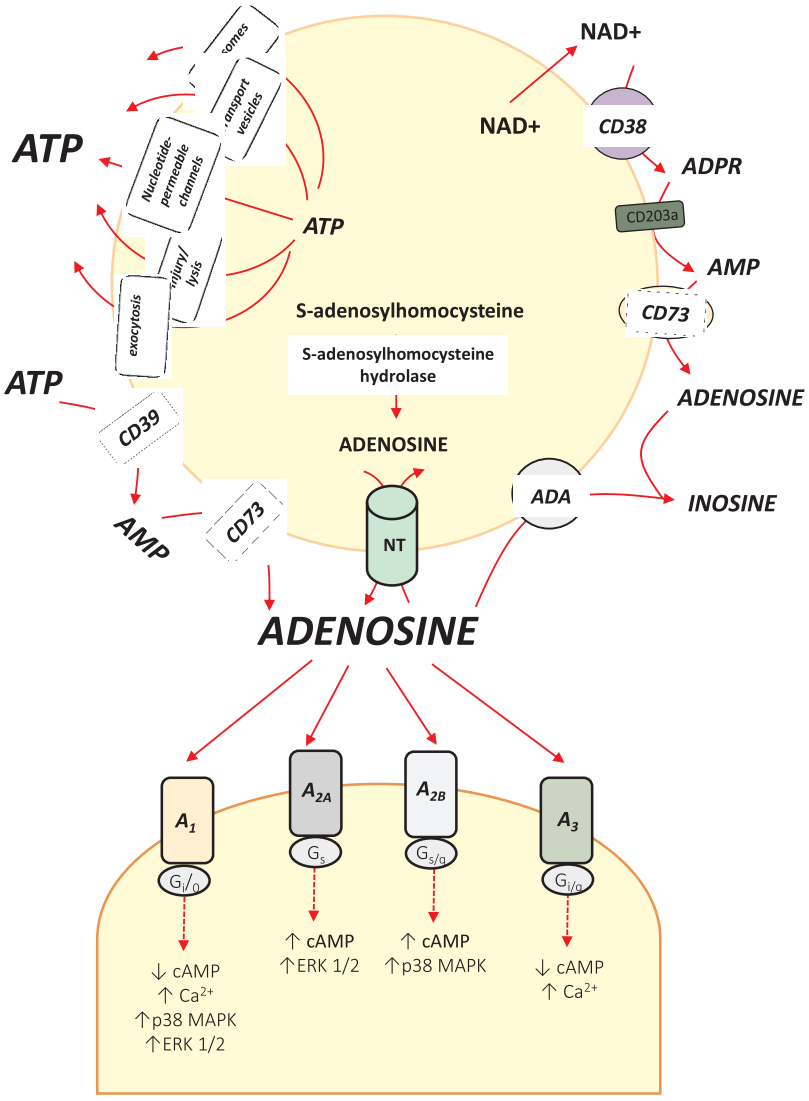

Fig. 2. Adenosine is generated intracellularly from AMP or S-adenosylhomocysteine and then released into the extracellular space via nucleoside transporters (NTs). Once internalized at intracellular level, adenosine undergoes quick phosphorylation to AMP by adenosine kinase (AK), or deamination to inosine by ADA, which can also metabolize adenosine on the cell surface or in the extracellular space. ATP released into the extracellular environment, via diffusion via connexin 43 or pannexin 1 hemichannels and exocytotic release from ATP enriched vesicles, is sequentially degradated into AMP by the cell surface enzyme CD39 (also known as ectonucleoside triphosphate diphosphohydrolase 1 or ecto-apyrase), and to adenosine by CD73 (also known as ecto-5′-nucleotidase). The CD38-CD203a enzyme axis on the cell surface, operating independently or in synergy with the conventional CD39/CD73 pathway, also contributes to the generation of the adenosine. Once released, adenosine can bind to four different G-protein-coupled receptors that either stimulate (mediated by A_{2A} and A_{2B} adenosine receptors) or inhibit (mediated by A_1 and A_3 adenosine receptors) adenylyl cyclase activity and cAMP production in the cell.
Abbreviations: ADA: adenosine deaminase; AK: adenosine kinase; AMP: adenosine monophosphate; ATP: adenosine triphosphate; NT: nucleoside transporter.

phenotypic switch of macrophages. In particular, the stimulation of A_{2A} and A_{2B} receptors seems to play a critical role in switching macrophages from M1 to M2 phenotype [37,69].

Dendritic cells. Dendritic cells (DCs) are professional antigen-presenting cells, whose main role is to activate adaptive immunity, thereby maintaining immune homeostasis and tolerance [70]. Adenosine has been shown to regulate several dendritic cell functions [1]. *Imma*ture human DCs express mainly A_1 and A_3 receptors, which are involved in the regulation of chemotaxis via an increase in intracellular calcium. Mature DCs mainly express A_{2A} receptors, which reduce the release of pro-inflammatory cytokines [71]. A_{2B} receptors have pro-inflammatory effects on dendritic cells as they can switch the differentiation of bone marrow cells to a $CD11c^+$,$Gr\text{-}1^+$ dendritic cell subset that promotes a Th17 response [72]. In addition, adenosine deaminase and A_{2B} receptor form a molecular complex on dendritic cells that by interacting with CD26 expressed on T cells elicits TNF and IFN-γ production by these cells [73]. Novitskiy et al. [74] showed that A_{2B} receptors drive DC differentiation towards a pro-angiogenic, pro-inflammatory phenotype. Indeed, the activation of A_{2B} receptors, by endogenous adenosine generated in a hypoxic milieu, stimulates the release of IL-6, IL-8, IL-10, transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), indoleamine 2,3 dioxygenase and cyclooxygenase (COX)-2, all of which have pro-angiogenic effects [74].

Mast cells. Mast cells are immune cells of the myeloid lineage and are ubiquitously present in connective tissues [75]. These cells are involved in the modulation of a number of physiological functions, such as vasodilation, angiogenesis, bacterial, and parasite elimination [75]. Moreover, mast cells regulate the functions of several cells types, including dendritic cells, macrophages, T and B cells, fibroblasts, eosinophils, endothelial cells, and epithelial cells [75]. The activation of A_{2B} and A_3 on murine mast cells stimulates their degranulation, thus causing histamine, serotonin, chemokine and protease release [1,76]. The role of adenosine receptors in regulating human mast cells is incompletely understood. Studies performed on human mast cells demonstrated that A_{2B} receptors are primarily involved in promoting mast cell degranulation, while A_3 receptors mediate anti-inflammatory effects [77]. In addition, the pharmacological stimulation of A_3 receptors potentiated FcεRI-induced degranulation of human lung mast cells but not that of skin mast cells, suggesting an involvement of A_3 receptors in the bronchoconstrictive response to adenosine in asthmatic subjects, but not in dermatologic allergy responses [78].

Neutrophils. Neutrophils are the most abundant leukocytes in the circulation, representing a first line of defense in the innate arm of the immune system Neutrophils are characterized by large phenotypic heterogeneity and functional versatility, placing these cells as important modulators of both inflammation and immune responses [79].

Neutrophils are an abundant source of adenosine, which in turn regulates neutrophil activation under both normal conditions and in the

presence of inflammation [80,81]. In particular, under adverse conditions, neutrophils release ATP via connexin 43 or pannexin 1 hemichannels, which ATP undergoes rapid conversion to adenosine via the CD39/CD73 axis expressed on the neutrophil surface [82]. In addition, in the presence of inflammation adenosine deaminase is deactivated [83] and the expression of equilibrative nucleoside transporters is reduced [81], thereby promoting an accumulation of adenosine in the biophase of neutrophils.

Neutrophils are endowed with all four adenosine receptors [82]. A_1 receptors facilitate neutrophil chemotaxis, in part, by up-regulating the neutrophil adhesion receptor Mac-1 and by enhancing the expression of the complement receptors [84]. By contrast, both A_{2A} and A_{2B} receptor engagement was found to mediate the inhibition of neutrophil adhesion to endothelial cells [85]. In particular, Yago et al. [86] showed that incubating neutrophils with the selective A_{2A} receptor agonist, ATL313, β2 integrin-mediated neutrophil rolling and adhesion were markedly inhibited both in TNF-challenged murine cremaster muscle postcapillary venules and in ex vivo flow chamber models. Furthermore, ATL313 counteracted the selectin-triggered activation of Src family kinases (SFKs) and p38 MAPK, the chemokine-triggered activation of Ras-related protein 1, and the β2 integrin-triggered activation of SFKs and Vav cytoskeletal regulatory proteins [86]. In another study, the stimulation of A_{2A} receptors with agonist CGS 21680 reduced the phosphorylation of p38 MAPK, Erk-1/2, PI3 K/Akt, Hck, and Syk, protein kinases in neutrophils [87]. A_{2A} receptors were shown also to blunt IL-8 release, a chemokine that is critically involved in promoting the chemoattraction of leukocytes to the inflammatory site, in the activation of phagocytosis and in neutrophil degranulation [88].

Adenosine can modulate neutrophil bactericidal functions. A dual regulatory effect has been reported for adenosine on phagocytosis. Indeed, the activation of A_1 receptors augments this process, while the stimulation of A_{2A} receptors was found to reduce the phagocytic activity of neutrophils [89]. In parallel, adenosine has a differential effect on reactive oxygen species (ROS) generation based on the receptor subtype activated [82]. In particular, the stimulation of A_1 receptors induces ROS production from activated neutrophils, whereas the activation of A_{2A} receptors down-regulates ROS generation [88,90]. Agonists for A_{2B} or A_3 receptors suppressed stimulus-induced superoxide production in wild type but not in A_{2B} or A_3 deficient neutrophils, respectively [91,92]. Of note, besides regulating chemotaxis and ROS generation, A_3 receptors mediate the formation of filipodia-like projections [93]. Indeed, the selective A_3 receptor agonist 2-Cl-IB-MECA promoted the formation and rapid extension of these structures, thus improving bacterial phagocytosis [93] and chemotaxis [94].

4. Adenosine receptors and the adaptive immunity

T lymphocytes are responsible for the cell-mediated immune response [95]. These cells can be stimulated by the presentation of antigenic moieties by APCs, such as dendritic cells or macrophages [96]. The presentation of antigenic molecules on the APC surface in conjunction with major histocompatibility proteins (MHC) causes the activation of T cell receptors on lymphocytes [96], therefore eliciting T cell differentiation, cytokine production, and cytotoxic activity [96]. Once activated, T cells orchestrate effector immune cell function by recruiting macrophages, neutrophils, eosinophils, and basophils to sites of infection and inflammation, and by increasing the microbicidal activity and cytokines and chemokine production of these cells [95].

Adenosine receptors can shape various lymphocyte functions [11]. A_{2A} receptors are the most important receptors in regulating lymphocyte activation, where the overall effect is suppressive [97]. A_{2A} receptors inhibit both IL4 and IFN-γ production by both naive $CD4^+$ T cells and T_h1 and T_h2 cells [98–100]. In addition, A_{2A} receptors upregulate the expression of the negative co-stimulatory molecules cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD1) and suppress the expression of the positive co-stimulatory molecule CD-40L [101]. In parallel, the activation of A_{2A} receptors inhibited IL2 release in polarized type 1 cytotoxic T (TC1) and TC2 $CD8^+$ cells [102]. A recent paper by Abbott et al. [103] demonstrated a critical role of A_{2A} receptors in maintaining T follicular help cell/T follicular regulatory cell ratios as well as the overall ratio between T to B cells into the germinal centers.

Regulatory T (T_{reg}) cells are a specialized sub-lineage of T lymphocytes with a critical role in controlling and suppressing autoreactive T cells [104]. Multiple suppression mechanisms are in place to suppress autoreactive T cells and prevent autoimmunity[104]. In this regard, early studies by Deaglio et al. [105] demonstrated that T_{regs} are endowed with the CD39/CD73 enzyme axis, which converts extracellular nucleotides into pericellular adenosine in the vicinity of T_{regs}. This adenosine in turn engages A_{2A} receptors expressed on T effector cells and suppresses their function. Further studies revealed that adenosine produced by T_{regs} reduced nuclear factor-κB activation in T effector cells via A_{2A} receptor stimulation, thus blunting the release of pro-inflammatory mediators [106]. There is a self-reinforcing loop in the immunosuppressive activity of T_{regs}, via adenosine generation. That is, A_{2A} receptor engagement on T_{regs} induces the expansion of these cells, thereby causing additional immunosuppression [107].

T_{regs} can, also infiltrate tumor tissues, where they create an immunosuppressive niche, which is facilitates cancer onset and development [108]. In this context, it has been observed that T_{reg} cells can release ATP, convert it to adenosine and cause cytotoxic T cell suppression in the local tumor environment [109].

B lymphocytes are found in blood, lymph nodes, spleen and tonsil and other mucosal tissues [110]. These cells originate in the bone marrow from a common progenitor shared with T, NK, and some DC subsets [111]. Progenitor B cells progress through the early stages of maturation, rearranging heavy- and light-chain genes at the pro- to pre-B cell stage until they express rearranged IgM receptors on the cell surface as immature B cells, at which point they exit the bone marrow to continue maturation in the peripheral immune system [111].

Murine and human B cells have been shown to express all four types of adenosine receptors [112,113], as well as the presence of a complex network of ectoenzymes (nucleotidases, deaminases, kinases) and nucleoside transporters [114,115]. Recently, a review by Przybyła et al. [115] summarized the involvement of the adenosine system in the modulation of B cell functions, pointing out a critical role of adenosine in regulating the development, implantation and maintenance of the plasma cell population in bone marrow for the primary immune response as well as in orchestrating immunoglobulin class switching, a key mechanism of humoral immune response [115]. In particular, it has been observed that unactivated B cells are characterized by a high pericellular concentration of adenosine, whereas once activated these lymphocytes increase their ATP release [115]. The presence of this "ATPergic halo" protects activated B cells from the adenosine-induced inhibitory effect and exerts a proinflammatory role and a stimulatory effect on IgM production [115].

Interestingly, as observed with T_{reg} cells, adenosine can regulate the function of B_{reg} cells, a subset of immunosuppressive cells that support immunological tolerance [115]. In particular, B_{regs} were able to regulate both their own function and T cell activity via an adenosine signaling originating from the enzymatic degradation of ATP, released in the extracellular space from activated immune cells [116]. Indeed, it has been observed that B_{reg} cells are endowed with CD39, CD73, CD25 but not CD26, thus allowing, in the presence of extracellular ATP, the production of adenosine by B_{regs} to a much larger extent than T_{regs} [116]. The biologic significance of this ability of B cells to produce adenosine can be appreciated in the context of their interactions with T cells [116]. Under resting condition, B_{reg} cells promoted responses of activated T cells. On the other hand, once activated, B_{reg} cells increase their ability to produce adenosine, becoming strongly suppressive toward T cells [116]. Of note, the ability of B_{reg} cells to counteract T-cell functions depends on the state of their activation and to the

microenvironmental context [116].

5. Conclusions

It is being increasingly appreciated that the adenosine pathway has a major role in protecting tissues against exuberant immune reactions. On the other hand, the excessive depression of the immune system induced by prolonged adenosine signaling can exacerbate tissue dysfunction in chronic diseases or hinder anti-tumor immunity, thereby promoting cancer progression.

The research efforts of the last four decades have provided a large body of evidence regarding the involvement of adenosine signaling in shaping immune system activity. These studies paved the way to the introduction of both innovative anti-inflammatory tools, such as A_3 receptor agonists and immune enhancing agents, such as immune checkpoint blockers in the oncology field (e.g., A_{2A} receptor antagonists and CD73 blockers), some of which have already entered into the clinical arena with encouraging results either in terms of efficacy and safety. However, there are still significant gaps to fill in our understanding about the complex liaison occurring between the adenosine pathway and the immune system aimed to its optimal therapeutic exploitation.

References

[1] G. Hasko, B.N. Cronstein, Adenosine: an endogenous regulator of innate immunity, Trends Immunol. 25 (2004) 33–39.
[2] L. Antonioli, R. Colucci, C. Pellegrini, G. Giustarini, D. Sacco, E. Tirotta, et al., The AMPK enzyme-complex: from the regulation of cellular energy homeostasis to a possible new molecular target in the management of chronic inflammatory disorders, Expert Opin. Ther. Targets 20 (2016) 179–191.
[3] G. Hasko, P. Pacher, Regulation of macrophage function by adenosine, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 865–869.
[4] G. Hasko, P. Pacher, E.A. Deitch, E.S. Vizi, Shaping of monocyte and macrophage function by adenosine receptors, Pharmacol. Ther. 113 (2007) 264–275.
[5] L. Antonioli, C. Blandizzi, P. Pacher, G. Hasko, Immunity, inflammation and cancer: a leading role for adenosine, Nat. Rev. Cancer 13 (2013) 842–857.
[6] M. Sitkovsky, D. Lukashev, Regulation of immune cells by local-tissue oxygen tension: HIF1 alpha and adenosine receptors, Nat. Rev. Immunol. 5 (2005) 712–721.
[7] M.V. Sitkovsky, A. Ohta, The 'danger' sensors that STOP the immune response: the A2 adenosine receptors, Trends Immunol. 26 (2005) 299–304.
[8] G. Hasko, B. Cronstein, Regulation of inflammation by adenosine, Front. Immunol. 4 (2013) 85.
[9] L. Antonioli, P. Pacher, E.S. Vizi, G. Hasko, CD39 and CD73 in immunity and inflammation, Trends Mol. Med. 19 (2013) 355–367.
[10] G. Hasko, B. Csoka, Z.H. Nemeth, E.S. Vizi, P. Pacher, A(2B) adenosine receptors in immunity and inflammation, Trends Immunol. 30 (2009) 263–270.
[11] G. Hasko, J. Linden, B. Cronstein, P. Pacher, Adenosine receptors: therapeutic aspects for inflammatory and immune diseases, Nat. Rev. Drug Discov. 7 (2008) 759–770.
[12] L. Antonioli, G.G. Yegutkin, P. Pacher, C. Blandizzi, G. Hasko, Anti-CD73 in cancer immunotherapy: awakening new opportunities, Trends Cancer 2 (2016) 95–109.
[13] B. Allard, M.S. Longhi, S.C. Robson, J. Stagg, The ectonucleotidases CD39 and CD73: novel checkpoint inhibitor targets, Immunol. Rev. 276 (2017) 121–144.
[14] F. Di Virgilio, E. Adinolfi, Extracellular purines, purinergic receptors and tumor growth, Oncogene 36 (2017) 293–303.
[15] S.M. Hatfield, M. Sitkovsky, A2A adenosine receptor antagonists to weaken the hypoxia-HIF-1alpha driven immunosuppression and improve immunotherapies of cancer, Curr. Opin. Pharmacol. 29 (2016) 90–96.
[16] D. Vijayan, A. Young, M.W.L. Teng, M.J. Smyth, Targeting immunosuppressive adenosine in cancer, Nat. Rev. Cancer 17 (2017) 765.
[17] Z.H. Nemeth, B. Csoka, J. Wilmanski, D. Xu, Q. Lu, C. Ledent, et al., Adenosine A2A receptor inactivation increases survival in polymicrobial sepsis, J. Immunol. 176 (2006) 5616–5626.
[18] H. Green, T. Chan, Pyrimidine starvation induced by adenosine in fibroblasts and lymphoid cells: role of adenosine deaminase, Science 182 (1973) 836–837.
[19] J.W. DePierre, M.L. Karnovsky, Ecto-enzyme of granulocytes: 5'-nucleotidase, Science 183 (1974) 1096–1098.
[20] K.R. Harrap, R.M. Paine, Adenosine metabolism in cultured lymphoid cells, Adv. Enzyme Regul. 15 (1976) 169–193.
[21] T. Hovi, J.F. Smyth, A.C. Allison, S.C. Williams, Role of adenosine deaminase in lymphocyte proliferation, Clin. Exp. Immunol. 23 (1976) 395–403.
[22] F.F. Snyder, J. Mendelsohn, J.E. Seegmiller, Adenosine metabolism in phytohemagglutinin-stimulated human lymphocytes, J. Clin. Invest. 58 (1976) 654–666.
[23] E.R. Giblett, J.E. Anderson, F. Cohen, B. Pollara, H.J. Meuwissen, Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity, Lancet 2 (1972) 1067–1069.
[24] K.L. Bradford, F.A. Moretti, D.A. Carbonaro-Sarracino, H.B. Gaspar, D.B. Kohn, Adenosine deaminase (ADA)-deficient severe combined immune deficiency (SCID): molecular pathogenesis and clinical manifestations, J. Clin. Immunol. 37 (2017) 626–637.
[25] F. Cohen, Adenosine deaminase and immunodeficiency, Birth Defects Orig. Artic. Ser. 11 (1975) 124–127.
[26] H.J. Meuwissen, R.J. Pickering, B. Pollara, Adenosine deaminase deficiency in combined immunologic deficiency disease, Birth Defects Orig. Artic. Ser. 11 (1975) 117–119.
[27] H. Fleit, M. Conklyn, R.D. Stebbins, R. Silber, Function of 5'-nucleotidase in the uptake of adenosine from AMP by human lymphocytes, J. Biol. Chem. 250 (1975) 8889–8892.
[28] J.J. Ballet, R. Insel, E. Merler, F.S. Rosen, Inhibition of maturation of human precursor lymphocytes by coformycin, an inhibitor of the enzyme adenosine deaminase, J. Exp. Med. 143 (1976) 1271–1276.
[29] P.W. Burridge, V. Paetkau, J.F. Henderson, Studies of the relationship between adenosine deaminase and immune function, J. Immunol. 119 (1977) 675–678.
[30] A.C. Allison, T. Hovi, R.W. Watts, A.D. Webster, The Role of De Novo Purine Synthesis in Lymphocyte Transformation, Ciba Foundation symposium, 1977, pp. 207–224.
[31] F.F. Snyder, J. Mendelsohn, J.E. Seegmiller, Adenosine and guanosine metabolism during phytohemagglutinin induced transformation of human lymphocytes, Adv. Exp. Med. Biol. 76A (1977) 441–447.
[32] J.E. Seegmiller, T. Watanabe, M.H. Schreier, The Effect of Adenosine on Lymphoid Cell Proliferation and Antibody Formation, Ciba Foundation symposium, 1977, pp. 249–276.
[33] J.E. Seegmiller, T. Watanabe, M.H. Shreier, T.A. Waldmann, Immunological aspects of purine metabolism, Adv. Exp. Med. Biol. 76A (1977) 412–433.
[34] A. Cohen, L.J. Gudas, B. Ullman, D.W. Martin Jr., Nucleotide Metabolism in Cultured T Cells and in Cells of Patients Deficient in Adenosine Deaminase and Purine Nucleoside Phosphorylase, Ciba Foundation symposium, 1978, pp. 101–114.
[35] B. Koscso, B. Csoka, E. Kokai, Z.H. Nemeth, P. Pacher, L. Virag, et al., Adenosine augments IL-10-induced STAT3 signaling in M2c macrophages, J. Leukoc. Biol. 94 (2013) 1309–1315.
[36] G. Hasko, D.G. Kuhel, J.F. Chen, M.A. Schwarzschild, E.A. Deitch, J.G. Mabley, et al., Adenosine inhibits IL-12 and TNF-[alpha] production via adenosine A2a receptor-dependent and independent mechanisms, FASEB J. 14 (2000) 2065–2074.
[37] B. Csoka, Z. Selmeczy, B. Koscso, Z.H. Nemeth, P. Pacher, P.J. Murray, et al., Adenosine promotes alternative macrophage activation via A2A and A2 B receptors, FASEB J. 26 (2012) 376–386.
[38] N.D. Khoa, M.C. Montesinos, A.B. Reiss, D. Delano, N. Awadallah, B.N. Cronstein, Inflammatory cytokines regulate function and expression of adenosine A(2A) receptors in human monocytic THP-1 cells, J. Immunol. 167 (2001) 4026–4032.
[39] B.N. Cronstein, R.I. Levin, M. Philips, R. Hirschhorn, S.B. Abramson, G. Weissmann, Neutrophil adherence to endothelium is enhanced via adenosine A1 receptors and inhibited via adenosine A2 receptors, J. Immunol. 148 (1992) 2201–2206.
[40] E.S. Chan, B.N. Cronstein, Mechanisms of action of methotrexate, Bull. Hosp. Joint Dis. 71 (Suppl. 1) (2013) S5–8.
[41] E.S. Chan, B.N. Cronstein, Methotrexate?how does it really work? Nat. Rev. Rheumatol. 6 (2010) 175–178.
[42] B.N. Cronstein, M. Van de Stouwe, L. Druska, R.I. Levin, G. Weissmann, Nonsteroidal antiinflammatory agents inhibit stimulated neutrophil adhesion to endothelium: adenosine dependent and independent mechanisms, Inflammation 18 (1994) 323–335.
[43] B.N. Cronstein, M.C. Montesinos, G. Weissmann, Salicylates and sulfasalazine, but not glucocorticoids, inhibit leukocyte accumulation by an adenosine-dependent mechanism that is independent of inhibition of prostaglandin synthesis and p105 of NFkappaB, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 6377–6381.
[44] L. Antonioli, B. Csoka, M. Fornai, R. Colucci, E. Kokai, C. Blandizzi, et al., Adenosine and inflammation: what's new on the horizon, Drug Discovery Today 19 (2014) 1051–1068.
[45] L. Antonioli, R. Colucci, C. La Motta, M. Tuccori, O. Awwad, F. Da Settimo, et al., Adenosine deaminase in the modulation of immune system and its potential as a novel target for treatment of inflammatory disorders, Curr. Drug Targets 13 (2012) 842–862.
[46] M.H. Silverman, V. Strand, D. Markovits, M. Nahir, T. Reitblat, Y. Molad, et al., Clinical evidence for utilization of the A3 adenosine receptor as a target to treat rheumatoid arthritis: data from a phase II clinical trial, J. Rheumatol. 35 (2008) 41–48.
[47] L. Antonioli, S.V. Novitskiy, K.F. Sachsenmeier, M. Fornai, C. Blandizzi, G. Hasko, Switching off CD73: a way to boost the activity of conventional and targeted antineoplastic therapies, Drug Discovery Today 22 (2017) 1686–1696.
[48] L. Antonioli, R. Colucci, C. Pellegrini, G. Giustarini, M. Tuccori, C. Blandizzi, et al., The role of purinergic pathways in the pathophysiology of gut diseases: pharmacological modulation and potential therapeutic applications, Pharmacol. Ther. 139 (2013) 157–188.
[49] I. Aymerich, S. Duflot, S. Fernandez-Veledo, E. Guillen-Gomez, I. Huber-Ruano, F.J. Casado, et al., The concentrative nucleoside transporter family (SLC28): new roles beyond salvage, Biochem. Soc. Trans. 33 (2005) 216–219.
[50] J.D. Young, The SLC28 (CNT) and SLC29 (ENT) nucleoside transporter families: a 30-year collaborative odyssey, Biochem. Soc. Trans. 44 (2016) 869–876.
[51] G. Hasko, L. Antonioli, B.N. Cronstein, Adenosine metabolism, immunity and joint health, Biochem. Pharmacol. 151 (May) (2018) 307–313.

[52] B.B. Fredholm, Adenosine–a physiological or pathophysiological agent? J. Mol. Med. 92 (2014) 201–206.
[53] E. Ferretti, A.L. Horenstein, C. Canzonetta, F. Costa, F. Morandi, Canonical and non-canonical adenosinergic pathways, Immunol. Lett. (2018) (in press).
[54] L. Antonioli, M. Fornai, R. Colucci, O. Awwad, N. Ghisu, M. Tuccori, et al., The blockade of adenosine deaminase ameliorates chronic experimental colitis through the recruitment of adenosine A2A and A3 receptors, J. Pharmacol. Exp. Ther. 335 (2010) 434–442.
[55] G. Hasko, M.V. Sitkovsky, C. Szabo, Immunomodulatory and neuroprotective effects of inosine, Trends Pharmacol. Sci. 25 (2004) 152–157.
[56] A. Thiele, R. Kronstein, A. Wetzel, A. Gerth, K. Nieber, S. Hauschildt, Regulation of adenosine receptor subtypes during cultivation of human monocytes: role of receptors in preventing lipopolysaccharide-triggered respiratory burst, Infect. Immun. 72 (2004) 1349–1357.
[57] E.T. Block, B.N. Cronstein, Interferon-gamma inhibits adenosine A2A receptor function in hepatic stellate cells by STAT1-mediated repression of adenylyl cyclase, Int. J. Interferon. Cytokine Mediat. Res. 2010 (2010) 113–126.
[58] A. Haschemi, O. Wagner, R. Marculescu, B. Wegiel, S.C. Robson, N. Gagliani, et al., Cross-regulation of carbon monoxide and the adenosine A2a receptor in macrophages, J. Immunol. 178 (2007) 5921–5929.
[59] H.B. Cohen, A. Ward, K. Hamidzadeh, K. Ravid, D.M. Mosser, IFN-gamma prevents adenosine receptor (A2bR) upregulation to sustain the macrophage activation response, J. Immunol. 195 (2015) 3828–3837.
[60] C. Szabo, G.S. Scott, L. Virag, G. Egnaczyk, A.L. Salzman, T.P. Shanley, et al., Suppression of macrophage inflammatory protein (MIP)-1alpha production and collagen-induced arthritis by adenosine receptor agonists, Br. J. Pharmacol. 125 (1998) 379–387.
[61] H.S. Lee, H.J. Chung, H.W. Lee, L.S. Jeong, S.K. Lee, Suppression of inflammation response by a novel A(3) adenosine receptor agonist thio-Cl-IB-MECA through inhibition of Akt and NF-kappaB signaling, Immunobiology 216 (2011) 997–1003.
[62] J. Mabley, F. Soriano, P. Pacher, G. Hasko, A. Marton, R. Wallace, et al., The adenosine A3 receptor agonist, N6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide, is protective in two murine models of colitis, Eur. J. Pharmacol. 466 (2003) 323–329.
[63] T.L. Bowlin, D.R. Borcherding, C.K. Edwards, 3rd, McWhinney CD. Adenosine A3 receptor agonists inhibit murine macrophage tumor necrosis factor-alpha production in vitro and in vivo, Cell. Mol. Biol. 43 (1997) 345–349.
[64] G. Hasko, C. Szabo, Z.H. Nemeth, V. Kvetan, S.M. Pastores, E.S. Vizi, Adenosine receptor agonists differentially regulate IL-10, TNF-alpha, and nitric oxide production in RAW 264.7 macrophages and in endotoxemic mice, J. Immunol. 157 (1996) 4634–4640.
[65] C.D. McWhinney, M.W. Dudley, T.L. Bowlin, N.P. Peet, L. Schook, M. Bradshaw, et al., Activation of adenosine A3 receptors on macrophages inhibits tumor necrosis factor-alpha, Eur. J. Pharmacol. 310 (1996) 209–216.
[66] A. Ohta, M. Sitkovsky, Role of G-protein-coupled adenosine receptors in downregulation of inflammation and protection from tissue damage, Nature 414 (2001) 916–920.
[67] Z.H. Nemeth, C.S. Lutz, B. Csoka, E.A. Deitch, S.J. Leibovich, W.C. Gause, et al., Adenosine augments IL-10 production by macrophages through an A2 B receptor-mediated posttranscriptional mechanism, J. Immunol. 175 (2005) 8260–8270.
[68] G. Joos, J. Jakim, B. Kiss, R. Szamosi, T. Papp, S. Felszeghy, et al., Involvement of adenosine A3 receptors in the chemotactic navigation of macrophages towards apoptotic cells, Immunol. Lett. 183 (2017) 62–72.
[69] C.J. Ferrante, G. Pinhal-Enfield, G. Elson, B.N. Cronstein, G. Hasko, S. Outram, et al., The adenosine-dependent angiogenic switch of macrophages to an M2-like phenotype is independent of interleukin-4 receptor alpha (IL-4Ralpha) signaling, Inflammation 36 (2013) 921–931.
[70] G. Ghislat, T. Lawrence, Autophagy in dendritic cells, Cell. Mol. Immunol. (2018) (in press).
[71] M. Schnurr, T. Toy, A. Shin, G. Hartmann, S. Rothenfusser, J. Soellner, et al., Role of adenosine receptors in regulating chemotaxis and cytokine production of plasmacytoid dendritic cells, Blood 103 (2004) 1391–1397.
[72] D. Liang, A. Zuo, H. Shao, M. Chen, H.J. Kaplan, D. Sun, A2 B adenosine receptor activation switches differentiation of bone marrow cells to a CD11c(+)Gr-1(+) dendritic cell subset that promotes the Th17 response, Immun. Inflammation Dis. 3 (2015) 360–373.
[73] R. Pacheco, J.M. Martinez-Navio, M. Lejeune, N. Climent, H. Oliva, J.M. Gatell, et al., CD26, adenosine deaminase, and adenosine receptors mediate costimulatory signals in the immunological synapse, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 9583–9588.
[74] S.V. Novitskiy, S. Ryzhov, R. Zaynagetdinov, A.E. Goldstein, Y. Huang, O.Y. Tikhomirov, et al., Adenosine receptors in regulation of dendritic cell differentiation and function, Blood 112 (2008) 1822–1831.
[75] M. Krystel-Whittemore, K.N. Dileepan, J.G. Wood, Mast cell a multi-functional master cell, Front. Immunol. 6 (2015) 620.
[76] Z.G. Gao, K.A. Jacobson, Purinergic signaling in mast cell degranulation and asthma, Front. Pharmacol. 8 (2017) 947.
[77] N. Rudich, K. Ravid, R. Sagi-Eisenberg, Mast cell adenosine receptors function: a focus on the a3 adenosine receptor and inflammation, Front. Immunol. 3 (2012) 134.
[78] G. Gomez, W. Zhao, L.B. Schwartz, Disparity in FcepsilonRI-induced degranulation of primary human lung and skin mast cells exposed to adenosine, J. Clin. Immunol. 31 (2011) 479–487.
[79] C. Rosales, Neutrophil a cell with many roles in inflammation or several cell types? Front. Physiol. 9 (2018) 113.
[80] J. Linden, Cell biology Purinergic chemotaxis, Science 314 (2006) 1689–1690.
[81] K.E. Barletta, K. Ley, B. Mehrad, Regulation of neutrophil function by adenosine, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 856–864.
[82] X. Wang, D. Chen, Purinergic regulation of neutrophil function, Front. Immunol. 9 (2018) 399.
[83] G. van Waeg, G. Van den Berghe, Purine catabolism in polymorphonuclear neutrophils. Phorbol myristate acetate-induced accumulation of adenosine owing to inactivation of extracellularly released adenosine deaminase, J. Clin. Invest. 87 (1991) 305–312.
[84] M.J. Bours, E.L. Swennen, F. Di Virgilio, B.N. Cronstein, P.C. Dagnelie, Adenosine 5'-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation, Pharmacol. Ther. 112 (2006) 358–404.
[85] H.K. Eltzschig, L.F. Thompson, J. Karhausen, R.J. Cotta, J.C. Ibla, S.C. Robson, et al., Endogenous adenosine produced during hypoxia attenuates neutrophil accumulation: coordination by extracellular nucleotide metabolism, Blood 104 (2004) 3986–3992.
[86] T. Yago, H. Tsukamoto, Z. Liu, Y. Wang, L.F. Thompson, R.P. McEver, Multi-inhibitory effects of A2A adenosine receptor signaling on neutrophil adhesion under flow, J. Immunol. 195 (2015) 3880–3889.
[87] M.S. Giambelluca, M. Pouliot, Early tyrosine phosphorylation events following adenosine A2A receptor in human neutrophils: identification of regulated pathways, J. Leukoc. Biol. 102 (2017) 829–836.
[88] A.P. Frasson, C.B. Menezes, G.K. Goelzer, S.C.B. Gnoatto, S.C. Garcia, T. Tasca, Adenosine reduces reactive oxygen species and interleukin-8 production by Trichomonas vaginalis-stimulated neutrophils, Purinergic Signal. 13 (2017) 569–577.
[89] S. Zalavary, T. Bengtsson, Adenosine inhibits actin dynamics in human neutrophils: evidence for the involvement of cAMP, Eur. J. Cell Biol. 75 (1998) 128–139.
[90] W.C. Sun, J.N. Moore, D.J. Hurley, M.L. Vandenplas, T.F. Murray, Effects of stimulation of adenosine A2A receptors on lipopolysaccharide-induced production of reactive oxygen species by equine neutrophils, Am. J. Vet. Res. 68 (2007) 649–656.
[91] D. van der Hoeven, T.C. Wan, E.T. Gizewski, L.M. Kreckler, J.E. Maas, J. Van Orman, et al., A role for the low-affinity A2 B adenosine receptor in regulating superoxide generation by murine neutrophils, J. Pharmacol. Exp. Ther. 338 (2011) 1004–1012.
[92] D. van der Hoeven, T.C. Wan, J.A. Auchampach, Activation of the A(3) adenosine receptor suppresses superoxide production and chemotaxis of mouse bone marrow neutrophils, Mol. Pharmacol. 74 (2008) 685–696.
[93] R. Corriden, T. Self, K. Akong-Moore, V. Nizet, B. Kellam, S.J. Briddon, et al., Adenosine-A3 receptors in neutrophil microdomains promote the formation of bacteria-tethering cytonemes, EMBO Rep. 14 (2013) 726–732.
[94] Y. Chen, R. Corriden, Y. Inoue, L. Yip, N. Hashiguchi, A. Zinkernagel, et al., ATP release guides neutrophil chemotaxis via P2Y2 and A3 receptors, Science 314 (2006) 1792–1795.
[95] J. Zhu, W.E. Paul, CD4 T cells: fates, functions, and faults, Blood 112 (2008) 1557–1569.
[96] J. Linden, C. Cekic, Regulation of lymphocyte function by adenosine, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 2097–2103.
[97] G. Hasko, P. Pacher, A2A receptors in inflammation and injury: lessons learned from transgenic animals, J. Leukoc. Biol. 83 (2008) 447–455.
[98] M. Naganuma, E.B. Wiznerowicz, C.M. Lappas, J. Linden, M.T. Worthington, P.B. Ernst, Cutting edge: critical role for A2A adenosine receptors in the T cell-mediated regulation of colitis, J. Immunol. 177 (2006) 2765–2769.
[99] C.M. Lappas, J.M. Rieger, J. Linden, A2A adenosine receptor induction inhibits IFN-gamma production in murine CD4+ T cells, J. Immunol. 174 (2005) 1073–1080.
[100] B. Csoka, L. Himer, Z. Selmeczy, E.S. Vizi, P. Pacher, C. Ledent, et al., Adenosine A2A receptor activation inhibits T helper 1 and T helper 2 cell development and effector function, FASEB J. 22 (2008) 3491–3499.
[101] C.P. Sevigny, L. Li, A.S. Awad, L. Huang, M. McDuffie, J. Linden, et al., Activation of adenosine 2A receptors attenuates allograft rejection and alloantigen recognition, J. Immunol. 178 (2007) 4240–4249.
[102] A.A. Erdmann, Z.G. Gao, U. Jung, J. Foley, T. Borenstein, K.A. Jacobson, et al., Activation of Th1 and Tc1 cell adenosine A2A receptors directly inhibits IL-2 secretion in vitro and IL-2-driven expansion in vivo, Blood 105 (2005) 4707–4714.
[103] R.K. Abbott, M. Silva, J. Labuda, M. Thayer, D.W. Cain, P. Philbrook, et al., The GS protein-coupled A2a adenosine receptor controls T cell help in the germinal center, J. Biol. Chem. 292 (2017) 1211–1217.
[104] M. Kasheta, C.A. Painter, F.E. Moore, R. Lobbardi, A. Bryll, E. Freiman, et al., Identification and characterization of T reg-like cells in zebrafish, J. Exp. Med. 214 (2017) 3519–3530.
[105] S. Deaglio, K.M. Dwyer, W. Gao, D. Friedman, A. Usheva, A. Erat, et al., Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression, J. Exp. Med. 204 (2007) 1257–1265.
[106] M. Romio, B. Reinbeck, S. Bongardt, S. Huls, S. Burghoff, J. Schrader, Extracellular purine metabolism and signaling of CD73-derived adenosine in murine Treg and Teff cells, Am. J. Physiol. Cell Physiol. 301 (2011) C530–539.
[107] A. Ohta, R. Kini, A. Ohta, M. Subramanian, M. Madasu, M. Sitkovsky, The development and immunosuppressive functions of CD4(+) CD25(+) FoxP3(+) regulatory T cells are under influence of the adenosine-A2A adenosine receptor pathway, Front. Immunol. 3 (2012) 190.
[108] A. Tanaka, S. Sakaguchi, Regulatory T cells in cancer immunotherapy, Cell Res. 27 (2017) 109–118.
[109] T. Maj, W. Wang, J. Crespo, H. Zhang, W. Wang, S. Wei, et al., Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade

resistance in tumor, Nat. Immunol. 18 (2017) 1332–1341.
[110] C. Huang, A.K. Stewart, R.S. Schwartz, B.D. Stollar, Immunoglobulin heavy chain gene expression in peripheral blood B lymphocytes, J. Clin. Invest. 89 (1992) 1331–1343.
[111] T.W. LeBien, T.F. Tedder, B lymphocytes how they develop and function, Blood 112 (2008) 1570–1580.
[112] M. Sakowicz-Burkiewicz, K. Kocbuch, M. Grden, I. Maciejewska, A. Szutowicz, T. Pawelczyk, Impact of adenosine receptors on immunoglobulin production by human peripheral blood B lymphocytes, J. Physiol. Pharmacol. 63 (2012) 661–668.
[113] M. Sakowicz-Burkiewicz, K. Kocbuch, M. Grden, A. Szutowicz, T. Pawelczyk, Protein kinase C mediated high glucose effect on adenosine receptors expression in rat B lymphocytes, J. Physiol. Pharmacol. 60 (2009) 145–153.
[114] G.G. Yegutkin, T. Henttinen, S.S. Samburski, J. Spychala, S. Jalkanen, The evidence for two opposite, ATP-generating and ATP-consuming, extracellular pathways on endothelial and lymphoid cells, Biochem. J. 367 (2002) 121–128.
[115] T. Przybyla, M. Sakowicz-Burkiewicz, T. Pawelczyk, Purinergic signaling in B cells, Acta Biochim. Pol. 65 (2018) 1–7.
[116] Z. Saze, P.J. Schuler, C.S. Hong, D. Cheng, E.K. Jackson, T.L. Whiteside, Adenosine production by human B cells and B cell-mediated suppression of activated T cells, Blood 122 (2013) 9–18.