

Adenosine receptors and fibrosis: a translational review

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Abstract

Adenosine—a purine nucleoside generated extracellularly from adenine nucleotides released by cells as a result of direct stimulation, hypoxia, trauma, or metabolic stress—is a well-known physiologic and pharmacologic agent. Recent studies demonstrate that adenosine, acting at its receptors, promotes wound healing by stimulating both angiogenesis and matrix production. Subsequently, adenosine and its receptors have also been found to promote fibrosis (excess matrix production) in the skin, lungs, and liver, but to diminish cardiac fibrosis. A commonly ingested adenosine receptor antagonist, caffeine, blocks the development of hepatic fibrosis, an effect that likely explains the epidemiologic finding that coffee drinking, in a dose-dependent fashion, reduces the likelihood of death from liver disease. Accordingly, adenosine may be a good target for therapies that prevent fibrosis of the lungs, liver, and skin.

Introduction

Although humans and other mammals have lost, for the most part, the ability to regenerate injured tissue, the capacity to heal wounds is of critical importance for restoring function and, in the skin, maintaining a barrier against the external environment. The processes involved in wound healing include cleaning up the damaged tissue and preventing tissue invasion by microorganisms (inflammation), rebuilding the vascular network in the wounded site and creating a scaffold of connective tissue (granulation tissue formation), surfacing the wound (re-epithelialization), and a much slower process of re-organization of the scar. In some people, such as individuals with diabetes or venous stasis, the process goes awry and the wounds do not heal in a timely fashion or at all. Although tissue repair is effective in re-establishing a barrier, the wound healing process may lead to scarring, fibrosis, and loss of function (as in the case of contractures). Internal organs may similarly be scarred and the fibrosis and loss of architectural integrity may lead to significant organ dysfunction. Moreover, some illnesses, such as scleroderma, are characterized by pathologic fibrosis of the skin and/or internal organs resulting in diffuse skin fibrosis and internal organ dysfunction. Many

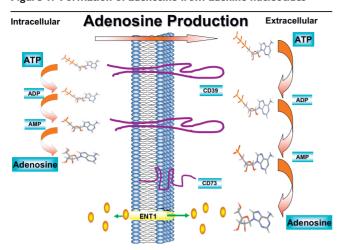
other ailments, such as liver cirrhosis, may lead to specific organ destruction with resulting fibrosis, scarring, and loss of function.

A variety of factors regulate the wound healing process, ranging from growth factors to small molecules released at the wounded site. One such factor is adenosine, a ubiquitous purine nucleoside that is generated in the extracellular space by dephosphorylation of adenine nucleotides released by cells as a result of metabolic factors, injury, and hypoxia (Figure 1). Adenosine mediates its effects on tissue regeneration and repair via binding and activation of a family of G protein-coupled receptors (adenosine A_1 , A_{2A} , A_{2B} , and A_3 receptors). In this review, we will discuss the role of adenosine and its receptors in wound healing, fibrosis, and scarring.

Adenosine in wound healing Inflammation

The first step in wound healing involves the inflammatory response. Neutrophils, mast cells, monocytes/macrophages, and basophils all play a role in eliminating debris at injured sites, preventing infection of healing tissue and secreting factors that promote recruitment of

Figure 1. Formation of adenosine from adenine nucleotides



Adenosine is formed both intracellularly and extracellularly from adenine nucleotides, which are sequentially dephosphorylated to adenosine. Intracellular adenosine may be transported into the extracellular space via facilitated transport, and extracellular adenosine is also taken up by cells through the same transporter, equilibrative nucleoside transporter I (ENTI). Two cell surface molecules, CD39 and CD73 (nucleoside triphosphate phosphohydrolase and ecto-5'-nucleotidase, respectively), catalyze the dephosphorylation of adenine nucleotides to adenosine in the extracellular space.

new blood vessels and restoration of injured tissue. Adenosine, acting at its receptors, promotes the transition from a purely inflammatory role to promotion of tissue restoration. Since the first demonstration that adenosine suppresses inflammatory neutrophil functions in 1983 [1], it has been clear that adenosine, acting primarily at A_{2A} receptors, diminishes the inflammatory functions of both blood-borne and tissue inflammatory cells and even cells of the adaptive immune response (reviewed in [2]). More recent studies demonstrate that adenosine promotes macrophage differentiation into M2-type macrophages [3-5], which help to promote wound healing by releasing factors such as vascular endothelial growth factor (VEGF) that stimulate restoration of tissue at sites of injury (Figure 2).

Angiogenesis

In 1997, Montesinos and colleagues [6] first reported that adenosine A_{2A} receptor agonists promote wound healing in mice. The mechanism by which adenosine A_{2A} receptor stimulation promoted wound healing was not apparent at the time, although endothelial cells and the vasculature were known to produce adenosine from adenine nucleotides, to respond to adenosine by increasing their migration and proliferation, and to be involved in stimulating vascular leakage and promoting coronary vasodilation [7-11]. Thus, it was likely that

adenosine, acting at its receptors, directly promoted angiogenesis, a key component of wound healing. Subsequent studies demonstrated that adenosine A_{2A} receptor activation stimulates endothelial VEGF production via both A_{2A} and A_{2B} receptors but that, in wounds, the loss of adenosine A_{2A} receptors completely abrogated the formation of new blood vessels in the wounds [12-16]. In addition to stimulating production of angiogenic factors, adenosine A_{2A} receptor activation also inhibits the production of the antiangiogenic factor thrombospondin 1 [15]. Moreover, in addition to the direct effects of adenosine receptors on vascular endothelium, adenosine stimulated macrophages to produce angiogenic factors, such as VEGF [5,17]. Finally, adenosine A_{2A} receptor stimulation promotes recruitment of bone marrow-derived endothelial precursor cells from the circulation [18]. Overall, the evidence seems clear that adenosine A_{2A} receptor activation is involved in the stimulation of at least one component of wound healing: angiogenesis.

Dermal collagen production

It was clear from the original description of adenosine receptor promotion of wound healing that adenosine A_{2A} receptor stimulation also increased matrix production in the healing wounds. Fibroblasts produce matrix, and human foreskin dermal fibroblasts were known to express both adenosine A_1 and A_2 receptors [19], which regulate intracellular cAMP (cyclic adenosine monophosphate) levels. Further studies from my group demonstrated that, in these cells, adenosine A2A receptor stimulation directly promotes collagen production and that, in some situations, this can be a two-edged sword [20]. In a model of diffuse bleomycin-induced dermal fibrosis, we showed that adenosine A_{2A} receptor stimulation is responsible for promotion of collagen production in the skin, since adenosine A2A receptor knockout mice or mice treated with an adenosine A2A receptor antagonist are protected from developing diffuse dermal fibrosis. This was later confirmed in experiments in mice lacking adenosine deaminase. Mice lacking this enzyme accumulate as much as 10-fold increases in adenosine levels and undergo diffuse dermal fibrosis, which is blocked by adenosine A_{2A} receptor blockade. In addition to direct stimulation of fibroblast collagen production, adenosine also exacerbates collagen production by promoting recruitment of bone marrow-derived fibrocytes from the circulation into the fibrotic skin.

Adenosine and fibrosis

Pulmonary fibrosis

As noted above, mice lacking adenosine deaminase suffer from severe dermal fibrosis. Interestingly, these animals die prematurely from pulmonary inflammation and

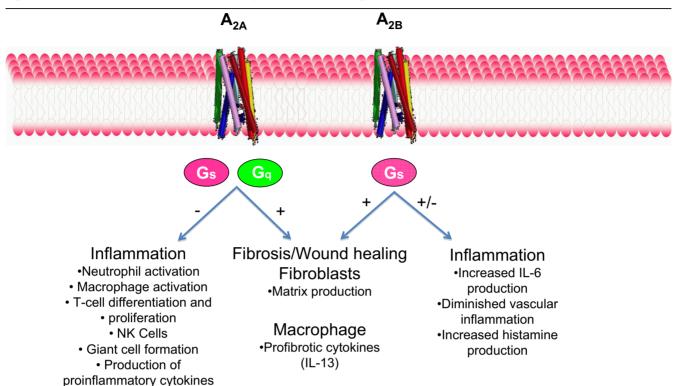


Figure 2. The role of adenosine A_{2A} and A_{2B} receptors in wound healing and inflammation

Adenosine in the extracellular space binds to either its A_{2A} or A_{2B} receptor, activating the G proteins Gq and Gs to mediate the effects shown. IL, interleukin; NK cell, natural killer cell.

fibrosis, which is related to increased collagen and interleukin (IL)-13 production [21]. In contrast to the skin, fibrosis and inflammation in the lung appears to be mediated primarily via A_{2B} receptors and, accordingly, more recent studies demonstrate that adenosine A_{2B} receptors play a role in the pathogenesis of chronic obstructive pulmonary disease and interstitial fibrosis [22,23]. It is likely that the capacity of A_{2B} receptors to stimulate IL-6 production [22,42] in the lung can stimulate fibrosis indirectly.

Hepatic fibrosis

Adenosine, generated in the extracellular space from adenine nucleotides by ecto-5'-nucleotidase, plays a role in the pathogenesis of alcoholic fatty liver [24,25] and, in the setting of chronic alcoholism, the transition of about 20% of patients to develop hepatic cirrhosis. Recent studies have demonstrated that adenosine, acting at A_{2A} receptors, stimulates hepatic stellate cell-mediated fibrosis of the liver [26-28] by increasing production of collagen I and III (the collagens present in scar tissue) via two distinct mitogen-activated protein kinase (MAPK)-dependent pathways, extracellular signal-regulated kinase 1/2 (ERK1/2) and p38MAPK, respectively [29].

Interestingly, caffeine, the most widely used drug in the world, mediates most of its pharmacologic effects by nonselectively blocking adenosine receptors, including A_{2A} receptors, and can prevent hepatic fibrosis in animal models [25] and, in a case-control study, patients with a variety of liver ailments [30]. It is, therefore, likely that the pharmacologic effect of caffeine on hepatic fibrosis explains the observation made in numerous epidemiologic studies in different countries that coffee drinking, in a dose-dependent fashion, significantly diminishes death rates due to liver disease [31-40].

Peritoneal fibrosis

A common complication of abdominal surgery or peritoneal dialysis is peritoneal fibrosis. Although peritoneal fibrosis is usually of little consequence, in some patients, peritoneal fibrosis can lead to bowel obstruction or other problems, so it is encouraging that recent studies in two different animal models of peritoneal fibrosis demonstrate that adenosine A_{2A} receptor blockade diminishes peritoneal fibrosis and adhesions [41].

Cardiac fibrosis

Dubey and colleagues [43] have reported that adenosine A_{2B} receptor activation inhibits cardiac fibroblast

production of collagen *in vitro*. In agreement with these original findings, Wakeno and colleagues [44] have reported that adenosine A_{2B} receptor stimulation diminishes fibrosis and remodeling of the myocardium after infarction.

Conclusion

Adenosine, a nucleoside that is generated in the extracellular space from adenine nucleotides released at inflamed and hypoxic sites or as a result of metabolic stresses in some tissues and organs, stimulates wound healing, angiogenesis and, in some tissues, under some circumstances, fibrosis. A number of studies demonstrate that stimulated adenosine receptors play different roles in the pathogenesis of fibrosis depending on the tissue. Adenosine A_{2B} receptors in the heart inhibit fibrosis, whereas these same receptors promote fibrosis in the lungs. In contrast, in the skin, liver, and lungs, adenosine A_{2A} and A_{2B} receptors both mediate an increase in fibrosis. It is also striking that different adenosine receptors appear to play a dominant role in fibrosis in different organs; adenosine A_{2A} receptors are the dominant receptors in the skin, peritoneum, and liver but A_{2B} receptors are responsible for pulmonary fibrosis. Adenosine blockade at these receptors provides novel targets for new therapies in these difficult clinical settings.

Abbreviations

IL, interleukin; MAPK, mitogen-activated protein kinase; VEGF, vascular endothelial growth factor.

Competing interests

Intellectual property: patents held or pending on the use of adenosine A2AR agonists to promote wound healing and use of A2AR antagonists to inhibit fibrosis; use of adenosine A1R antagonists to treat osteoporosis and other diseases of bone; use of adenosine A1R and A2BR antagonists to treat fatty liver; and use of adenosine A2AR agonists to prevent prosthesis loosening.

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