Review

Adenosine metabolism, immunity and joint health

György Haskó[a], Luca Antonioli[b], Bruce N. Cronstein[c],*

[a] Department of Anesthesiology, Columbia University, New York, NY 10032, USA
[b] Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy
[c] Department of Medicine, New York University, NY 10016, USA

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ABSTRACT

The purine nucleoside adenosine is a present in most body fluids where it regulates a wide variety of physiologic and pharmacologic processes. Adenosine mediates its effects through activating 4 G protein-coupled receptors expressed on the cell membrane: A1, A2A, A2B, and A3. The adenosine receptors are widely distributed in the body, and tissues with high expression include immune tissues, cartilage, bone, heart, and brain. Here we review the source and metabolism of adenosine and the role of adenosine in regulating immunity and cartilage biology.

1. Introduction

Adenosine is an endogenous purine nucleoside, a catabolite of ATP, that binds and activates one or more of four transmembrane G-protein-coupled cell surface adenosine receptors (R)s, which are A1R, A2AR, A2BR and A3R [1]. Extracellular adenosine can accumulate during inflammation, hypoxia, and associated cellular damage and stress and several studies indicate that it may contribute to innate inflammation [2–4]. The accumulation of extracellular adenosine is the result of a multistep process, where ATP is first released from its intracellular pool to the pericellular space, and is then degraded to adenosine by a cascade of cell surface ectonucleotidases, including CD39 (ectonucleoside triphosphate diphosphohydrolase 1 (E-NTPDase1)) and CD73 (5′-ecto-nucleotidase or Ecto5′NTase) [4–9]. Adenosine, the pharmacologic effects of which were first described by Drury and Szent-Gyorgy [10], regulates every organ system in the body, most notably the cardiovascular, nervous, gastrointestinal and immune systems. Indeed, all four of the adenosine receptors are widely expressed throughout the body and different cell types express different combinations of adenosine receptors. In this review we will discuss two newly described regulatory functions of adenosine and adenosine receptors in regulation of Type 2 immunity and chondrocyte homeostasis.

2. Sources of adenosine

In a cell type and context-dependent manner, several mechanisms for ATP liberation have been proposed, including channel-dependent, cell death, and vesicular release mechanisms [7]. ATP release in response to immune activation occurs mostly through Connexin (Cx) and Pannexin (Panx) channels. Cx channels were first described in the 1970 s as the principal proteins comprising intercellular gap junctions [11–13]. Cx channels are half channels or hemichannels that can readily dock unapposed hemichannels on adjacent cells to form gap junctions. However, they can also remain unapposed and serve as conduits for extracellular ATP liberation. Of the ~25 Cx channels, the ubiquitous Cx43 has been shown to be the major Cx to release ATP [11–13]. Panx channels (Panx1, Panx2, and Panx3) are single membrane channels that share several topological and structural features with Cx channels. Panx1 is ubiquitously expressed whereas Panx2 is localized in the bone and Panx3 in cartilage and the central nervous system [11–13]. Panx1 channels are the principal Panx channels through which ATP is released [11–13]. Macrophages release ATP in response to *B. anthracis* infection, which is blocked by both pharmacological Cx inhibition and siRNA-mediated Cx43 depletion [14]. Eltzschig et al. [15] showed that neutrophils liberate ATP in response to N-formyl-Met-Leu-Phe (fMLP) or leukotriene B4, and that this ATP release is blocked by a peptide inhibitor of Cx43 or in Cx43 knockout (KO) neutrophils. In another study, the fMLP-mediated ATP release by neutrophils was Panx1-dependent [16]. T cells release ATP during T cell activation via Panx1 channels [17]. In addition to host cells, bacteria or fungi can also release ATP [18,19]. The mechanisms of ATP release during helminth-induced type 2 immune responses are unknown.

CD39 is the most prominent member of the cell surface E-NTPDase family [7,20]. It has two membrane-spanning domains at its N- and C-termini and its extracellular domain contains five apyrase conserved

regions, which are responsible for its catalytic activity. CD39 is widely expressed, whereas the other E-NTPDases are localized to neural tissue or pericytes. CD39 is the major nucleotide-metabolizing enzyme in peripheral blood leukocytes, spleen, lung, and placenta [21], and is expressed on intestinal epithelial cells [22], macrophages [23], neutrophils [15], Tregs [24], Langerhans cells [25], and endothelial cells [26]. CD73 is the only surface associated 5′-ectonucleotidase and is anchored to the plasma membrane at the C-terminus by glycosyl-phosphatidylinositol (GPI). CD73 is ubiquitously expressed and the highest expression levels are seen in the gut, brain, kidney, liver, and lung [6,7]. CD73 is readily detected on cells from intestine, blood, spleen, lymph nodes, and bone marrow, and endothelium [6], and within the immune system CD73 is found on the surface of macrophages [27], Treg cells [28], and dendritic cells [29]. There is evidence that the expression and function of both CD39 and CD73 are upregulated in the gut following tissue stress and inflammation [22,30,31]. The regulation of CD39 and CD73 in the gut during a type 2 response is poorly understood.

The CD38-CD203a enzyme axis on the cell surface, operating independently or in synergy with the conventional CD39/CD73 pathway, also contributes to the regulation of the adenosine levels [32,33]. CD38 catalyzes the synthesis of cyclic ADP-ribose from nicotinamide adenine dinucleotide (NAD^+), and also mediates the hydrolysis of cyclic ADP-ribose to ADP-ribose (ADPR) on the cell surface [34] (see Fig. 1) The pyrophosphatase/phosphodiesterase CD203a can hydrolyze both NAD^+ and ADPR to produce AMP, which can then be catabolized to adenosine by CD73 [34,35] (see Fig. 1). In contrast, the adenosine-metabolizing enzyme adenosine deaminase, which is present in plasma and other extracellular fluids at high levels, attenuates extracellular adenosine levels through the conversion of adenosine into inosine [36] (see Fig. 1). In addition to regulating immune activation, this enzyme has also been found to play a crucial role in the development of the immune system [36], as illustrated by the severely decreased T and B cell numbers in patients affected by genetic deficiency of adenosine deaminase [37]. Adenosine is also taken up by cells via specific nucleoside transporters, which can be inhibited by a number of pharmacologic agents including dipyridamole and ticagrelor [38,39]. Thus, adenosine molecules have a half-life measured in seconds in blood [40] and presumably there is a similarly short half-life in other bodily fluids.

Fig. 1. Adenosine metabolism pathways.

3. Adenosine receptors

Adenosine in the extracellular space mediates its physiologic and pharmacologic effects via interaction with a family of 4 related 7-transmembrane spanning G protein coupled receptors (GPCRs). These receptors have been named historically in order of their discovery as A1R, A2AR, A2BR and A3R. A1R and A2AR are the most sensitive adenosine receptors and are active in the nanomolar range whereas A2BR and A3R are active in the micromolar range [1]. The A1R and A3R signal through G_i-linked proteins and suppress cAMP generation whereas A2AR and A2BR signal through G_s and G_{olf} and activate adenylate cyclase and cAMP-dependent pathways (Fig. 2).

Adenosine receptors are expressed ubiquitously although different tissues/cell types express different combinations of adenosine receptors. Moreover, in a given tissue specific adenosine receptor expression may be increased or decreased by different external stimuli. A2AR expression increases during many inflammatory reactions as a result of NFkB-mediated stimulation [41–44] and serves as a feedback regulator of inflammation. Moreover, A2AR function increases as a result of inflammatory stimulation; there is diminished desensitization of A2AR after cytokine-mediated stimulation [45].

4. Regulation of type 2 immunity by adenosine receptors

Based on emerging knowledge on the different effector T-cell and innate lymphoid cell (ILC) lineages, 3 major kinds of cell-mediated effector immunity exist, which are denoted type 1, type 2, and type 3 [46]. Type 1 immunity encompasses IFN-γ–secreting group 1 ILCs (ILC1 and natural killer cells), cytotoxic $CD8^+$ T cells, and $CD4^+$ T_H1 cells, which protect against intracellular pathogens through recruitment of mononuclear phagocytes. Type 2 immunity, which developed to expulse intestinal and other helminths, consists of ILC2s and T_H2 cells which are described in detail below. Type 3 immunity is mediated by ILC3s and T_H17 cells producing IL-17, IL-22, or both, which recruit mononuclear phagocytes but also activate neutrophils and induce epithelial antimicrobial responses, therefore mediating protection against extracellular bacteria and fungi.

ARs are widely distributed practically on all types of immune cells, including cells involved in type 1, 2, and 3 immunity [9,47–54]. Whereas the role ARs in regulating type 1and type 3 immunity has been the subject of many recent reviews [55], how ARs regulate type 2 immunity has not been summarized. This is especially important and timely because chronic malnutrition induced by infection with gastrointestinal helminths results in significant morbidity and increased susceptibility to infectious agents. Although primary health care and effective public sanitation can successfully eliminate human gastrointestinal parasitism, immunological intervention may promote control in situations where gastrointestinal parasitism remains endemic and intractable. Immune protection against murine gastrointestinal roundworm infection, manifested by rapid expulsion of nematode larvae during infection, has been shown in many cases to be associated with increases in the type 2 cytokines IL-4, IL-5, IL-9 and IL-13, produced by both innate immune cells and T cells, alternatively activated macrophages (M2) in granulomas, mucosal mastocytosis, eosinophilia, and IgE secretion [56–58]. Recent studies suggest that in humans a similar set of cytokines and immune cells are triggered after helminth infection [59]. The same immune response (type 2) that orchestrates rapid and effective worm expulsion can also promote tolerance of invading pathogens with recent studies suggesting that the helminth-induced type 2 immune response may have incorporated a wound-healing component as an adaptation to the considerable tissue damage that helminth parasites can cause as they migrate through vital tissues, such as the lung or intestine [60–63]. Thus the components of the helminth-induced type 2 immune response may serve multiple functions during infection including effector functions leading to worm expulsion, anti-inflammatory effects, and induction of wound healing.
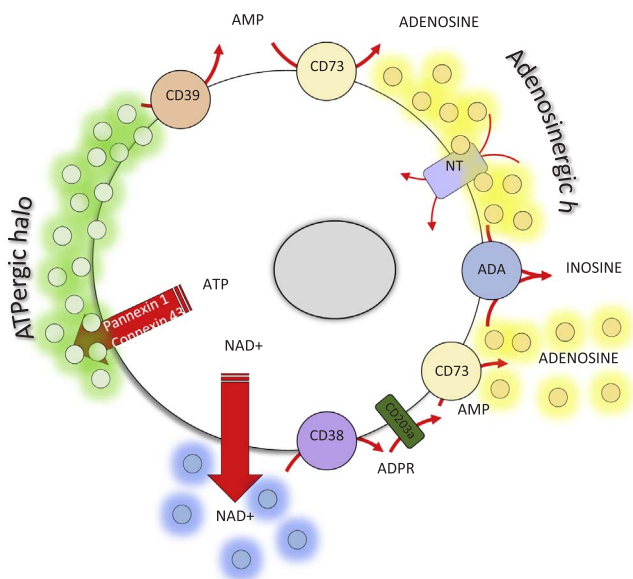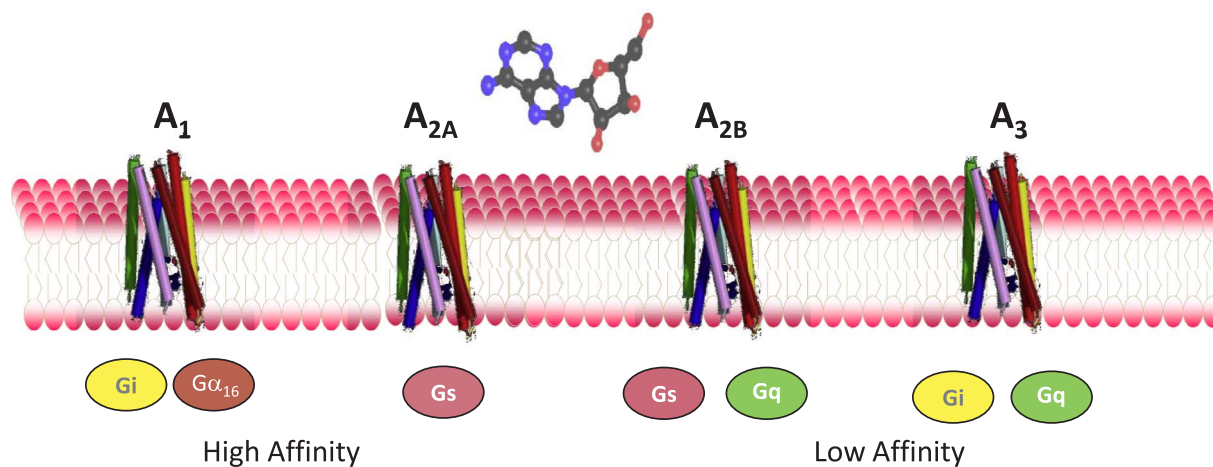
Fig. 2. Adenosine receptor signaling pathways.

While type 2 immunity mounted against parasites is crucial for the control of parasitic disease, type 2 immunity can also be triggered by allergens, which can harm the host. IL-4, IL-5, IL-9, and IL-13 are also the major drivers of allergic asthma, and studies in both mice and humans, have shown that they mediate many inflammatory processes, including bronchoconstriction, mucus production, eosinophilia, and immunoglobulin E class switching by B cells [64]. In addition to asthma, type 2 immune responses are also central to the development of atopic dermatitis, food allergy, anaphylaxis [65], and a number of fibrotic conditions [66].

It is now also clear that type 2 immunity is also important for the maintenance of homeostasis in adipose tissue and liver, and that dysregulation of the various components of type 2 inflammation results in obesity, metabolic syndrome and diabetes [67–69].

As yet though the pathways that initiate the type 2 immune response have only begun to be elucidated. Immune responses to viruses and bacteria are in many cases triggered by recognition of pathogen associated molecular patterns (PAMPS), that in turn bind pattern recognition receptors (PRRs), which can include toll like receptors (TLRs). Interestingly, TLR-signaling is not generally required for helminth-induced type 2 immune responses, although PAMPs binding other ligands have been proposed as contributing to the helminth response [70]. It is increasingly clear that endogenously produced danger signals, or DAMPs, elicited following tissue damage may also trigger signaling pathways that promote immune responses [61]. A number of potential DAMPs have been proposed including Trefoil factor 2 (TFF2), DNA, and nucleotides (ATP and ADP), all of which may be released into the extracellular space following cellular disruption and there bind cellular receptors that trigger immune responses [71,72].

Recent studies have suggested that adenosine interacting with A2BR may contribute to components of type 2 immunity and thus can be a DAMP that initiates and promotes type 2 immune responses. In vitro studies have indicated that A2BR signaling can activate mast cells to secrete IL-4 in vitro [73]. IL-4 amplifies A2BRs on mast cells indicating the existence of a positive feedback loop consisting of A2BRs and secreted IL-4 in mast cells [74].

A2BRs stimulate dendritic cells to upregulate production of the type 2-skewing cytokine IL-10, and A2BRs skew dendritic cells to promote CD4$^+$ T cell IL-4 production under hypoxia [75,76]. Our studies have shown A2BRs enhance IL-4- or IL-10 mediated alternatively activated (M2) macrophage differentiation [77–80].

In an early in vivo study, A2BR signaling enhanced allergen-induced chronic pulmonary inflammation in an ovalbumin model system [81]. Subsequent studies confirmed this proinflammatory role of A2BRs in a cockroach allergen model of asthma [82]. Our studies showed that A2BR signaling was required for the development of both innate and

adaptive components of the helminth-induced type 2 immune response, including the memory host protective response [83]. We further provided intriguing findings suggesting that one mechanism through which A2BR signaling drives type 2 immunity may be through induction of IL-33 expression and downstream upregulation of IL-5 and IL-13 [83]. In a recent in vitro study, we found that A2BR signaling down-regulates IL-15 and IL-13 production by group 2 innate lymphoid cells or ILC2s [84], which indicates that the A2BR-mediated enhancement of anti-helminth immunity is independent of ILC2s.

Adenosine also contributes to pulmonary fibrosis by interfering with type 2 inflammation and especially IL-13 [85]. In an experimental mouse model of pulmonary fibrosis, A2BRs on alternatively activated macrophages contributed to the progression of fibrosis [86,87].

The role of other ARs in regulating type 2 immunity is less clear. An in vivo study using adenosine deaminase deficient mice, which have increased systemic adenosine levels, showed that genetic removal of A1Rs was associated with exaggerated production of IL-4 and Il-13 in the lung [88]. We demonstrated in an in vitro study that A2ARs suppress the development of T helper 2 lymphocytes [49]. In addition, A2AR activation decreases IL-4 production by naïve T cells [89]. In agreement with these in vitro results, A2AR activation has anti-inflammatory effects in allergic lung inflammation in vivo [90].

5. The role of adenosine and adenosine receptors in maintaining chondrocyte and cartilage homeostasis

Depending on the species and the condition, chondrocytes express primarily A2AR and A2BR although in some studies A1R expression has also been documented to play a role in regulating chondrocyte function [91–93]. In addition, A3R have been reported to inhibit the development of osteoarthritis by diminishing joint inflammation [94]. Direct effects of A2AR and A2BR stimulation on chondrocyte function have been more frequently described [91,95–98]. Interestingly, Mistry and colleagues reported that very high doses of adenosine, achievable only in the presence of inhibitors of enzymes (adenosine deaminase) that degrade adenosine, are toxic to chondrocytes and induce chondrocyte apoptosis [99].

Chondrocytes, the resident cells of cartilage, maintain cartilage by synthesizing new matrix to replace cartilage matrix as it ages. Because cartilage is an avascular tissue chondrocytes obtain their nutrients by diffusion from the synovial fluid. With aging and inflammation there is a growing imbalance between chondrocyte production of matrix and destruction of matrix. We have recently shown that adenosine, derived from ATP released from chondrocytes, plays an important homeostatic role in chondrocyte and cartilage biology and replacement of adenosine in the joint of affected joints prevents progression of osteoarthritis in a rat model of post-traumatic osteoarthritis [95].

Johnson and colleagues first reported that diminished oxidative phosphorylation in chondrocytes leads to diminished ATP levels and diminished matrix replacement [100]. In subsequent work this same group reported that chondrocyte ATP depletion leads to the spontaneous development of knee osteoarthritis in a guinea pig model [101]. In subsequent work Wang and colleagues reported that human osteoarthritis chondrocytes made less ATP and lower intracellular levels of ATP than unaffected chondrocytes [102]. Increasing age and inflammatory cytokines are consistent stimuli for these changes in chondrocyte metabolism [103–105]. This process has been termed inflammaging.

Consistent with these observations in aging and osteoarthritic cartilage we have recently reported a novel homeostatic mechanism in cartilage and chondrocytes, disruption of which leads to chondrocyte dysfunction and cartilage loss [95]. We discovered that diminished ATP levels, a feature typical of OA chondrocytes, are associated with diminished ATP export into the extracellular space resulting in reduction of extracellular adenosine. Reduction of adenosine in the extracellular space results in less stimulation of A2AR which is required for maintenance of chondrocyte homeostasis. Observations in mice lacking A2AR and ecto-5′nucleotidase confirm this overall hypothesis; A2AR and ecto-5′nucleotidase deficient mice develop spontaneous osteoarthritis. Humans lacking ecto-5′nucleotidase also develop spontaneous osteoarthritis in addition to a number of other abnormalities. Further evidence for the role of adenosine as a homeostatic factor was provided in a rat model of post-traumatic osteoarthritis in which intra-articular injection of liposomal suspensions of adenosine rescue the osteoarthritis phenotype. Whereas much of the effect of exogenous adenosine on suppression of OA activity is likely due to adenosine-mediated suppression of inflammation (cf [106]), in preliminary studies there is clearly a direct anabolic effect of A2AR stimulation on chondrocyte function (aggrecan) and suppression of production of catabolic proteins (MMP13) and markers of chondrocyte hypertrophy (col10a1), consistent with previous reports on the effect of A2AR ligation on chondrocyte production of NO, PGE2 and release of cartilage breakdown products (glycosaminoglycans, [107–109]).

Excess adenosine also appears to play a role in chondrocyte and cartilage biology since children lacking adenosine deaminase, in whom plasma adenosine levels increase to the micromolar level [110,111], develop chondrodysplasia [112]. The mechanism for this chondrodysplasia is not well understood and recent studies from mice suggest that although the very high levels of adenosine present in adenosine deaminase-deficient children induce chondrocyte apoptosis [99] these are changes that are not consistent with the cartilage changes observed in children lacking adenosine deaminase.

6. Summary and conclusion

Adenosine is a potent regulator of many different physiologic and pharmacologic processes. Adenosine is, for the most part, generated from the extracellular hydrolysis of ATP although it can be transported into the extracellular space directly. While adenosine is present in pharmacologically relevant concentrations in nearly all bodily fluids its concentration can be rapidly increased or decreased. Acting at its receptors adenosine plays an important role in mediating and regulating responses to pathogens and in maintaining homeostasis in the joint. We expect that by capitalizing on our increasing understanding of the role of adenosine in regulating immunity and joint homeostasis, we will be able to use this information to develop new drugs to treat immune and joint diseases. Specifically, as A2BRs are important in initiating and promoting type 2 immunity, A2BR agonists may be used in the future as part of novel vaccine regimens to treat and prevent helminth infections. In disease states, where type 2 immunity is overly activated, such as in asthma, fibrosis, and allergic skin diseases, A2BR antagonists may be beneficial.

The current approaches to medical therapy of osteoarthritis are inadequate; anti-inflammatory drugs (corticosteroids), either injected intra-articularly or by mouth (NSAIDs) dominate the therapeutic approaches to osteoarthritis. Other agents, such as intra-articular injection of hyaluronic acid, are of questionable value as well and joint replacement is an increasingly common option for patients. The development of new therapies targeted to adenosine receptors on chondrocytes could provide a turning point in the treatment of this widespread and debilitating condition.

Acknowledgements

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