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Adenosine Signaling During Acute and Chronic Disease States

Harry Karmouty-Quintana, **Yang Xia**, and **Michael R. Blackburn**
Department of Biochemistry and Molecular Biology, The University of Texas Medical School at Houston, 6431 Fannin St., Houston, TX 77030 USA

Abstract

Adenosine is a signaling nucleoside that is produced following tissue injury, particularly injury involving ischemia and hypoxia. The production of extracellular adenosine and its subsequent signaling through adenosine receptors plays an important role in orchestrating injury responses in multiple organs. There are four adenosine receptors that are widely distributed on immune, epithelial, endothelial, neuronal and stromal cells throughout the body. Interestingly, these receptors are subject to altered regulation following injury. Studies in mouse models and human cells and tissues have identified that the production of adenosine and its subsequent signaling through its receptors plays largely beneficial roles in acute disease states, with the exception of brain injury. In contrast, if elevated adenosine levels are sustained beyond the acute injury phase, adenosine responses can become detrimental by activating pathways that promote tissue injury and fibrosis. Understanding when during the course of disease adenosine signaling is beneficial as opposed to detrimental and defining the mechanisms involved will be critical for the advancement of adenosine based therapies for acute and chronic diseases. The purpose of this review is to discuss key observations that define the beneficial and detrimental aspects of adenosine signaling during acute and chronic disease states with an emphasis on cellular processes such as inflammatory cell regulation, vascular barrier function and tissue fibrosis.

Keywords

adenosine receptors; inflammation; fibrosis; vascular barrier function; CD73; ADORA2B; ADORA2A; ADORA3; ADORA1; acute lung injury; remodeling; anti-inflammatory

Introduction

Tissue responses to ischemia, acute inflammation or fibrosis involve severe levels of hypoxia [1]. Studies over the past decade provide strong evidence that cellular responses to hypoxia include robust increases in extracellular adenosine and signaling events through adenosine receptors. In acute injury settings, this hypoxic adenosine response activates pathways that promote tissue adaptation during hypoxia [1]. These pathways include restoration of normal oxygen levels, enhancing metabolic ischemia tolerance and dampening inflammation. Indeed, preclinical studies show that adenosine signaling is beneficial in ischemic acute injury in the lung [2–6], kidney [7–9], heart [10, 11], gastrointestinal track [12] and liver [13]. However, if elevated adenosine levels are sustained beyond the acute

Address correspondence to: Michael R. Blackburn, Ph.D., Department of Biochemistry and Molecular Biology, The University of Texas Medical School at Houston, 6431 Fannin Blvd, Suite 6.200, Houston, TX 77030, Office: 713-500-6087, Fax: 713-500-0652, michael.r.blackburn@uth.tmc.edu.

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injury phase, hypoxic adenosine responses can become detrimental by activating pathways that promote tissue injury and fibrosis [14]. For example, chronic elevations of adenosine can contribute to tissue fibrosis in different organs including the lungs [15–17], liver [18, 19], skin [20], kidney [21] penis [22, 23] and following transplant [24]. Under these conditions of chronically elevated adenosine, blockade of adenosine signaling appears to be beneficial. Thus, adenosine signaling plays different roles in acute and chronic disease states.

Pharmaceutical companies are advancing adenosine-based therapies toward clinical trials for various diseases [25–27]. Understanding when during the course of disease adenosine signaling is beneficial as opposed to detrimental and defining the mechanisms involved will be critical for the advancement of such therapies. The purpose of this review is to discuss key observations that define the beneficial and detrimental aspects of adenosine signaling during acute and chronic disease states, with an emphasis on cellular processes such as inflammatory cell regulation, vascular barrier function and tissue fibrosis that may serve as biological readouts that can be targeted for the treatment of various diseases.

Adenosine Signaling in Acute Tissue Injury

Tissue Protective Roles of Adenosine

In response to injury, cells release ATP and other adenine nucleotides that are then converted to extracellular adenosine by ecto-nucleotidases [28]. Interestingly, these enzymes (CD39, which converts ATP to ADP/AMP and CD73, which converts AMP to adenosine) are regulated by transcriptional mechanisms involving the hypoxia-dependent transcription factor “hypoxia-induced factor” 1a (HIF1a) [29, 30]. Production of extracellular adenosine through these orchestrated pathways is the major source of extracellular adenosine following injury [28, 31, 32] (Figure 1). Increases in extracellular adenosine in turn elicit various responses on target cells by engaging cell surface adenosine receptors [33, 34]. There are four adenosine receptors (ADORA1, ADORA2A, ADORA2B, and ADORA3). All four of these receptors have been shown to be involved in cellular processes implicated in the regulation of tissue injury and are potential targets for the treatment of both acute and chronic diseases.

The importance of extracellular adenosine generation and signaling in acute tissue injury is highlighted by a series of studies using knockout mice for CD39 and CD73 and inhibitors of these enzymes that demonstrate enhanced inflammation and tissue injury in models of hypoxia and ischemic injury [29, 30, 32, 35–38] in association with diminished adenosine production. These studies demonstrate that elevations in extracellular adenosine play an important protective role following acute injury associated with hypoxia, and suggest that pharmacologic approaches to enhance adenosine elevations may have therapeutic benefit in acute injury settings. One mechanism for enhancing extracellular adenosine levels is through the prevention of adenosine uptake by equilibrative nucleoside transporters (ENTs) [39]. In a recent study, Almut Grenz and colleagues demonstrated that treatment with dipyridamole, an inhibitor of ENTs led to increased adenosine levels in association with tissue protection in a mouse model of ischemic acute kidney injury [40]. Collectively, these studies demonstrate that extracellular adenosine generation is a beneficial response in acute injury states.

The ADORA2A in Acute Injury Settings

Studies using adenosine receptor agonists, antagonist and knockout mice have assigned specific anti-inflammatory and tissue protective roles to the different adenosine receptors. One of the best characterized biological effects of adenosine is its ability to regulate immune responses [41, 42]. All immune cells express adenosine receptors and signaling through the

various adenosine receptors can impact immune function in manners that directly influence tissue responses to injury. In acute injury settings, all of the adenosine receptors have been shown to serve anti-inflammatory roles [43] (Figure 1). Perhaps the best characterized are the anti-inflammatory actions on the ADORA2A. This receptor is coupled to G-stimulatory alpha subunits to increase cAMP levels in the cell [34]. Anti-inflammatory properties of this receptor have been demonstrated in T cells [44], NK T cells [45, 46], invariant NK T cells [46], macrophages [47], neutrophils [48], dendritic cells [49], and T regulatory cells [50] where ADOR2A signaling is associated with inhibition of proliferation, inflammatory cytokine production and increased production of anti-inflammatory cytokines. Based on these observations, preclinical studies, largely in mice, have shown that treatment with ADORA2A agonists is beneficial in models of ischemia reperfusion injury and other acute disease settings. These include reperfusion injury in the heart [11], liver [13], kidney [9] and lung [6]. In addition, treatment with the ADORA2A agonist ATL146e was shown to attenuate pulmonary dysfunction in a mouse model of sickle cell disease [46], a condition that can be viewed as a repetitive ischemia reperfusion disorder. The mechanism identified for this protection included the activation of up regulated ADORA2A receptors on invariant natural killer cells. These findings highlight the importance of heightened adenosine signaling following injury settings and the potential for targeting this pathway for the prevention and resolution of acute injuries, particularly those involving ischemia.

ADORA2A signaling is also protective in models that can be viewed as more chronic in nature, including the bleomycin model of acute lung injury and fibrosis [51], allergic models of asthma [52, 53], and a model of bronchiolitis obliterans [54]. In these settings, ADORA2A signaling appears to exert anti-inflammatory effects that are beneficial to the resolution of chronic aspects of these disorders. Other tissue protective effects of ADORA2A signaling include the promotion of wound healing in lung epithelial cells [55] and the skin [56] and pathological angiogenesis [57]. Collectively, these studies support the use of ADORA2A agonists for the treatment of various acute disease states and the promotion of wound healing.

The ADORA2B in Acute Injury Settings

ADORA2B signaling has also been shown to be anti-inflammatory. A study by Katia Ravid and colleagues demonstrated that ADORA2B knockout mice have increased baseline and LPS stimulated immune responses [58]. In addition, a series of studies by Holger Eltzschig and colleagues went on to use a combination of adenosine receptor knockout mice and ADORA2B agonists to demonstrate that this receptors serves anti-inflammatory and tissue protective roles in various acute injury tissue models associated with hypoxic or ischemic injury including the heart [10], lung [2, 4], intestine [12] and kidney [8, 40]. A recent study by Tobias Eckles and colleagues demonstrated that the protective effects of ADORA2B signaling in ischemic heart injury were linked to activation of the circadian transcription factor Per2 [59], providing an interesting and potentially clinically important connection to light induced activation of these ADORA2B mediated protective pathways in the heart. In acute injury in the intestine [12], lung [2, 5] and kidney [40], enhanced ADORA2B signaling is not only associated with diminished inflammation, but also with pronounced improvement in vascular barrier function (Figure 1). Moreover, the use of mice with conditional deletion of the ADORA2B specifically in endothelial cells demonstrated that the ADORA2B on endothelial cells plays an important role in regulating the protective vascular responses to ischemic injury during acute kidney injury [40]. Collectively, these studies demonstrate that the ADORA2B plays an important role in regulating adenosine's anti-inflammation and tissue protective properties and suggests ADORA2B agonists may prove useful in the treatment of acute injuries to the heart, gastrointestinal tract, lung and kidney.

Adenosine Signaling in Chronic Tissue Injury

Converse to acute tissue injury, elevated levels of adenosine have been implicated in the progression of chronic disease states [14]. In such settings, the primary function of adenosine appears to be in promoting aberrant wound healing leading to fibrosis in organs including the lung [15, 60], skin [20, 61], kidney [18, 21], heart [62], liver [63] and penis [22, 23]. In addition, adenosine signaling has been implicated in wide array of chronic conditions including diabetes mellitus [64, 65], sickle cell disease [66], transplant rejection [24], Parkinson's disease [67] and rheumatoid arthritis [68].

Adenosine in Patients with Chronic Disease

Several studies demonstrate elevated levels of adenosine in patients with chronic lung disease. Perhaps the most well-known effect of adenosine in chronic disease comes from its capacity to induce airway hyperresponsiveness in asthmatic but not normal individuals [69], a phenomenon reproduced in animal models [70]. However, it was not until 1993 that elevated levels of adenosine in the lavage fluid from asthmatic subjects were first documented [71]. These observations were later validated in exhaled breath condensate of patients with asthma [72]. In addition to asthma, increased levels of adenosine have been reported in sputum from patients with cystic fibrosis [73]. Recent studies have also demonstrated elevated adenosine levels in the exhaled breath condensate of patients with chronic obstructive pulmonary disease (COPD; [74]) that negatively correlated with lung function. In tandem with these observations, a reduced activity of adenosine deaminase (ADA), the major enzyme that breaks down adenosine, was observed in patients with COPD [75, 76], and in patients with idiopathic pulmonary fibrosis (IPF; [76]). In addition to the reduced levels of ADA activity in patients with chronic lung disease, increased levels of the enzyme CD73, the major enzyme of extracellular adenosine production, were observed in lung tissue from patients with COPD and IPF [76]. Together with these findings, heightened levels of ADORA2B were documented in both COPD and IPF patients [76] implicating a potential role of this receptor in the pathogenesis of chronic lung disease.

Adenosine also plays a role in other chronic diseases. In the context of ethanol-induced liver cirrhosis, increased adenosine levels, as a consequence of ethanol metabolism [77, 78], contribute to the development of cirrhosis [19, 63]. In support of these findings is the observation that many of the drugs used to treat rheumatoid arthritis, most notably methotrexate (MTX), cause increases in extracellular adenosine that appear to be pivotal for the beneficial effects of MTX [68, 79, 80]; however, a well-documented side effect of MTX is its capacity to induce liver fibrosis [81], a phenomenon consistent with the heightened levels of extracellular adenosine.

In chronic diseases affecting the skin, high levels of adenosine have been reported in dermal lesions obtained from patients with psoriasis [82], where treatment with caffeine, a non-selective adenosine receptor antagonist, was considered an effective therapy [83]. In scleroderma and systemic scleroris (SSc) skin biopsies from patients with SSc presented with higher levels of IL-6 in fibroblasts following exposure to ATP [84]. Recently, increased levels of ADORA2A were evident and treatment with CGS21680 (a selective ADORA2A agonist) resulted in increased collagen production and myo-fibroblast differentiation [85] in fibroblasts from patients with SSc. Involvement of ADORA2A is also observed in patients with chronic heart failure where increased ADORA2A receptor expression, density, was found in both circulating cells and in the explanted hearts of heart failure patients [86].

In the framework of other chronic disease affecting the circulatory system, adenosine has been recently shown to be elevated in patients with sickle cell disease where elevated levels of adenosine are postulated to promote sickling of erythrocytes [66]. In addition to these

observations, ADORA2B gene expression has been postulated as a biomarker for patients with elevated tricuspid regurgitation velocity in sickle cell disease [87]. These findings suggest that agents that lower adenosine levels or block the ADORA2B receptor may prove beneficial in the treatment of sickle cell disease.

Adenosine Signaling in Chronic Disease Models

The use of experimental models of chronic disease has led to a much better understanding of the role of adenosine in orchestrating the pathophysiology of chronic diseases [14]. In chronic lung disease, the use of ADA knockout mice demonstrated that persistently high levels of adenosine can lead to changes in lung pathology similar to those seen in chronic lung injury including airspace enlargement and fibrosis, cardinal signs of COPD and IPF [15, 16, 88]. In addition to these experiments, chronic exposure of mice to bleomycin was shown to lead to extensive fibrosis [16, 89, 90] altered lung function and gas exchange and the development of hallmarks of pulmonary hypertension [89] a fatal complication of IPF [91]. In these experiments, the ADORA2B was found to be up regulated in association with mediators involved in remodeling such as IL-6 and matrix metalloproteins, and molecules such as endothelin-1 that are involved in the development of pulmonary hypertension [16, 89]. In both ADA-knockout mice and the bleomycin model, treatment with an ADORA2B antagonist, or genetic removal of ADORA2B was able to abrogate the development of lung injury, including fibrosis [15, 16], airspace enlargement [16] and pulmonary hypetension [89]. Similarly, in allergic models of asthma, genetic deletion of the ADORA2B [17] or treatment with ADORA2B antagonists [92] were associated with decreased airway disease including airway remodeling.

The ability of the ADORA2B to regulate the differentiation of immune effector cells may represent a major mechanism by which adenosine contributes to the development or progression of chronic lung disease. In a model of bronchiolitis obliterans, a form of chronic allograft rejection in the lung, the ADORA2B was found to contribute to fibrosis associated with transplant rejection [24]. In this study, ADORA2B knockout mice exhibited decreased fibrosis associated with elevations in the numbers of T regulatory cells, suggesting ADORA2B signaling may promote transplant rejection by inhibiting regulatory T cell infiltration. The ADORA2B has also been shown to promote the differentiation of myeloid suppressor cells that could contribute to cancer progression [93] and alternatively activated macrophages [94] that can produce remodeling mediators that drive the progression of fibrotic diseases such as IPF [14]. Along these lines, alternatively activated macrophages isolated from the airways of patients with IPF have been shown to produce pro-fibrotic mediators in response to ADORA2B stimulation [14]. Continued efforts to understand the role of adenosine signaling through the ADORA2B to regulate the appearance of immune effector cells that impact tissue remodeling could be helpful in identifying when ADORA2B antagonist are most effective in attenuating aspects of chronic disease (Figure 1).

The use of ADA knockout mice has also provided further understanding of the role of adenosine in other chronic diseases (Figure 1). Using this model, Yang Xia and colleagues identified a role for adenosine and ADORA2B in chronic kidney disease [21] as well as a role in penile fibrosis [95]. In experiments looking at the lung and kidney in ADA knockout mice, the activation of ADORA2B has been demonstrated to contribute to the development of remodeling processes through the release of mediators such as IL-6 [21, 89, 96] and osteopontin [97]. Similarly, studies looking at cardiac remodeling following a model of myocardial infarction in mice demonstrated that blockade of ADORA2B lead to improved remodeling of the heart via inhibition of IL-6 and TNF-α [62].

Models have also been useful in examining the observation that ADORA2B signaling promotes erythrocyte sickling and tissue injury. In a transgenic model of SCD, elevated

levels of adenosine promoted sickling and hemolytic damage to several organs and treatment with ADA enzyme therapy to lower adenosine or an with and ADORA2B antagonist proved beneficial for the treatment of SCD [98]. Activation of ADORA2B has recently been shown to contribute to insulin resistance via the enhanced production of IL-6 from macrophages and endothelial cells of diabetic animals [65]. Taken together these results point at ADORA2B as a key mediator in chronic disease that is not restricted to tissue remodeling but that is implicated in other functions such as erythrocyte integrity and metabolic disease.

Similar to the role of ADORA2B in fibrosis, several studies demonstrate that engagement of ADORA2A contributes to tissue remodeling (Figure 1). In a model of carbon tetrachloride (CCl 4) or thioacetamide-induced hepatic fibrosis, ADORA2A but not ADORA3 knockout mice were protected from the development of fibrosis [63]. However, in a separate mouse model of liver damage resulting from ethanol ingestion, investigators showed that ADORA1, ADORA2B or CD73-deficient mice were protected from ethanol-induced hepatic steatosis, consistent with mice treated with an ADORA1 or ADORA2B antagonist [19]. In the skin, studies using ADA-deficient mice demonstrated that elevated levels of adenosine contribute to dermal fibrosis via IL-13, TGF-beta and connective tissue growth factor production that is abrogated in ADORA2A knockout mice or following treatment with the ADORA2A antagonist ZM241385 [61]. These observations are consistent with studies where deletion or blockade of ADORA2A inhibits bleomycin-induced dermal fibrosis by preventing infiltration of fibrocytes [99]. These data support the use of ADORA2A antagonists for the treatment of chronic disease, particularly those affecting the skin or liver.

An exciting area of adenosine signaling is the involvement of ADORA2A in Parkinson’s disease (PD) where several clinical trials have been initiated to analyze the therapeutic potential of adenosine ADORA2A antagonists in the treatment of this chronic neurodegenerative disease [27]. In the brain, postsynaptic activation of ADORA2A neutralizes the inhibitory effect of dopamine [100]; as such blockade of ADORA2A in conditions of dopamine scarcity is hypothesized to have therapeutic benefits in PD. These observations were first made clinically where a reduced risk of developing PD following consumption of caffeinated coffee was reported [101]. Since then a vast library of ADORA2A antagonists have been tested in animal models of PD and clinically. Interestingly, Jiang-Fan Chen and colleagues have conducted a series of studies that suggest that ADORA2A stimulation may also be detrimental in other aspects of brain injury. For an extensive review see Armentero et al.[27]

Not all the effects of adenosine are detrimental in chronic diseases. As discussed earlier, increases in adenosine are thought to play an important role in the mechanism of action of MTX, a drug commonly prescribed to treat RA [68, 79, 80]. Experiments characterizing the role of adenosine receptors in lymphocytes from patients with RA have also shown increases in ADORA2A and ADORA3 levels [102]. Interestingly, in these studies, activation of either ADORA2A or ADORA3 inhibited the NF-kB pathway and diminished inflammatory cytokines such as TNF-α, IL-1β and IL-6 [102]. These results and the development of ADORA3 agonists for the treatment of chronic disease such as RA or dry eye syndrome [103] demonstrate the vast effects that adenosine can have through activation of its membrane-bound receptors in chronic disease and point at the necessity of further dissecting the signaling pathways in chronic disease in order to better understand its function in disease. This review has largely focused on the effects of ADORA2A and ADORA2B in the processes due to the large amount of literature supporting the involvement of these receptors; however, the ADORA1 and ADORA3 have also been implicated in many of the

same processes. Please see the following reviews for more information on the functions of these receptors in acute and chronic disease processes [25, 42, 43].

Conclusions

The production of extracellular adenosine has emerged as a major cellular process for orchestrating tissue responses to injury. The rapid release of ATP from cells, its conversion to adenosine and subsequent stimulation of adenosine receptors has likely evolved as a mechanism to protect tissues from stress, particularly stress associated with hypoxia. Harnessing these protective aspects of adenosine signaling will likely prove beneficial in the treatment of acute injuries where approaches to elevate extracellular adenosine, such as dipyridamole treatment, or stimulate adenosine receptors with selective agonists, will promote vascular barrier function, decrease inflammation and enhance aspects of wound healing. Interestingly, many chronic diseases display histopathological changes such as fibrosis that can be viewed as an overactive wound healing response. The observation that excessive adenosine elevations are associated with chronic disease progression suggests that adenosine may activate unremitting wound healing processes in chronic environments. Accordingly, adenosine receptor antagonism, may prove beneficial in treating various chronic diseases.

It will be critical to decipher when during the course of disease progression adenosine signaling is beneficial or detrimental. Clarity of this issue will emerge as the specific mechanisms of adenosine regulated responses in specific diseases become better understood. Aspects to consider include the observation that the levels of adenosine receptors, particularly the ADORA2A and ADORA2B, are substantially up regulated on immune and stromal cells in injured environments. Moreover, the ability of adenosine to regulate the differentiation of effector cells that directly impact tissue remodeling, such as alternatively activated macrophages, dendritic cells or regulatory T cells may provide mechanisms for screening when blockade or activation of the adenosine signaling pathway is beneficial.

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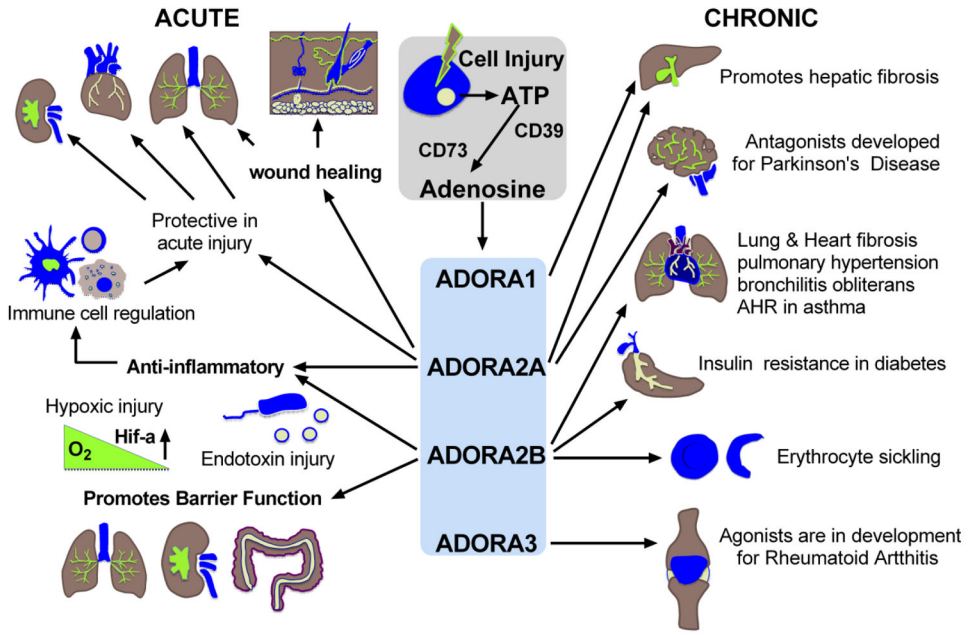

Figure 1. Adenosine Signaling in Acute and Chronic Disease

Cellular injury associated with hypoxia and inflammation promote the release of ATP that is subsequently dephosphorylated by membrane bound CD39 and CD73. Extracellular adenosine then stimulates cell surface adenosine receptors (ADORA1, ADORA2A, ADORA2B, ADORA3) to influence tissue responses to injury. In acute disease states, adenosine largely contributes to anti-inflammatory and tissue protective responses such as the promotion of vascular barrier function. This signaling pathway also promotes wound healing. These adenosine responses are largely regulated by ADORA2A and ADORA2B signaling pathways. In chronic disease states, adenosine signaling can promote cellular processes such as fibrosis that contribute to disease progression. Depicted is fibrosis in the liver, lung and heart; however, findings suggest excessive adenosine signaling also contributes to fibrosis in the skin, kidney and penis. These responses are regulated by ADORA2A and ADORA2B signaling pathways. In addition, ADORA2B signaling promotes sickling of erythrocytes that can contribute to the progression of tissue injury, and promotes insulin resistance that can impact the development of diabetes.