Published in final edited form as:
Pharmacol Ther. 2007 February ; 113(2): 264–275.

Shaping of monocyte and macrophage function by adenosine receptors

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Abstract

Adenosine is an endogenous purine nucleoside that, following its release into the extracellular space, binds to specific adenosine receptors expressed on the cell surface. Adenosine appears in the extracellular space under metabolically stressful conditions, which are associated with ischemia, inflammation, and cell damage. There are 4 types of adenosine receptors (A_1, A_{2A}, A_{2B} and A_3) and all adenosine receptors are members of the G protein-coupled family of receptors. Adenosine receptors are expressed on monocytes and macrophages and through these receptors adenosine modulates monocyte and macrophage function. Since monocytes and macrophages are activated by the same danger signals that cause accumulation of extracellular adenosine, adenosine receptors expressed on macrophages represent a sensor system that provide monocytes and macrophages with information about the stressful environment. Adenosine receptors, thus, allow monocytes and macrophages to fine-tune their responses to stressful stimuli. Here, we review the consequences of adenosine receptor activation on monocyte/macrophage function. We will detail the effect of stimulating the various adenosine receptor subtypes on macrophage differentiation/proliferation, phagocytosis, and tissue factor (TF) expression. We will also summarize our knowledge of how adenosine impacts the production of extracellular mediators secreted by monocytes and macrophages in response to toll-like receptor (TLR) ligands and other inflammatory stimuli. Specifically, we will delineate how adenosine affects the production of superoxide, nitric oxide (NO), tumor necrosis factor-α, interleukin (IL)-12, IL-10, and vascular endothelial growth factor (VEGF). A deeper insight into the regulation of monocyte and macrophage function by adenosine receptors should assist in developing new therapies for inflammatory diseases.

Keywords

Infection; Autoimmunity; Asthma; Sepsis; Arthritis; Colitis

1. Introduction

Macrophages are a heterogeneous population of mononuclear phagocytes found ubiquitously in the body. These cells have a role in orchestrating and executing most homeostatic, immunological, and inflammatory processes (Mosser, 2003; Stout & Suttles, 2004). Owing to their ubiquitous tissue distribution these cells are ideally suited to mount an immediate attack against foreign elements prior to the migration of polymorphonuclear neutrophils and, thus,

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macrophages are major factors in the body's first line of immune defense. Newly formed macrophages that are called monocytes are produced from bone marrow progenitor cells (Naito et al., 1996; Valledor et al., 1998). After differentiating as a result of exposure to local cytokines such as granulocyte-macrophage colony-stimulating factor, interleukin (IL)-3, and macrophage colony-stimulating factor, they leave the bone marrow and enter the blood. In the blood they come in contact with a plethora of regulatory molecules (including cytokines, chemokines, hormones, fatty acids, immunoglobulins), which impact their functional and phenotypic characteristics. Circulating monocytes represent a mobile source of functionally competent immune cell that upon appropriate stimuli can invade the tissue. This homing process takes place in response to chemotactic cytokines and other tissue-specific homing factors (Muller & Randolph, 1999). After their infiltration into tissues, monocytes go through further differentiation to become macrophages. It is becoming widely accepted that the distinct phenotypes of macrophages in different tissues reflect an effect of the actual tissue environment, rather than originating from a lineage specificity (Muller & Randolph, 1999).

The biological functions of activated monocytes/macrophages are numerous and well investigated (Gordon, 2003; Mosser, 2003; Stout & Suttles, 2004). As crucial elements of innate immune responses, monocytes/macrophages capture, process, and nonspecifically kill antigens, and then activate specific lymphocyte effector mechanisms. Lymphocyte activation crucially depends on the expression of macrophage cell surface molecules such as major histocompatibility complex and costimulatory molecules, as well as production of a wide range of mediators, which include cytokines and free radicals (Unanue, 1984). These activated lymphocytes representing the specific arm of the immune response in turn cooperate with macrophages to further *destroy* pathogens, as well as virus-infected cells, apoptotic host cells, and tumor cells.

Once the inflammatory/immune response has eliminated an injurious agent, the process of inflammatory resolution ensues, which is orchestrated by endogenous 'pro-resolving' mediators in a highly coordinated way (Duffield, 2003; Gilroy et al., 2004; Wells et al., 2005). These factors turn off leukocyte movement to the inflamed site, decrease vasodilatation and vascular permeability, and cause the safe removal of inflammatory neutrophils, exudate and fibrin, thereby restoring the integrity of the inflamed tissue to its prior physiological function. Macrophages have central roles in dictating inflammatory resolution and there is ample evidence that adenosine can interfere with features of the inflammatory resolution. Successful resolution will restrict excessive tissue injury and thwart the development of chronic, immune-mediated inflammation (Gilroy et al., 2004).

The aim of this Review article is to highlight the studies that have uncovered how adenosine interferes with the various facets of macrophage activation thereby modifying inflammatory/immune processes.

2. Adenosine receptors

Adenosine was first recognized as a physiologic regulator of coronary vascular tone by Drury and Szent-Gyorgyi (1929), however it was not until 1970 that Sattin and Rall showed that adenosine regulates cell function via occupancy of specific receptors on the cell surface (Sattin & Rall, 1970). It is now clear that there are at least 4 different subtypes of adenosine receptor, any one or combination of which may be expressed on the cell surface (Ralevic & Burnstock, 1998; Fredholm et al., 2001; Linden, 2001; Hasko & Cronstein, 2004; Fredholm et al., 2005). Four adenosine receptors have been cloned and the deduced sequence reveals that all 4 are members of the large family of 7-transmembrane spanning G protein coupled receptors. Three of the adenosine receptor subtypes, A_1, A_{2A} and A_{2B}, are highly conserved throughout evolution (80–95% sequence homology) whereas A_3 receptors vary significantly among

species. In general, A_1 and A_3 receptors are coupled to pertussis toxin-inhibited G_i coupled signal transduction proteins or directly to ion channels whereas A_2 receptors (A_{2A} and A_{2B}) are $G\alpha_S$-linked receptors and stimulate adenylyl cyclase and camp accumulation. Adenosine receptors or receptor-mediated effects have been demonstrated in virtually every tissue or organ examined (Hasko & Szabo, 1998; Ralevic & Burnstock, 1998; Fozard & Hannon, 1999; Fredholm et al., 2001; Linden, 2001; Fozard & McCarthy, 2002; Hasko et al., 2002; Hasko & Cronstein, 2004; Fredholm et al., 2005).

3. Adenosine metabolism

Most physiological effects of adenosine arise from its stimulation of cell surface adenosine receptors and the activation of downstream signaling pathways. Adenosine concentrations at its receptors are determined by a variety of processes, which include extracellular and intracellular adenosine generation, adenosine release from cells, cellular reuptake and metabolism. These processes are closely intertwined and strictly regulated. For, example, under hypoxic conditions, the increased intracellular dephosphorylation of adenosine 5′-triphosphate (ATP) to adenosine by the metabolic enzyme 5′-nucleotidase is accompanied by a suppression of the activity of the salvage enzyme adenosine kinase, which prevents the rephosphorylation of adenosine (Deussen, 2000). These processes lead to adenosine reaching high concentrations inside the cell and the release of adenosine into the extracellular space through nucleoside transporters (Hyde et al., 2001; Pastor-Anglada et al., 2001). The other major pathway that contributes to high extracellular adenosine concentrations during metabolic stress is release of precursor adenine nucleotides (ATP, ADP and AMP) from the cell. This is followed by extracellular degradation to adenosine by a cascade of ectonucleotidases, which include CD39 (nucleoside triphosphate diphosphohydrolase [NTPDase]) and CD73 (5′-ectonucleotidase) (Kaczmarek et al., 1996; Resta et al., 1998; Zimmermann, 1999; Eltzschig et al., 2004; Thompson et al., 2004; Sperlagh et al., 2006). Adenosine accumulation is limited by its catabolism to inosine by adenosine deaminase. Inosine is finally degraded to the stable end product uric acid (Jennings & Steenbergen, 1985; Hasko, Kuhel, Nemeth et al., 2000; Cristalli et al., 2001; Hasko et al., 2004).

There are several important producer cell types of extracellular adenosine. Neutrophils and endothelial cells release large amounts of adenosine at sites of metabolic distress, inflammation and infection (Cronstein et al., 1983; Gunther & Herring, 1991; Madara et al., 1993; Rounds et al., 1994). We recently documented that nerve terminals are a major contributor to extracellular adenosine accumulation in the ischemic spleen (Sperlagh et al., 2000) and ADP released by platelets can be a significant source of adenosine after dephosphorylation (Marcus et al., 1995). Activated macrophages can also serve as a major source of extracellular adenosine via ATP production. We recently reported that bacterial lipopolysaccharide (LPS) augmented the release of ATP from macrophages (Sperlagh et al., 1998). Because the inhibitory effects of exogenously added ATP on macrophage TNF-α production can be abrogated by administering exogenous adenosine deaminase (Hasko, Kuhel, Salzman et al., 2000), it can be proposed that endogenously released ATP is also degraded to adenosine by macrophages.

Lower concentrations of adenosine activate the high affinity A_1, A_{2A}, and A_3 receptors, and high adenosine concentrations stimulate the low affinity A_{2B} receptors. Thus, since the degree of metabolic distress can determine the concentration of extracellular adenosine, the more pronounced the metabolic distress is, the more likely it is that A_{2B} receptors are activated. Further factors that determine the net effect of adenosine on macrophage function are adenosine receptor expression and coupling efficacy to intracellular signaling pathways, factors that are all very dynamically regulated.

4. Effect of adenosine on monocyte/macrophage maturation and proliferation

The differentiation, maturation, and proliferation of macrophages are tightly regulated processes that are important in determining the nature and degree of macrophage responsiveness to activating agents and stimuli. Evidence indicates that adenosine can alter the course of macrophage proliferation and differentiation. The first evidence supporting the concept that endogenous adenosine is capable of preventing human monocyte maturation was provided by demonstrating that adenosine deaminase activity is increased during early monocyte differentiation and that adenosine deaminase inhibition during this period delayed the maturation process (Fischer et al., 1976). High concentrations of exogenous adenosine seem to prevent monocyte development into macrophages and arrest monocyte development at a stage with high accessory function, a phenotype that is similar to dendritic cells (Najar et al., 1990; Fig. 1). Adenosine influences monocyte maturation also by promoting the formation of multinucleated giant cells via A_1 receptor stimulation, whereas A_2 receptor activation prevents the generation of giant cells (Merrill et al., 1997; Fig. 1). The specific intracellular mechanisms through which adenosine receptor signaling influences the maturation of monocytes are unclear and remain an important area for future study.

We know little about how adenosine receptor occupancy impacts macrophage proliferation. Macrophage colony-stimulating factor-induced proliferation of mouse bone marrow macrophages is suppressed by adenosine, which is mediated through A_{2B} receptors (Xaus, Valledor et al.,1999; Fig. 1). The mechanism of action of adenosine involves induction, in a PKA-dependent manner, of the expression of $p27^{kip-1}$, a cyclin-dependent kinase inhibitor that leads to growth arrest at the G_1 phase of the cell cycle.

In human monocytes, the non-selective adenosine receptor agonist 5′-*N*-ethylcarboxamidoadenosine (NECA) but not 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethyl-carboxamidoadenosine (CGS 21680), a selective agonist of A_{2A} receptors, down-regulated the proliferation of human peripheral blood mononuclear cells obtained from healthy subjects. On the other hand, the selective A_1 receptor agonist N^6-cyclopentyladenosine (CPA), but not other agonists, inhibited the proliferation of mononuclear cells in asthmatic patients (Landells et al., 2000). Because high, non-selective drug concentrations (10 μM) were used, the authors argued that their results did not support a major role for adenosine receptors in the regulation of mononuclear cell proliferation. Thus, further studies to examine the effect of extracellular adenosine on macrophage proliferation are warranted.

5. A_1 and A_2 receptors differentially modulate Fcγ receptor-mediated phagocytosis

Phagocytosis is the process by which macrophages ingest, degrade and eventually present peptides derived from particulate antigens. When a small particle is coated (opsonized) with IgG, the Fc regions of the IgG antibody molecules bind to Fc receptors that are expressed on the macrophage plasma membrane and trigger a phagocytic response (Swanson & Hoppe, 2004). The regulation of Fcγ receptor-mediated phagocytosis by adenosine was one of the first effects described for this nucleoside in modulating the activity of monocytes/macrophages (Pike et al., 1978). Adenosine, in the presence, but not in the absence, of the adenosine deaminase inhibitor erytho-9-(2-hydroxy-3-nonyl) adenine (EHNA) enhanced, in a dose-dependent manner, Fcγ-mediated phagocytosis by undifferentiated monocytes of IgG-coated sheep erythrocytes. The fact that the presence of EHNA was necessary for adenosine to affect this monocyte function indicates that monocytes contain high concentrations of adenosine deaminase, which metabolize adenosine leading to a loss of its activity. Contrary to the stimulatory effect on phagocytosis in human monocytes, adenosine in the presence of EHNA diminished Fcγ-mediated phagocytosis of erythrocytes by mouse peritoneal macrophages

(Leonard et al., 1978; Sung & Silverstein, 1985) indicating that adenosine can have differential effects on phagocytosis depending on the cellular source. Later studies have helped to explain the opposing effects of adenosine on phagocytosis by undifferentiated monocytes and peritoneal macrophages which are a differentiated macrophage population. Eppell et al. (1989) demonstrated that adenosine in the absence of EHNA is unable to alter phagocytosis by undifferentiated monocytes; however, monocytes that were in culture for 2 days or more responded to adenosine by a diminished phagocytic response. The kinetics of this change was tightly associated with specific adenosine binding to the cells, suggesting that certain adenosine receptor(s) emerge on monocytes during in vitro differentiation into macrophages. The suppressive effect of adenosine on phagocytosis was due to A_2 (A_{2A} or A_{2B}) receptor occupancy, because the order of potency of agonists was NECA>adenosine>N^6-*R*-phenylisopropyladenosine (R-PIA, an A_1 receptor agonist) when measured following 2 days of culture. Furthermore, the suppressive effect of adenosine on phagocytosis was prevented using a selective protein kinase A (PKA) inhibitor, further implicating A_2 receptors, because A_2 but not other adenosine receptors are positively coupled to the cAMP-PKA second messenger system. Although these results helped to elucidate why adenosine inhibits phagocytosis in macrophages (Leonard et al., 1978; Sung & Silverstein, 1985), they did not explain why adenosine in the presence of EHNA augments phagocytosis by fresh, undifferentiated monocytes (Pike et al., 1978). A subsequent study employing selective, stable adenosine receptor analogs in freshly isolated monocytes appeared to resolve this issue. Salmon et al. (1993) showed that in undifferentiated monocytes, the A_1 receptor agonist CPA was capable of enhancing phagocytosis, indicating a role for A_1 receptors in promoting Fcγ-receptor-mediated phagocytosis. These pharmacological results were confirmed by flow cytometry, because the A_1 receptor was expressed on the surface of immature monocytes. Thus, when the degradation of adenosine is inhibited either by EHNA or A_1 receptors are stimulated by a stable ligand, the stimulatory effect of A_1 receptor activation on monocyte phagocytosis is unveiled. Concurrently, NECA moderated phagocytosis even in these fresh monocytes, which observation seems to challenge the earlier conclusion of Eppell et al. (1989) that A_2 adenosine receptors are not present on these immature cells. It is possible that by using the stable adenosine receptor agonist NECA, the inhibitory effect of A_2 receptors could be unmasked even in these immature monocytes. A_2 receptor expression increases with time, because the degree of suppression of phagocytosis in fresh monocytes by NECA is less than that seen in more mature cells. Taken together, monocyte/macrophage phagocytosis is regulated in a contrasting and temporal manner by A_1 and A_2 receptors, where in fresh monocytes the stimulatory effect of A_1 receptors is overcome by an A_2 receptor-mediated suppression of phagocytosis in mature macrophages. Because the selectivity of the agents used is these studies that were *carried out* over 10 years ago is questionable, it is clear that additional studies on the involvement of the various adenosine receptor subtypes in regulating phagocytosis are warranted.

6. Adenosine inhibits monocyte/macrophage oxidative burst

Monocytes and macrophages secrete reactive oxygen species (mostly superoxide and H_2O_2) during phagocytosis or stimulation with a wide variety of agents, a process, which is crucial for the bactericidal activation of macrophages (Forman & Torres, 2002). Recent evidence documents that adenosine and adenosine analogs are potent inhibitors of the respiratory burst of monocyte/macrophages. Leonard and coworkers (1987) were the first to demonstrate that adenosine-treated human monocytes displayed diminished oxidative burst following stimulation with f-Met-Leu-Phe (fMLP) but not phorbol myristate acetate (PMA). Since adenosine did not decrease the PMA-induced respiratory burst, it was proposed that the mode of action of adenosine was not related to a direct effect on protein kinase C (PKC). Two later studies, one using fMLP (Broussas et al., 1999) and the other LPS (Thiele et al., 2004) to stimulate oxidative burst, confirmed that the effect of adenosine could be attributed primarily

to A_3 receptor stimulation. This idea was supported by the observations that the A_3 receptor agonist N^6-(3-iodobenzyl)-adenosine-5′-*N*-methyluronamide (IB-MECA) was more potent than the A_{2A} agonist CGS 21680 or A_1 receptor agonist R-PIA. mRNA for all 4 adenosine receptor subtypes was expressed in freshly isolated monocytes, and while the expression of A_1, A_{2B}, and A_3 receptors did not vary during a 7-day cultivation period, the mRNA for A_{2A} receptors was up-regulated after day 1 and disappeared by day 7 of culture (Thiele et al., 2004). In agreement with the pharmacological data that IB-MECA was more potent than CGS 21680, an agonist which elicits its cellular effects mainly by activating the cAMP-PKA pathway (Lupica et al., 1990), the cAMP-dependent protein kinase inhibitor KT5720 failed to reverse the inhibitory effect of adenosine on fMLP-induced monocyte respiratory burst (Broussas et al., 1999). The inhibitory effect of adenosine on human monocyte/macrophage respiratory burst was recapitulated using both mouse (Si et al., 1997) and rat (Edwards et al., 1994) peritoneal macrophages; however, there was no detailed analysis of the adenosine receptors involved in either study.

7. Adenosine modulates nitric oxide production by monocyte/macrophages

Nitric oxide (NO) synthases (NOS) catalyze the oxidation of one of the guanidino nitrogens of L-arginine to the reactive nitrogen species NO (Southan & Szabo, 1996). Along with reactive oxygen species, NO is another important factor which contributes to the bactericidal activity of macrophages, especially in rodents. Of the several NOS isoforms that can catalyze NO synthesis, iNOS is the primary one that is responsible for antimicrobial activity by producing high levels of NO. Host expression of iNOS is first and foremost regulated at the transcriptional level and can be stimulated in response to microbial products or by cytokines such as IL-1, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) (Nathan & Hibbs, 1991). We demonstrated that both the selective A_1 receptor agonist 2-chloro-N^6-cyclopentyladenosine (CCPA) and A_{2A} agonist CGS 21680 suppressed NO production by LPS-stimulated RAW264.7 macrophages, both with low efficacy (IC_{50} > 100 μM) (Hasko et al., 1996). Subsequent studies determined that several adenosine receptor agonists (0–100 μM) increased NO production under very similar conditions (Hon et al., 1997; Min et al., 2000), which is difficult to reconcile with our results showing a lack of effect of adenosine receptor agonists at these concentrations. Conversely, treatment of IFN-γ-activated bone marrow macrophages with NECA decreased both iNOS induction and NO production in these cells (Xaus, Mirabet et al., 1999). Experiments employing radioligands and antibodies documented the presence of both A_{2B} and A_3 receptors on these bone marrow macrophages; however, a detailed pharmacological analysis was not carried out to clarify the receptor type responsible for the down-regulation of NO production. Although the receptor type that suppressed iNOS expression was not addressed directly in this study, the A_{2B} receptor appears to be the primary receptor that influences the IFN-γ-induced activation of bone marrow-derived macrophages. This contention is based on the observation that NECA, but not selective A_1, A_{2A}, or A_3 agonists attenuated the IFN-γ-induced up-regulation of major histocompatibility complex II expression on bone marrow-derived macrophages (Xaus, Mirabet et al., 1999). Taken together, further research will be required to examine the impact of adenosine on NO production by macrophages and to determine whether any modulatory effect results in altered bactericidal activity by these cells.

8. Adenosine receptor signaling regulates pattern recognition receptor-mediated cytokine production

Pattern recognition receptors (PRR) are a class of proteins, which are employed by the cells of the immune system to identify molecules common to microbial pathogens. They are key elements in innate immunity as well as influence the development of adaptive immunity. They include the toll-like receptors (TLR), members of the nucleotide-binding oligomerization

domain (NOD; NOD1 and NOD2) proteins, scavenger receptors, and mannose-binding lectins. Among the molecules recognized by these PRR are LPS of Gram-negative bacteria, peptidoglycans and lipotechoic acids from Gram-positive bacteria, mannose residues, bacterial DNA, *N*-formylmethionine, viral double-stranded RNA and fungal glucans. The specific molecular sequences identified by a given PRR are its pathogen-associated molecular patterns (PAMP). Activation of PRR on monocytes and macrophages triggers a series of biological responses including cytokine secretion (Gordon, 2002; Janeway & Medzhitov, 2002).

There is a large body of evidence documenting that adenosine receptor stimulation can alter intracellular signaling pathways activated by PRR. The best-studied aspect of the interaction between the 2 pathways is the effect of adenosine receptor stimulation on cytokine production by monocytes/macrophages.

8.1. Adenosine suppresses TNF-α production by monocytes and macrophages

TNF-α is a well-known pro-inflammatory cytokine with a wide range of biological functions, which is secreted primarily by monocytes and macrophages (Hehlgans & Pfeffer, 2005). TNF-α plays an important role in the pathophysiology of chronic disease states such as rheumatoid arthritis (RA), Crohn's disease, graft-versus-host disease (GVHD), and the cachexia accompanying cancer and acquired immunodeficiency syndrome (AIDS). Because TNF-α was one of the first cytokines to be discovered, there is a plethora of information available on the regulation of TNF-α production by adenosine receptors.

8.1.1. Human monocytes/macrophages—In initial studies (Le Vraux et al., 1993) adenosine receptor agonists were shown to suppress TNF-α production by LPS (TLR4 ligand)-challenged human monocytes with the following rank order of potency: NECA>R-PIA=CGS 21680>2-CADO (2-chloroadenosine)=CHA (N^6-cyclohexyladenosine). Because NECA was the most potent agonist, a role for the A_{2B} receptor can be considered, because if NECA is the most potent agonist in a system, it indicates a predominant role for A_{2B} receptors (Feoktistov & Biaggioni, 1997). In another early study, NECA was more potent than CPA supporting the conclusion that A_2 receptors were responsible for the suppressive effect of adenosine on TNF-α secretion (Bouma et al., 1994). However, selective A_{2A} agonists were not tested in these studies, precluding a clear distinction between A_{2A} and A_{2B} receptors. In another study utilizing human monocytes, CGS 21680 was more potent than CPA and the selective A_2 receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX), but not A_3 antagonist 1,3-dipropyl-8-phenylxanthine amine congener (XAC) reversed the effect of CGS 21680 (Prabhakar et al., 1995). These results might implicate A_{2A} receptors, however, the role of A_{2B} receptors can not be excluded because NECA and A_{2B} antagonists were not tested. In a recent study utilizing the selective A_{2B} receptor antagonist *N*-(4-cyano-phenyl)-2-[4-(2,6-dioxo-1,3-dipropyl-2,3,4,5,6,7-hexahydro-1H-purin-8-yl)-phenoxy]-acetamide (MRS 1754, 100 nM), Zhang et al. (2005) were unable to confirm the role of A_{2B} receptors in moderating TNF-α production.

In subsequent studies following the discovery of A_3 receptors, Sajjadi et al. (1996) employing PMA-differentiated U937 (human monocyte) cells found that the order of agonist potency in inhibiting LPS-induced TNF-α production was IB-MECA >2-CADO = I-ABA (N^6-(4-amino-3-iodobenzyl) adenosine)> N^6-benzyl NECA>NECA>CGS 21680>CHA, which is indicative of a principal role of A_3 receptors. In addition, the selective A_1/A_3 receptor antagonist XAC, but not A_1 antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) or A_2 antagonist DMPX prevented the suppressive effect of the selective A_3 agonist I-ABA. Northern blot analysis revealed the presence of A_3 receptors in these cells, although A_1 and A_2 receptors were also detected. The inhibitory effect of I-ABA on TNF-α secretion was correlated with a decrease in TNF-α mRNA accumulation, indicating a pre-translational effect. A

comprehensive analysis of multiple intracellular signaling mechanisms found that the decrease in TNF-α production after I-ABA exposure was associated with changes in activation of the activator protein-1 (AP-1) transcription factor system, whereas the activity of I-ABA was independent of mitogen-activated protein (MAP) kinases and nuclear factor-κB (NF-κB), as well as PKA, PKC, and PLC. The inability of adenosine, at least at physiological concentrations, to attenuate LPS-induced NF-κB activation was confirmed by other studies (Majumdar & Aggarwal, 2003; Nemeth et al., 2003; Pinhal-Enfield et al., 2003).

Although, as illustrated in the aforementioned studies, A_1 receptors do not have a role in diminishing TNF-α production in LPS-stimulated human monocytes, A_1 receptors can decrease TNF-α release following different monocyte-activating stimuli. Upon stimulation with a combination of PMA and phytohemagglutinin (PHA), peripheral blood mononuclear cell TNF-α release was attenuated by A_1 receptor activation (Mayne et al., 1999). Evidence to support this conclusion was based on the observation that the selective A_1 receptor antagonist DMPX counteracted the inhibitory effect of the A_1 agonist R-PIA on TNF-α secretion. Importantly, this response was confined to healthy patients but not individuals afflicted with multiple sclerosis, pointing to a possible role of dysregulated A_1-receptor-mediated cytokine modulation as an etiological factor in multiple sclerosis. In addition to A_1 receptors, A_{2A} receptors might also decrease TNF-α release induced by PMA/PHA, because the inhibitory effect of CGS 21680 was abolished by a selective A_{2A} antagonist in U937 cells (Fotheringham et al., 2004). The mechanism of action of CGS 21680 was post-transcriptional because it decreased the stability of TNF-α mRNA, an effect that was closely associated with a reduction in p38 MAPK activation, an important regulator of TNF-α mRNA stability (Kotlyarov et al., 1999).

8.1.2. Mouse monocytes/macrophages—Adenosine is a strong inhibitor of TNF-α production by monocytes and macrophages. Early studies with the mouse macrophage cell line RAW264.7 demonstrated that CCPA and CGS 21680 were equipotent in suppressing LPS-induced TNF-α secretion, leaving open the question of which adenosine receptors are dominant in mouse cells (Hasko et al., 1996). Recent studies using RAW264.7 cells showed that CGS 21680 was ineffective at reducing TNF-α production, but IB-MECA did suppress TNF-α levels (Martin et al., 2006), lending support to the notion that A_3 receptors can regulate TNF-α production. Studies with the murine macrophage cell line J774.1 reinforced the idea that A_3 receptors may be involved in the reduction of TNF-α production as the A_3 receptor agonist N^6-(2-(4-aminophenyl)ethyl)-adenosine (APNEA) was more potent than various A_1 and A_2 agonists, and a selective A_3 antagonist reversed the effect of APNEA (McWhinney et al., 1996). In addition, A_3 receptor mRNAwas 10-fold more abundant than A_1 or A_{2A} receptor mRNA. The reason for the discrepancy between the findings of these studies regarding the role of A_{2A} receptors is not clear but the differences may be a reflection of the different LPS concentrations and incubation times used.

Recent studies using a combination of KO and pharmacological approaches have helped to resolve these controversies. Our studies utilizing knockout mice for the A_{2A} receptors showed that A_{2A} receptors clearly contribute to the adenosine suppression of TNF-α production by LPS-stimulated murine macrophages (peritoneal), because the suppressive effect of adenosine on TNF-α production was impaired in macrophages isolated from A_{2A} receptor KO animals when compared to WT controls (Hasko, Kuhel, Chen et al., 2000). In addition, CGS 21680 potently decreased TNF-α production by A_{2A} WT macrophages but it failed to influence TNF-α release by KO cells (Hasko, Kuhel, Chen et al., 2000). On the other hand, A_3 receptors are not involved in the suppressive effect of adenosine, because adenosine inhibited TNF-α production with the same potency by macrophages isolated from A_3 receptor KO mice as by cells from WT mice (Kreckler et al., 2006). Moreover, the A_{2A} receptor-independent portion of the adenosine effect that we observed (Hasko, Kuhel, Chen et al., 2000) appears to be

secondary to A_{2B} receptors, because MRS 1754 was able to completely antagonize this adenosine-induced A_{2A}-independent effect (Kreckler et al., 2006).

In summary, TNF-α production by monocytes/macrophages can be subject to inhibition by A_1, A_{2A}, and A_3 receptors and the receptor subtype involved depends on many factors, which include the source of cell, the species, and the inflammatory stimulus used. Remarkably, the inhibitory effect of adenosine on TNF-α production by macrophages is not limited to TLR4-mediated (LPS) induction of this cytokine because adenosine down-regulates TNF-α production when induced by agonists of TLR2, TLR3, TLR4, TLR7 and TLR9 (Pinhal-Enfield et al., 2003). Although it is probable that adenosine receptor occupancy inhibits a common major intracellular pathway that leads to TNF-α production in response to TLR activation, the nature of this intracellular target is unclear at this point. Nevertheless, the fact that the various adenosine receptors all inhibit TNF-α production suggests that endogenous adenosine may represent a crucial negative feedback signal on inflammatory processes.

8.2. Adenosine inhibits IL-12 production by monocytes and macrophages

The IL-12 family of heterodimeric cytokines includes IL-12, and the recently discovered IL-23, and IL-27. IL-12 itself was identified in 1989, as a soluble factor that could stimulate natural killer (NK) cells to produce IFN-γ (Kobayashi et al., 1989). This discovery paved the way for studies in which it was determined that macrophages and dendritic cells produced this cytokine in response to certain bacterial and parasitic infections and that this, in turn, led to the polarization of naive T cells to produce a T helper 1-cell response (Hunter, 2005). IL-12 is a covalently linked heterodimer composed of a light chain (IL-12p35) and a heavy chain (IL-12p40). The IL-12p40 component of IL-12 can also dimerize with IL-23p19 to form IL-23. The last member of this family of cytokines is IL-27, which is composed of Epstein-Barr-virus-induced molecule 3 (EBI3) and IL-27p28. IL-12 and IL-23 are important factors that promote cell-mediated immunity and inflammation, whereas IL-27 appears to have a role in limiting the intensity and duration of adaptive immune responses.

Studies so far have assessed the effect of adenosine receptor ligation on IL-12 and IL-12p40 production. Using A_{2A} receptor knockout mice, our group (Hasko, Kuhel, Chen et al., 2000) documented that adenosine down-regulates IL-12 p40 production by LPS-stimulated mouse peritoneal macrophages and that this effect is dependent, in part, on A_{2A} receptors. Further evidence implicating A_{2A} receptors came from studies with human monocytes, in which CGS 21680 potently blunted LPS-induced IL-12 (both IL-12p40 and IL-12) production, which effect was reversed by A_{2A} antagonists. The effect of A_{2A} stimulation is suppressing IL-12 production was linked to increased intracellular cAMP concentrations (Link et al., 2000; Khoa et al., 2001). A_{2A} receptor stimulation lead to decreased levels of IL-12 p40 mRNA, implying a pre-translational mechanism of action (Link et al., 2000). Khoa et al. (2001) reported recently that the degree to which IL-12 production is down-regulated following A_{2A} receptor stimulation is strongly influenced by the inflammatory environment that the cells encounter. The pro-inflammatory cytokines TNF-α and IL-1 augmented responsiveness to A_{2A} receptor stimulation resulting in a more impaired IL-12 production after administering CGS 21680. On the other hand, the presence of IFN-γ attenuated the inhibitory effect of A_{2A} receptor stimulation on IL-12 secretion. Corresponding with these observed functional changes in response to treatment with pro-inflammatory cytokines or IFN-γ was the expression of A_{2A} receptor mRNA and protein, which was found to be increased or decreased, respectively.

A_3 receptor stimulation can also negatively regulate IL-12 production, because the selective A_3 receptor agonist IB-MECA moderates IL-12 production both in LPS-treated mice (Hasko et al., 1998) and by human monocytes (la Sala et al., 2005). IB-MECA activated the phosophatidyl inositol-3-kinase (PI3K) pathway, and the activity of both PI3K and Akt was required for its suppressive effect (la Sala et al., 2005).

Taken together, since IL-12 has an eminent role in mediating a strong T helper 1-type inflammatory response, the suppression of IL-12 production by adenosine is probably one of the pivotal mechanisms by which adenosine receptor activation exerts its strong anti-inflammatory effects that are observed in animal models of autoimmunity (Hasko & Cronstein, 2004; Sitkovsky et al., 2004). Further studies are warranted to uncover how adenosine regulates the production of IL-23 and IL-27.

8.3. Adenosine facilitates IL-10 release by monocytes and macrophages

IL-10 is the founding member of a growing family of structurally related cytokines, which includes IL-19, IL-20, IL-22, IL-24, and IL-26 (Kotenko, 2002). IL-10 is a relatively unique cytokine in that it has been documented to have potent immune inhibitory activity. IL-10 was initially described as a T helper 2 product that reduced the production of cytokines by T helper 1 T cell clones (Mosmann et al., 1990). Subsequently, it has become clear that IL-10 is also produced by cells of the monocyte/macrophage lineage (de Waal Malefyt et al., 1991; Barsig et al., 1995; Moore et al., 2001). IL-10 was also described as cytokine synthesis inhibitory factor, because IL-10 can inhibit the secretion of a variety of proinflammatory cytokines, including TNF-α and IL-12. IL-10 synthesis comes after the induction of proinflammatory cytokines allowing termination of proinflammatory responses and the resolution of inflammation (Moore et al., 2001).

One of the most consistent actions of adenosine across various experimental systems is its ability to increase IL-10 production by monocytes/macrophages (Hasko et al., 1996; Le Moine et al., 1996; Hasko, Kuhel, Chen et al., 2000; Link et al., 2000; Khoa et al., 2001; Nemeth et al., 2005) (Fig. 2). In human monocytes activated with TNF-α, H_2O_2, or LPS, adenosine up-regulated IL-10 production, an effect that was not mimicked by administering NECA, 2-CADO, or R-PIA (Le Moine et al., 1996). In addition, the non-selective adenosine receptor antagonist theophylline was unable to reverse the stimulatory effect of adenosine, which led the authors to conclude that the stimulatory effect of adenosine on IL-10 secretion was not receptor-mediated. In spite of these observations the involvement of cell surface adenosine receptors mediating the stimulatory effect of adenosine on IL-10 production can not be precluded for several reasons. Firstly, selective A_{2A} or A_3 agonists and selective adenosine receptor antagonists were not examined in this study. Secondly, theophylline, used at *high* concentration (100 μM), is also a potent inhibitor of phosphodiesterases (Barry, 1988), and phosphodiesterase inhibition has been shown to increase IL-10 production (Mascali et al., 1996), thereby potentially masking its adenosine receptor antagonistic property. Thirdly, the adenosine uptake blocker dipyridamole was also incapable of preventing the stimulatory effect of adenosine on IL-10 production, secluding an intracellular, receptor-independent effect of adenosine. A subsequent study using selective adenosine receptor agonists documented that adenosine receptor agonists potentiated IL-10 production by LPS-activated monocytes (Link et al., 2000). In addition, adenosine receptor agonists markedly up-regulated LPS-induced IL-10 production in human whole blood, and the order of potency of agonists indicated a predominant role of A_{2A} receptors (Link et al., 2000). The A_{2A} antagonist (8-(3-chlorostyryl) caffeine) CSC, but not antagonists of the other adenosine receptors blocked the stimulatory effect of the agonist CGS 21680. Adenosine receptor activation up-regulated also *Staphylococcus aureus*-induced IL-10 production. A_{2A} receptor stimulation enhanced IL-10 production also in THP-1 monocytes (Khoa et al., 2001). IL-1 and TNF-α pretreatment potentiated the stimulatory effect of adenosine and CGS 21680 on LPS-induced IL-10 production, whereas IFN-γ treatment almost completely abolished this effect.

In a study employing murine peritoneal macrophages, we found that adenosine augmented IL-10 production (Hasko, Kuhel, Chen et al., 2000) to a similar extent (approximately by 100%) as in human monocytes. The receptor subtype(s) responsible for this stimulatory effect of

adenosine on IL-10 production by peritoneal macrophages have not been defined. On the other hand, we recently found that the stimulatory effect of adenosine on IL-10 production in RAW264.7 mouse macrophages was mediated through the A_{2B} receptor, because the order of potency of selective agonists was NECA>IB-MECA>CCPA=CGS 21680 (Nemeth et al., 2005). Also, the selective A_{2B} antagonist, alloxazine, prevented the effect of adenosine. The possible role of A_{2B} receptor was further highlighted by the fact that RAW264.7 cells expressed the A_{2B} receptor, which was further increased following LPS treatment.

In conclusion, the facilitation of IL-10 production may contribute to the anti-inflammatory and immunosuppressive effects of A_{2A} and A_{2B} receptor stimulation.

9. Adenosine decreases tissue factor expression

Tissue factor (TF) is a transmembrane glycoprotein that initiates the coagulation cascade and may also participate in angiogenesis; its regulation is responsive to inflammation and mechanical forces. Baseline (resting) monocyte TF activity is extremely low, but a several-fold increase occurs upon incubation for some hours (4–6 h) with several stimulators, such as LPS or certain pro-inflammatory cytokines (Osterud, 1998; Morrissey, 2004).

The platelet inhibitory drug dilazep exerts its anti-thrombotic effects by augmenting the adenosine level in the extracellular fluid through inhibition of adenosine transporters (Parks et al., 1985). In addition to its direct effects on platelets that are mediated via binding to A_{2A} receptors (Ledent et al., 1997), dilazep was reported to also block TF expression on monocytes and thereby inhibit blood coagulation (Deguchi et al., 1997; Zhou et al., 2004) implicating adenosine as a modulator of TF expression. Adenosine inhibits TF expression on LPS-stimulated human monocytes through the activation of A_3 receptors, because IB-MECA is the most potent agonist in reducing TF expression and the mixed A_1/A_3 antagonist XAC, but not selective A_1, A_{2A}, or A_{2B} antagonists prevented the effect of adenosine (Broussas et al., 2002).

10. Adenosine regulates vascular endothelial growth factor production

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is a potent inducer of angiogenesis and vascular permeability (Semenza, 2003). VEGF is required for endothelial cell differentiation during vasculogenesis, and for the sprouting of new capillaries from pre-existing vessels. Among all the pro-angiogenic factors, VEGF is considered the most essential for the differentiation of the vascular system. VEGF is thus an important mediator of both inflammation and repair, and is critical for the resolution of injury through the process of wound healing. Macrophages are primary producers of VEGF in wound healing, as well as in chronic inflammation (Semenza, 2003). Because VEGF is a crucial factor for tumor angiogenesis and tumor growth, it is an important target for clinical therapy in cancer (Lewis et al., 1995).

There is accumulating evidence that adenosine can facilitate angiogenesis, in part, by promoting VEGF production (Adair, 2005). Stimulation of A_2 receptors in U-937 human macrophages elicits VEGF mRNA accumulation (Hashimoto et al., 1994). Moreover, hypoxia, which is a major trigger of VEGF expression in most cell types (Semenza, 2003), augmented VEGF mRNA expression in U-937 cells, a process that could be prevented by adenosine deaminase and DMPX, indicating that hypoxia triggers the release of adenosine and the adenosine released so increases VEGF mRNA abundance. By contrast, although both hypoxia and A_{2A} stimulation acted as potent inducers of VEGF production by murine peritoneal macrophages, the effect of hypoxia in inducing VEGF secretion did not require adenosine and adenosine receptors (Leibovich et al., 2002). A_{2A} receptor stimulation and LPS through TLR4 activation synergistically facilitated the production of VEGF (Leibovich et al., 2002). In a

recent study our group documented that this synergistic interaction in inducing VEGF production was not confined to TLR4, and we observed a similar synergistic interaction between A_{2A} receptors and TLR2, TLR7, and TLR9 (Pinhal-Enfield et al., 2003). The mechanistic basis for this synergistic activity between A_{2A} receptors and TLRs remains to be explored.

11. Therapeutic implications

Macrophages/monocytes have emerged as a cell type that has a key role in shaping inflammation, immunity, wound healing, and cancer. Adenosine receptor activation can influence macrophage function depending on the receptor subtypes expressed and the environment in which macrophages are exposed to extracellular adenosine. The fact that the distinct adenosine receptors can selectively regulate discrete macrophage functions makes adenosine receptors a promising target for pharmacological interventions in a wide range of disease states that involve macrophage activation. For example, the therapy of autoimmune processes or ischemia–reperfusion injury, diseases that are associated with exuberant inflammation may capitalize on the use of adenosine receptor ligands that can suppress the pro-inflammatory activity of macrophages. Protective effects of adenosine receptor stimulation (mainly A_{2A} and A_3) have been observed in models of ischemia–reperfusion (Day et al., 2003, 2005; Yang et al., 2005), as well as autoimmune diseases, such as RA (Szabo et al., 1998), multiple sclerosis (Tsutsui et al., 2004), colitis (Odashima et al., 2005), and hepatitis (Ohta & Sitkovsky, 2001). A further possibility for the therapeutic use of the adenosine receptor system is to exploit the ability of A_{2A} receptor agonists to suppress inflammation and promote wound healing in disease processes such as diabetic ulcers (Montesinos et al., 1997). On the other hand, adenosine receptor ligands that have the ability to facilitate the inflammatory/immune responses of macrophages represent potential therapies for infectious diseases. A good example for this notion is our recent observation that A_{2A} receptor blockade can promote antibacterial immunity and bacterial clearance in septic animals (Nemeth et al., 2006). Finally, there is convincing evidence that selective adenosine receptor antagonists (A_{2B} and A_3) are potential therapeutics for asthma and chronic lung disease (Fozard & Hannon, 1999; Fozard & McCarthy, 2002; Blackburn, 2003; Fozard, 2003; Mohsenin & Blackburn, 2006; Spicuzza et al., 2006). Hopefully, the success of adenosinergic ligands as therapeutic interventions in experimental disease models will be replicated in human ailments in the not so distant future.

Acknowledgements

This work was supported by the National Institutes of Health Grant R01 GM66189 (G. Hasko), National Research and Development Program, Hungary (1A-036-2004, G. Hasko) and in part by the Intramural Research Program of NIH-NIAAA (P. Pacher).

Abbreviations

2Cl-IB-MECA
2-cloro-N^6-(3-iodobenzyl)-adenosine-5′-*N*-methyluronamide

ATP
adenosine 5′-triphosphate

CCPA
2-chloro-N^6-cyclopentyladenosine

CGS 21680
2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethyl-carboxamidoadenosine

CPA

N^6-cyclopentyladenosine

CSC
8-(3-chlorostyryl)caffeine

DPCPX
8-cyclopentyl-1,3-dipropylxanthine

IB-MECA
N^6-(3-iodobenzyl)-adenosine-5′-*N*-methyluronamide

IFN
interferon

IL
interleukin

LPS
bacterial lipopolysaccharide

MRS 1220
(9-chloro-2-(2-furanyl)-5-[(phenylacetyl)amino][1,2,4]-triazolo[1,5-c] quinazoline

NO
nitric oxide

PACPX
1,3-dipropyl-8-(2-amino-4-chlorophenyl)-xanthine

TF
tissue factor

VEGF
vascular endothelial growth factor

ZM241385
4-(2-[7-amino-2-(2-furyl)-{1,2,4}-triazolo{2,3-a}{1,3,5} triazin-5-ylamino] ethyl)phenol

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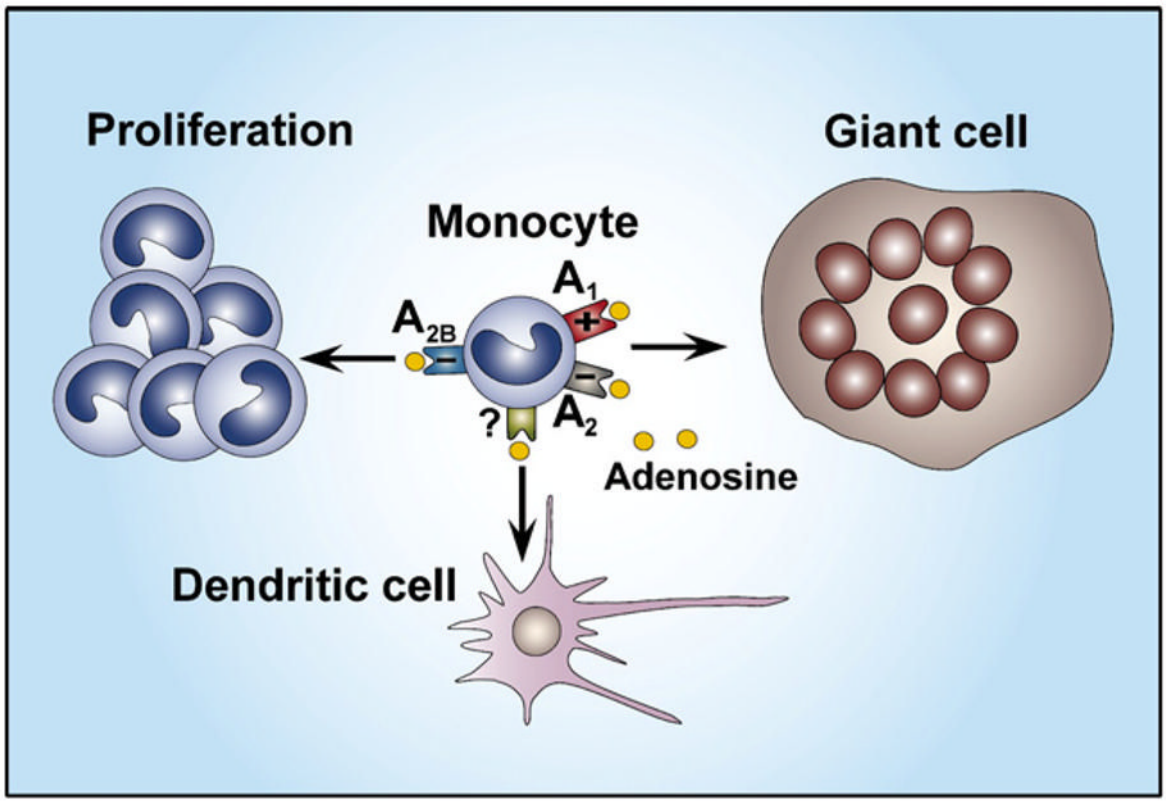

Fig. 1.

Adenosine suppresses macrophage proliferation through A_{2B} receptors. Adenosine facilitates the formation of multinucleated giant cells via the activation of A_1 receptors and inhibits it via A_2 (A_{2A} or A_{2B}) receptors. Adenosine promotes monocyte differentiation toward a phenotype resembling dendritic cells.

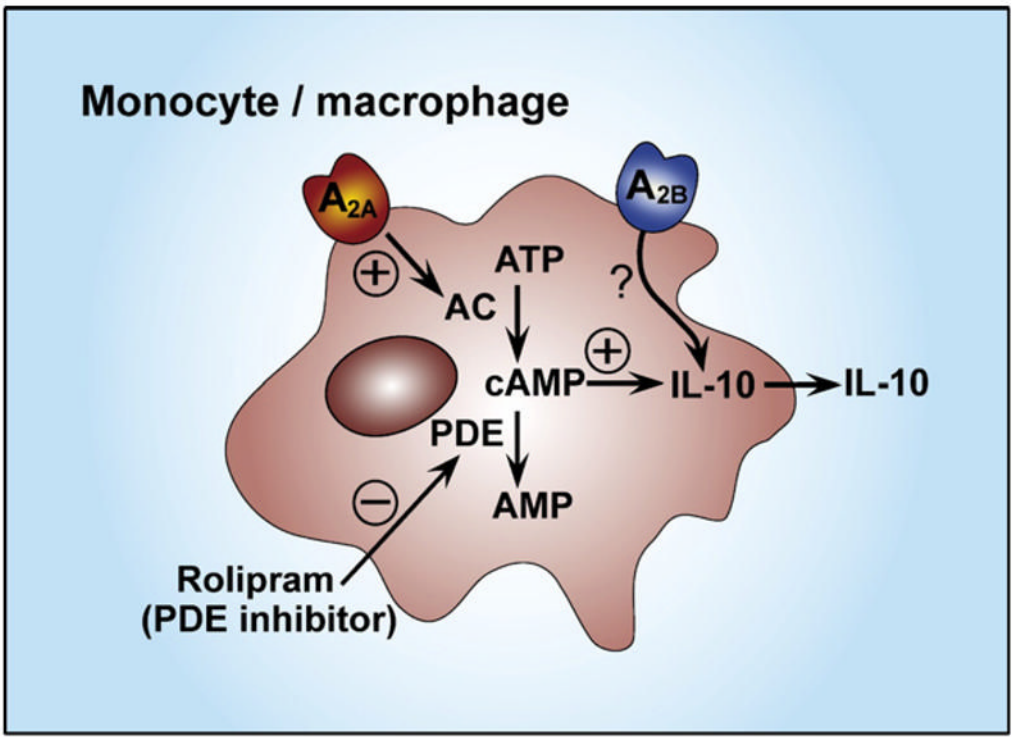

Fig. 2.

A_{2A} receptor activation augments IL-10 production by monocytes and macrophages through a cyclic adenosine monophosphate (cAMP)-mediated pathway. A_{2A} receptor activation stimulates adenylate cyclase (AC) leading to elevated intracellular cAMP levels. Phosphodiesterase (PDE) inhibition with rolipram can mimic the effect of A_{2A} receptor stimulation in augmenting IL-10 production. A_{2B} receptor activation also facilitates IL-10 production.