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Adenosine in fibrosis

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Abstract

Adenosine is an endogenous autocoid that regulates a multitude of bodily functions. Its anti-inflammatory actions are well known to rheumatologists since it mediates many of the anti-inflammatory effects of a number of antirheumatic drugs such as methotrexate. However, inflammatory and tissue regenerative responses are intricately linked, with wound healing being a prime example. It has only recently been appreciated that adenosine has a key role in tissue regenerative and fibrotic processes. An understanding of these processes may shed new light on potential therapeutic options in diseases such as scleroderma where tissue fibrosis features prominently.

Keywords

Adenosine receptor; Fibrosis; Collagen; Cirrhosis

Introduction

Adenosine is a potent physiologic and pharmacologic regulator. Adenosine was first recognized as a physiologic regulator of coronary vascular tone by Drury and Szent-Gyorgy in 1929 [1]. However, it was not until 1970 that Sattin and Rall [2] showed that adenosine regulates cell function via occupancy of specific receptors on the cell surface. It is now clear that there are at least four different subtypes of adenosine receptors, any one or combination of which may be expressed on cell surfaces (recently reviewed in [3]). All four adenosine receptors have been cloned, and the deduced sequence reveals that all four 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 receptors are coupled to pertussis toxin-inhibited Gi-coupled signal transduction proteins or directly to ion channels, whereas A_2 receptors (A_{2A} and A_{2B}) are coupled to

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Conflict of interest statement Dr. Cronstein has patents on the use of adenosine A_{2A} receptor agonists to promote wound healing, the use of adenosine A_{2A} receptor antagonists for the treatment of fibrosis, the use of adenosine A_1 receptor antagonists to treat osteoporosis and other bone diseases, the use of adenosine A_1 and A_{2B} receptor antagonists to treat fatty liver, and the use of adenosine A_{2A} receptor agonists to treat prosthesis loosening. During the past 2 years Dr. Cronstein has consulted for the following companies(<US $10,000): Cephalon, Cypress Bioscience, Inc., King Pharmaceutical (licensee of patents above), CanFite Biopharmaceuticals, Bristol-Myers Squibb, Cellzome, Takeda Pharmaceuticals, Prometheus Laboratories, Re-generon (Westat, DSMB), Sepracor, Amgen, Endocyte, Protalex, Allos, Inc., Combinatorx, Kyowa Hakka, Hoffman-LaRoche, Savient, and Avidimer Therapeutics. Dr. Cronstein owns equity in CanFite Biopharmaceuticals and has received grants from the National Institutes of Health, King Pharmaceuticals, and the Vilcek Foundation. Dr. Cronstein is on the board of directors of the Vilcek Foundation. Dr. Edwin Chan holds a patent on the use of adenosine A_{2A} receptor antagonists for use in fibrosis.

$G_{\alpha S}$-linked signaling molecules and stimulate adenylyl cyclase and cyclic adenosine monophosphate (cAMP) accumulation. Adenosine receptors or receptor-mediated effects have been demonstrated in virtually every tissue or organ examined. Some of the more prominent physiologic or pharmacologic effects mediated by adenosine receptors include: neurotransmission [A_1 and A_{2A} receptors; the central nervous system (CNS) effects of caffeine are thought to result from adenosine receptor antagonism]; modulation of cardiac conduction (A_1 receptors; intravenous boluses of adenosine are widely used for the treatment of supraventricular tachycardia); coronary vasodilation (A_{2A} receptors; infusions of adeno-sine are licensed for clinical use as a coronary vasodilator for pharmacologic stress testing); regulation, indirectly, of airway tone (A_1 and A_{2B} receptors); and inhibition of inflammation (in part mediating the anti-inflammatory effects of low-dose methotrexate, the most commonly used disease-modifying antirheumatic drug for the treatment of rheumatoid arthritis) (reviewed in [4–6]). It has been demonstrated that adenosine modulates neutrophil function via interaction with A_1 and A_2 receptors and, when released from cells in increased concentrations, inhibits inflammation (reviewed in [5]). In many tissues and cell types, A_1 and A_{2A} receptors have opposing actions not only on cAMP levels but on function as well (cf. [7–9]). More recently we have demonstrated that topical application of an adenosine A_{2A} receptor agonist promotes wound healing, a process dependent upon the proliferation of blood vessels and increased matrix formation, in both normal mice and diabetic rats [9–11].

Adenosine in inflammation

Inflammation is a homeostatic response to tissue injury, and the resolution of inflammation is generally tightly linked to matrix regeneration. Many of the growth factors that play a role in tissue repair and regeneration also possess anti-inflammatory activity; the best known of these is transforming growth factor-beta (TGF-β), which is a powerful anti-inflammatory mediator and potent stimulus for tissue regeneration. Our prior work and that of others clearly demonstrates that adenosine plays a role parallel to that of TGF-β in regulating the transition from inflammation to matrix and tissue regeneration.

The anti-inflammatory effects of adenosine were first suggested by our observation that adenosine, acting at a site on the surface of the neutrophil, inhibits stimulated neutrophil generation of superoxide anion [12]. Subsequent pharmacological studies from our laboratory [13] and others [14] revealed that the effects of adenosine were mediated by interaction with a specific cell surface receptor (formerly the A_2 receptor, now clearly identified as the A_{2A} receptor). That endogenously released adenosine could diminish inflammation was first demonstrated in our studies of neutrophils [12] and later confirmed in our laboratory using a model of neutrophil-mediated vascular injury [15]. Rosengren and colleagues first reported that endogenously generated adenosine acting at its receptors exercised a tonic suppressive effect on inflammation in vivo [16], and Ohta and Sitkovsky [17] expanded on this finding by identifying adenosine, acting at A_{2A} receptors, as the endogenous signal terminating acute inflammation in several models of inflammation. Endogenously released adenosine clearly diminishes reperfusion injury in a variety of different animal models [18–20] and also inhibits atherosclerosis in an in vivo model [21].

Most of the anti-inflammatory effects of adenosine are mediated via A_{2A} and A_3 receptors. Adenosine, via inter-action with A_{2A} receptors, inhibits stimulated neutrophil adhesion, generation of toxic oxygen metabolites, phagocytosis, and neutrophil-mediated cell injury [7, 12, 13, 22]. Adenosine, most likely acting at A_{2A} receptors, also inhibits lymphocyte proliferation and induces suppressor function and phenotype [23–34]. Occupancy of adenosine A_{2A} receptors on monocytes inhibits cytokine production [tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-8, and IL-12] and enhances release of the anti-inflammatory cytokine IL-10 [14, 17, 32, 35–40]. Adenosine, acting at A_2 receptors (probably

originally misidentified as A_{2B} receptors), inhibits inhibitory-κB (IκB) kinase and nuclear factor-κB (NFκB) translocation to the nucleus, a central step in the pathogenesis of inflammation [41, 42]. In murine cells A_3 receptors also downregulate inflammatory cytokine secretion. Adenosine, acting at A_{2B} receptors, inhibits synoviocyte collagenase production without affecting production of either stromelysin or tissue inhibitor of metalloprotease [43]. Various adenosine receptor agonists are anti-inflammatory in animal models. Interestingly, in in vivo studies, A_1 adenosine receptor agonists were found to be the most anti-inflammatory, and other studies have suggested that the anti-inflammatory effects of A_1 receptor agonists are mediated through the CNS and CNS-stimulated adenosine release in inflamed tissues [44]. More recent studies also suggest a role for peripheral A_1 receptors, most probably on monocyte/macrophages, in suppression of inflammation in the lung. It is unclear how A_1 receptors mediate this effect in this animal model of adenosine deaminase deficiency, but in the absence of A_1 receptors there is a significant increase in pulmonary content of chemotactic and growth factors for eosinophils [45].

In general, the role of adenosine as a regulator of inflammation has been established in models of acute inflammation, but adenosine, acting at its receptors, modulates chronic inflammation and adaptive immune responses as well. In particular, adenosine A_{2A} receptors on dendritic cells diminish the capacity of these cells to promote Th1-type responses [46] and diminish monocyte production of IL-12 [39, 40, 47], a central promoter of Th1 immunologic responses. Adenosine, acting through its receptors, also modulates T cell responses to antigen [32, 46, 48, 49]. Our laboratory has previously reported that adenosine A_1 receptors promote and adenosine A_{2A} receptors inhibit fusion of human peripheral blood mono-cytes to form giant cells, although the role of adenosine A_1 receptors in granuloma formation has not been well studied [50].

Wound healing

Based on preliminary evidence that adenosine A_{2A} receptor agonists enhanced migration of fibroblasts and endothelial cells into artificial wounds, we first examined the fibro-genic effects of adenosine in an in vivo model of excisional wound healing. Topical application of an adenosine A_{2A} receptor agonist, CGS-21680, significantly enhanced excisional wound closure in this model, with 50% wound closure achieved by day 2, compared with day 6 in untreated control BALB/c mice [9]. Another adenosine A2A receptor agonist, MRE0094, was similarly effective in promoting excisional wound closure in BALB/c mice, its effects more rapid than recombinant human platelet-derived growth factor (becaplermin gel), an agent marketed for use in diabetic ulcers [11]. Promotional effects of CGS-21680 on wound closure were also seen in rats rendered diabetic following injection of streptozotocin [9].

Pulmonary fibrosis

Pulmonary fibrosis is an important component of many interstitial lung diseases. The involvement of adenosine in pulmonary fibrosis is perhaps unsurprising considering its involvement in many other pulmonary diseases and that adenosine levels are elevated in humans with diseases such as asthma and chronic obstructive pulmonary disease [51, 52]. Furthermore, murine models of these pulmonary disorders as well as murine idiopathic pulmonary fibrosis displayed similar changes in adenosine [53–55]. The induction of fibrotic changes in the lungs, much as elsewhere, takes place over a substantial period of time and under the influence of a host of profibrotic cytokines, growth factors, and other tissue mediators. One of these recently highlighted is interleukin-13 (IL-13), and trans-genic IL-13 has also been identified to have potent fibro-genic effects in a variety of tissues including both lung and liver [56–59]. Blackburn et al. [53] first reported a vast increase in adenosine levels in the lungs of IL-13 trans-genic mice, and this elevation was associated

with a sig-nificant suppression of the activity of adenosine deaminase, a major catabolizing enzyme of adenosine. In concert with the anticipated effects of IL-13, these mice developed substantial subepithelial airway fibrosis histologically, along with marked elevation in pulmonary collagen content. Interestingly, the fibrotic phenotype was reversed by administration of pegylated adenosine deaminase therapy, thereby reversing the IL-13-induced tissue elevation in adenosine. This was one of the earliest demonstrations of the importance of adenosine in mediating organ fibrosis.

Blackburn's group substantiated these findings by studying a murine model of high tissue adenosine, adenosine deaminase-deficient mice. These mice were developed in their laboratory, and targeted gene deletion resulting in the deficiency of a key enzyme that catabolizes adenosine into inosine renders both circulating and tissue adenosine levels extremely high [60, 61]. One of the potential benefits of using this model is that adenosine deaminase enzyme therapy can be administered by injection to these mice, much as it is used as therapy for adenosine deaminase in humans, thus enabling direct manipulation of tissue adenosine levels through varying the dose of adenosine deam-inase injected. Furthermore, induction of fibrosis in this model is spontaneous and does not require administration of exogenous chemical agents, or genetic manipulation as has been employed by most other in vivo models of tissue fibrosis. Thus, any changes observed are directly attributable to changes in tissue adenosine itself. In mice completely deficient for adenosine deaminase, mortality from lung disease arose within a few weeks of birth, and these mice did not live long enough to develop significant pulmonary fibrosis [62]. The use of an adenosine deaminase minigene expressed in the upper gastrointestinal tract allowed for the creation of a new line of animals only partially deficient for adenosine deaminase, and adenosine deaminase is not expressed in tissues outside the gastrointestinal tract [63]. These animals are able to live for up to 5 months and develop a number of pulmonary pathologies, including fibrosis, and die from apparent respiratory distress. Using this partially adenosine deaminase-deficient mouse model, the authors were able to show that elevation of adenosine in this model was associated with increases in the transcript levels of a number of profibrotic mediators that included TGF-β1, IL-1β, IL-13, plasminogen activator inhibitor-1 (PAI-1), and osteopontin. Significant elevations in transcript levels of adenosine A_1 and A_{2B} receptors were also reported [64]. These changes correlated with histo-logically demonstrable fibrosis with an increased number of pulmonary myofibroblasts and collagen deposition following staining with Masson's trichrome as well as semi-quantitative assessment of fibrosis by Ashcroft's fibrosis scoring system [60, 64]. Excessive collagen deposition was not limited to the lungs, but was also seen in the liver and kidney glomeruli. All of these profibrotic effects of adenosine were reversed by administration of high-dose adenosine deaminase. Despite partial enzyme replacement therapy in this model, elevation of adenosine levels was still evident along with histological evidence of pulmonary fibrosis. These observations were later confirmed in a model of IL-4-induced pulmonary fibrosis in C57BL/6 mice [54].

Generation of adenosine in the extracellular milieu relies on one of two main sources: intracellular adenosine that is transported out of the cell, and the dephosphoryla-tion of AMP by the enzyme 5′-nucleotidase (CD73) or alkaline phosphatase, which can in turn be dephosphoryl-ated from adenosine triphosphate (ATP) or adenosine diphosphate (ADP) by ectonucleoside triphosphate di-phosphohydrolase 1 (CD39) or alkaline phosphatase [65–67]. Thus, deletion of CD73 or CD39 eliminates one of the major routes of adenosine formation, and gene deletion in mice provides a model of low tissue adenosine.

Using the CD73-deficient mouse model, Volmer et al. challenged animals with injections of bleomycin, a well-known fibrogenic stimulant for both lung and skin. Pulmonary adenosine levels increased by threefold following bleomycin challenge in wild-type mice compared

with controls injected with saline, along with a concomitant increase in membrane AMPase [55]. This increase in adenosine that results from bleomycin administration was dependent on CD73, since CD73-deficient animals did not exhibit the same adenosine accumulation. While injection of bleomycin was associated with an increase in pulmonary a-1 procollagen transcript, collagen protein, and histolog-ical fibrosis, as well as transcript levels of proinflammatory and profibrotic mediators IL-1β, TNF-α, TGF-β1, PAI-1, and osteopontin, loss of CD73 was associated with exacerbation of bleomycin-induced pulmonary injury. Restoration of AMPase activity by intranasal administration of exogenous nucleotidase conjugated to polyethylene glycol (PEG) resulted in a reduction of both inflammation and fibrosis in this model, along with elevation in pulmonary adenosine levels.

Among the four known adenosine receptors, the A_{2B} receptor is known to possess the ability to induce differentiation of pulmonary fibroblasts into myofibroblasts [68]. Expression of A_{2B} receptors is increased in the lungs of adenosine deaminase-deficient mice [63]. Using a novel A_{2B} receptor antagonist, Sun et al. [69] were able to show that accumulation of myofibroblasts and α-smooth muscle actin staining in adenosine deaminase-deficient mice were reduced by A_{2B} receptor antagonist treatment. This was accompanied by a reduction in collagen deposition in the airways seen on Masson's trichrome staining as well as reversal of the increase in whole-lung a1-procollagen transcript levels and collagen protein levels in bronchoal-veolar lavage fluid seen in control animals. Administration of the A_{2B} receptor antagonist also suppressed production of the profibrotic mediators, TGF-β1, and osteopontin by alveolar macrophages. This protective effect of A_{2B} receptor antagonist treatment on pulmonary fibrogenesis was associated with a decrease in inflammatory cells recovered from bronchoalveolar lavage fluid, including alveolar macrophages, lymphocytes, neutrophils, and eosinophils. Treatment with the A_{2B} receptor antagonist also significantly reduced production of cytokines and chemokines including TNF-α, IL-6, chemokine (C-C motif) ligand 11 (CCL11), CCL17, chemokine (C-X-C motif) ligand 1 (CXCL1), and CXCL2. Alveolar airspace enlargement akin to that seen in emphysema, present in adenosine deaminase-deficient control animals, was als prevented by A_{2B} receptor antagonist treatment, along with normalization of the increase in metalloproteases and inhibitors of proteases, tissue inhibitor of metalloprotein-ase-1 (TIMP-1), matrix metalloproteinase (MMP)-9, and MMP-12, seen in control mice. To verify the effect of A_{2B} receptor antagonism on the protection of development of pulmonary fibrosis, the authors also examined A_{2B} receptor antagonist treatment in the bleomycin-induced pulmonary fibrosis model. Whereas intratracheal administration of bleomycin induced myofibroblast differentiation, collagen deposition and production, as well as histological fibrosis in the lungs of experimental animals, A_{2B} receptor antag-onist treatment reversed all of these. The role of the adenosine A_3 receptor in murine pulmonary fibrogenesis has also been studied following bleomycin exposure [70]. While levels of TFG-β1 message were found to be elevated in whole-lung extracts and bronchoalveolar lavage fluid cell pellets of A_3 receptor-deficient mice, no change in the active form of TFG-β1 protein was seen, although reductions in message levels and activities of MMP-9 and TIMP-1 were evident. Little difference in the degree of pulmonary fibrosis was observed between A_3 receptor-deficient mice and wild-type control mice following bleomycin exposure. Thus, despite its importance as an anti-inflammatory regulator, the A_3 receptor is unlikely to be a key player in the control of fibrogenesis in the lung.

Hepatic fibrosis

Release of adenosine is an important mechanism responsible for the anti-inflammatory effects of some common antirheumatic drugs, including salicylates, sulfasalazine, and most notably methotrexate [6, 71, 72]. The mechanism of action of methotrexate is complex and may involve folate antagonism as well as polyamine inhibition, although recent data have

suggested that adenosine release is pivotal to many cellular anti-inflammatory effects of methotrexate not otherwise explainable by alternative mechanisms. One of the most serious and well-documented side-effects of methotrexate therapy is fibrosis of the liver. It is notable that ethanol, one of the most common causes of cirrhosis worldwide, inhibits adenosine uptake via the nucleoside transporter and thereby increases extracellular adenosine levels [73]. This is associated with an increase in intra-cellular cAMP and desensitization of cAMP signaling. It has long been known that, in humans, ethanol consumption is associated with an increase in urinary purine metabolites and turnover of adenine nucleotide pool [74]. Some of the central nervous system hypnotic effects of ethanol are also mediated through adenosine release [75]. It is possible, therefore, that the fibrosing effect of methotrexate in the liver may also be mediated through the release of adenosine. It is worth noting that there has been extensive epidemiologic demonstration of the protective effects of coffee in liver cirrhosis [76, 77]. It is possible that these protective effects may be attributable to caffeine, an effective and nonselective antagonist of adenosine receptors.

The hepatic stellate cell is the principal fibrogenic cell type in the liver [78–81]. Many known soluble stimuli can cause hepatic stellate cell proliferation, activation, differentiation, and subsequently production of fibrous matrix proteins including collagen. We have previously shown that both ethanol and methotrexate induce the release of adenosine from hepatocytes to over threefold baseline levels at pharmacologically relevant levels of these stimuli [82]. The known hepatic fibrosing agents, carbon tetrachloride and thioacetamide, also promote adenosine release from murine liver slices ex vivo. Hepatic adenosine promotes collagen production by stellate cells and at the same time suppresses the expression and activities of the metalloproteinases MMP-9 and MMP-14. These profibrotic actions of adenosine in the liver are mediated through the A_{2A} receptor, and indeed cirrhotic mouse livers show increased expression of adenosine A_{2A} receptors. Adenosine A_{2A} receptor-deficient mice are resistant to the development of hepatic fibrosis following administration of carbon tetrachloride or thioacetamide, as are mice treated with an adenosine A_{2A} receptor antagonist. Adenosine also inhibits platelet-derived growth factor (PDGF)-induced stellate cell chemotaxis via the A_{2A} receptor [83]. Activation of the A_{2A} receptor induces a loss of actin stress fibers in hepatic stellate cells, and endothelin-1 and lyso-phosphatidic acid-mediated stellate cell contraction are diminished [84]. There have also been previous contradictory reports of protective effects of adenosine in carbon tetrachloride-induced cirrhosis in rats [85]. However, adenosine was administered to experimental animals intraperitoneally only three times a week in this model. Since adenosine has an extremely short half-life in blood and tissues of less than 10 s, much as adenosine administered as an intravenous bolus to patients with supraven-tricular tachyarrhythmias has a very short-lasting effect amounting to seconds, it is difficult to be able to attribute the reported protective effects directly to adenosine itself.

Upregulation of collagen production by adenosine involves at least two of the principal subtypes of collagen seen in the fibrotic liver, collagen types I and III [86]. Interestingly, signal transduction mechanisms for the two collagen subtypes appear to be different. While production of collagen type I is regulated by protein kinase A, src, and extracellular signal-regulated kinase (ERK), collagen type III is dependent upon p38 mitogen-activated protein kinase (MAPK). These results were confirmed both by pharmacologic inhibition and small interfering RNA-mediated knockdown of the respective signaling molecules.

Dermal fibrosis

Since activation of the adenosine A_{2A} receptor increases matrix synthesis in wounds and promotes wound healing, it is no surprise that adenosine also has an important role in the development of more diffuse dermal fibrosis (Fig. 1). A_{2A} receptor occupancy stimulates the

production of collagen types I and III by human dermal fibroblasts, an effect associated with an increase in ERK phosphorylation [87]. Suppression of the expression and activities of metallo-proteases, MMP-9 and MMP-14, but not MMP-2, is also observed with A_{2A} receptor activation. Pharmacologic inhibition of MEK-1, an upstream activator of ERK, mitigates the stimulating effect of A_{2A} receptor occupancy on collagen production. Adenosine A_{2A} receptor-deficient mice or C57BL/6 mice treated with an A_{2A} receptor antagonist are both protected against bleomycin-induced dermal fibrosis, a murine model of scleroderma, with reductions in skin thickness and tensile strength, a decrease in total hydroxyproline content, and histological reduction in fibrous tissue in the skin following staining with picrosirius red. The A_{2A} receptor-mediated fibrosing effect in the skin may be due in part to more avid recruitment of fibrocytes into the skin [88].

Adenosine deaminase-deficient mice, described above and whose adenosine levels in the skin is vastly elevated at around 12-fold that of control mice, spontaneously develop dermal fibrosis with increased dermal collagen content even in the absence of bleomycin or any other inciting fibrosing stimuli [61]. The development of dermal fibrosis in these mice is diminished by administration of an A_{2A} receptor antagonist, again confirming the role of the A_{2A} receptor in mediating fibrogenesis in the skin. Dermal fibrogenesis in adenosine deaminase-deficient mice is associated with elevations of a number of key profibrotic mediators, including TGF-β1, connective tissue growth factor (CTGF), PDGF-AA, IL-13, and IL-6.

Adenosine in fibrosis elsewhere in the body

The cardiac fibroblast, as a key producer of matrix proteins in the heart, is an important participant in cardiac remodeling whether as part of the normal ageing process or as a result of long-standing hypertension, after myocardial infarction, or in hypertrophic conditions such as hypertrophic obstructive cardiomyopathy. Cardiac fibroblasts synthesize adenosine, and fibroblast-derived adenosine inhibits fetal calf serum-induced growth of atrial and left ventricular rat fibroblasts via activation of adenosine A_{2B} receptors [89, 90]. The A_1 receptor in rat cardiac fibroblasts participates in the regulation of extracellular adenosine levels [91]. Adenosine A_{2B} receptor stimulation has been shown to suppress collagen production by cardiac fibro-blasts, suggesting a protective effect of this receptor in myocardial fibrosis [92]. These results are consistent with the observation that A_{2B} receptor stimulation prevents cardiac remodeling and protects against elevations in cardiac collagen volume and cardiac fibrosis following induction of myocardial infarction by ligation of left anterior descending coronary artery in Wistar rats, with subsequent improvement in cardiac function [93].

Modulation of metalloproteinase activity by adenosine has also been demonstrated in fibroblast-like synoviocytes, where A_{2B} receptor stimulation suppresses collagenase, but not stromelysin or tissue inhibitor of metalloproteinase 1 (TIMP-1) gene expression [43]. Finally, adenosine deam-inase-deficient mice also display evidence of elevation in adenosine levels and adenosine A_{2B} receptor activation in the penis. It has been suggested that this is an important mechanism for the development of priapism in these mice, and is associated with histologically demonstrable fibrosis in the corpus spongiosum and corpus cavernosum on Masson's trichrome staining [94].

Conclusions

Work in the last decade has clearly demonstrated an important role for adenosine in the pathophysiologic control of tissue fibrosis. Adenosine receptor subtypes may vary in their differential responses in the regulation of fibrosis, similar to what has been known about the

influence of adenosine receptors in monitoring other physiologic processes such as giant cell formation. The physiologic response of each receptor in turn may be tissue specific, perhaps dependent on inciting stimuli that induce adenosine release and modulate receptor expression and function. In this respect, the heart and lung, organs constantly exposed to a vast number of antigens, may respond differently to adenosine than the skin or liver. Developments in modern receptor pharmacology may one day put this new-found knowledge to good use, and therapy for some of these hitherto untreatable fibrotic conditions may soon be on the horizon. Indeed, adenosine receptor antagonism provides a promising therapeutic strategy for the future. Adenosine A_{2A} receptor antagonists have already been used for the treatment of Parkinson's disease, reducing occurrences of the on–off phenomenon, although their overall clinical benefit in Parkinson's disease has been called into question. Thus, targeting the relevant adenosine receptor may be a novel therapeutic option in the treatment of fibrotic diseases, for instance, adenosine A_{2A} receptor antagonism for the treatment of dermal and hepatic fibrosis, or A_{2B} receptor antagonism for the treatment of pulmonary fibrosis.

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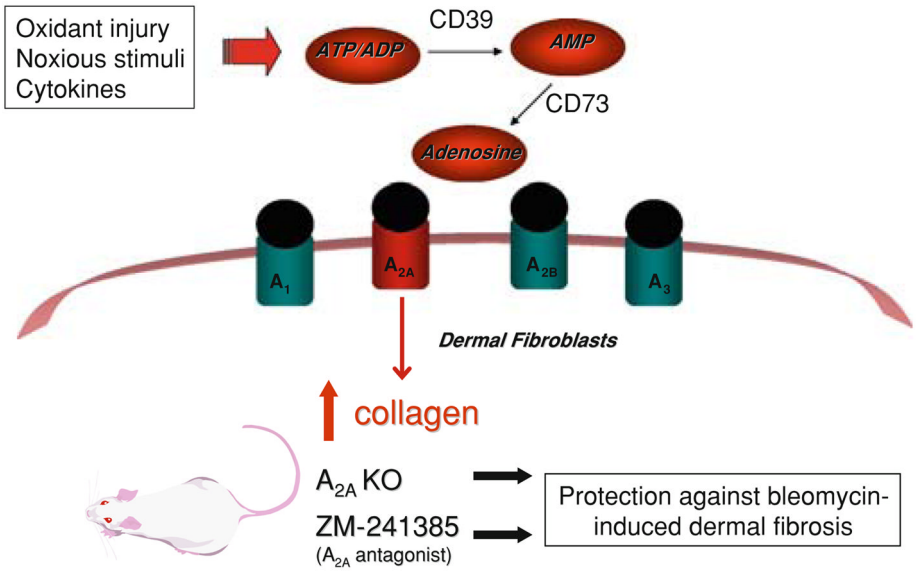

Fig 1.
Schematic representation of proposed mechanism of involvement of adenosine in dermal fibrosis