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Adenosine Receptors in Wound Healing, Fibrosis and Angiogenesis

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Abstract

Wound healing and tissue repair are critical processes, and adenosine, released from injured or ischemic tissues, plays an important role in promoting wound healing and tissue repair. Recent studies in genetically manipulated mice demonstrate that adenosine receptors are required for appropriate granulation tissue formation and in adequate wound healing. A_{2A} and A_{2B} adenosine receptors stimulate both of the critical functions in granulation tissue formation (i.e., new matrix production and angiogenesis), and the A_1 adenosine receptor (AR) may also contribute to new vessel formation. The effects of adenosine acting on these receptors is both direct and indirect, as AR activation suppresses antiangiogenic factor production by endothelial cells, promotes endothelial cell proliferation, and stimulates angiogenic factor production by endothelial cells and other cells present in the wound. Similarly, adenosine, acting at its receptors, stimulates collagen matrix formation directly. Like many other biological processes, AR-mediated promotion of tissue repair is critical for appropriate wound healing but may also contribute to pathogenic processes. Excessive tissue repair can lead to problems such as scarring and organ fibrosis and adenosine, and its receptors play a role in pathologic fibrosis as well. Here we review the evidence for the involvement of adenosine and its receptors in wound healing, tissue repair and fibrosis.

Keywords

Adenosine receptors; Wound healing; Fibrosis; Angiogenesis; Neovascularization

1 Introduction

Tissue repair is an essential homeostatic mechanism that involves a series of coordinated and overlapping phases: inflammation, neovascularization, new tissue generation, and tissue reorganization. In acute inflammation, tissue damage is followed by resolution, whereas in chronic inflammation, damage and repair continue concurrently. Inflammatory cells neutralize invading pathogens, remove waste and debris, and promote restoration of normal function, either through resolution or repair. Inflammation also promotes angiogenesis and vasculogenesis, the formation of new blood vessels, which in turn may enhance the recruitment of inflammatory cells and the subsequent laying down of extracellular matrix to repair tissue damage. Although usually beneficial to the organism, inflammation may lead to tissue damage, resulting in escalation of chronic inflammation. Furthermore, aberrant or inadequate repair can lead to excessive and poorly ordered matrix deposition and fibrosis, which affects normal tissue architecture and can ultimately disable the proper functioning of organs. Like matrix generation, overly exuberant vessel formation may lead to medical

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problems as well, and diabetic retinopathy and macular degeneration are examples of this phenomenon.

Extracellular accumulation of adenosine in response to tissue damage is an important event in the control of all aspects of tissue repair. The nature of adenosine's action depends on the magnitude of changes in extracellular adenosine concentrations as well as on the identity and expression levels of each adenosine receptor subtype on individual cell types. The role of adenosine in the regulation of inflammation is extensively covered in other chapters of this book. In this chapter, we will discuss the roles of specific adenosine receptors in the regulation of neovascularization and fibrosis in different organs and tissues.

2 Role of Adenosine in Neovascularization

Accumulating evidence indicates that adenosine is an important regulator of neovascularization, including angiogenesis and vasculogenesis. Stimulation of new blood vessel formation by adenosine was demonstrated in the chick chorioallantoic membrane and embryo (Adair et al. 1989; Dusseau et al. 1986; Dusseau and Hutchins 1988), the mouse retina (Afzal et al. 2003; Mino et al. 2001), and the optical tectum of *Xenopus leavis* tadpoles (Jen and Rovainen 1994). Adenosine reportedly modulates a number of steps involved in angiogenesis, including endothelial cell proliferation (Dubey et al. 2002; Ethier et al. 1993; Grant et al. 1999, 2001; Meininger et al. 1988; Meininger and Granger 1990; Van Daele et al. 1992), migration (Dubey et al. 2002; Grant et al. 2001; Lutty et al. 1998; Meininger et al. 1988; Teuscher and Weidlich 1985), and tube formation (Grant et al. 2001; Lutty et al. 1998). Adenosine has been also suggested to play an important role in adult vasculogenesis by directing the homing of endothelial progenitor cells to the site of tissue injury (Montesinos et al. 2004; Ryzhov et al. 2008b).

Adenosine has direct mitogenic effects on vascular cells that may contribute to angiogenesis (Ethier and Dobson Jr. 1997; Meininger et al. 1988; Sexl et al. 1995; Van Daele et al. 1992). However, the main proangiogenic actions of adenosine have been attributed to its ability to regulate the production of pro- and antiangiogenic substances. Adenosine modulates the release of angiogenic factors from various cells and tissues (Feoktistov et al. 2003, 2004; Gu et al. 1999, 2000; Hashimoto et al. 1994; Leibovich et al. 2002; Olah and Roudabush 2000; Pueyo et al. 1998; Takagi et al. 1996; Wakai et al. 2001; Zeng et al. 2003), thus regulating capillary growth in a paracrine fashion. In addition, adenosine can modulate release of angiogenic factors from endothelial cells (Desai et al. 2005; Feoktistov et al. 2002; Fischer et al. 1995, 1997; Grant et al. 1999; Khoa et al. 2003; Takagi et al. 1996), which may regulate capillary growth in an autocrine fashion.

All four adenosine receptor (AR) subtypes have been implicated in the regulation of neovascularization. In a similar manner to our early observation that the stimulation of A_1ARs on neutrophils increased their adherence to vascular endothelium (Cronstein et al. 1992), we have recently demonstrated that A_1ARs located on embryonic endothelial progenitor cells promote their adhesion to cardiac microvascular endothelial cells, suggesting an important role of this receptor subtype in vasculogenesis (Ryzhov et al. 2008b). A_1ARs have been also reported to upregulate vascular endothelial growth factor (VEGF) production from monocytes, thus promoting angiogenesis in an in vitro model (Clark et al. 2007). Among all of the AR subtypes, A_1ARs have the highest affinity to adenosine (Fredholm et al. 2001). It is possible, therefore, that engagement of the high-affinity A_1ARs is especially important for circulating cells moving toward a gradient of adenosine concentrations generated by tissue injury and/or hypoxia, whereas the lower-affinity A_2ARs are more important for the regulation of cells located in the vicinity of the injured or ischemic loci, where concentrations of adenosine are the highest.

Indeed, both A_2AR subtypes, A_{2A} and A_{2B}ARs, have been implicated in regulation of angiogenesis and vasculogenesis. Depending on tissue or cell studied, either one of these receptor subtypes can take the lead and play a dominant role in the regulation of angiogenic factors. For example, A_{2B}ARs upregulate the proangiogenic factors VEGF, basic fibroblast growth factor (bFGF), insulin-like factor 1, and IL-8 in human microvascular endothelial cells (Feoktistov et al. 2002; Grant et al. 1999). Conversely, A_{2A}ARs were reported to upregulate VEGF in macrophages (Leibovich et al. 2002; Pinhal-Enfield et al. 2003). However, A_{2B}ARs may also contribute to regulation of VEGF in these cells, since genetic deletion of A_{2B}ARs significantly decreased adenosine-dependent secretion of VEGF in mouse peritoneal macrophages (our unpublished observations). In addition, the stimulation of A_3ARs in mast cells and some tumors can result in the upregulation of certain proangiogenic factors, complementing the actions of adenosine mediated via A_{2B}ARs (Feoktistov et al. 2003; Merighi et al. 2005, 2007). Thus, the contribution of adenosine to the regulation of neovascularization can be dictated by the expression profile of AR subtypes and by the intracellular machinery to which they are coupled in specific cell types. Furthermore, the expressions of AR subtypes and their functions are subject to dynamic regulation by conditions present during inflammation, such as hypoxia and cytokine exposure (Bshesh et al. 2002; Eltzschig et al. 2003; Feoktistov et al. 2004; Khoa et al. 2003). Because the A_{2B}AR promoter contains a functional binding site for hypoxia-inducible factor (Kong et al. 2006), the onset of hypoxia strongly induces A_{2B}AR expression. Hypoxia-induced upregulation of A_{2B}ARs has been reported in human tumor cells (Zeng et al. 2003), rat hippocampus (Zhou et al. 2004), and human dermal microvascular endothelial cells (Eltzschig et al. 2003). This may have important functional implications for regulation of angiogenesis. For example, in human bronchial smooth muscle cells and human umbilical vein endothelial cells, adenosine does not stimulate VEGF secretion under normoxic conditions, but hypoxia increases expression of A_{2B}ARs, which are then able to stimulate VEGF release (Feoktistov et al. 2004). Similarly, treatment of human dermal microvascular endothelial cells with interferon (IFN)-γ increases A_{2B}AR expression but decreases A_{2A}AR levels. In contrast, other proinflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor alpha (TNF-α) increase both A_{2A} and A_{2B} AR expression and function (Khoa et al. 2003). Because the expression and function of adenosine receptor subtypes may differ depending on the tissue and the nature of the tissue injury, we will next examine the role of AR subtypes in specific organs and pathological states.

2.1 Regulation of Neovascularization in the Skin

We have previously reported (Montesinos et al. 2002) that mice with genetically disrupted A_{2A}ARs form significantly fewer microvessels in healing wounds and in response to mechanical trauma by the formation of an air pouch (Montesinos et al. 2002). Furthermore, application of an A_{2A}AR agonist to wounds increases microvessel formation from both pre-existing endothelial cells and bone marrow-derived endothelial progenitors as compared to vehicle-treated mice, observations that provide the first in vivo evidence that A_{2A}AR occupancy promotes angiogenesis and vasculogenesis (Montesinos et al. 2002, 2004). Further studies indicate that the angiogenic effects of A_{2A}AR occupancy are mediated both directly on endothelial cells (increased endothelial cell migration and microvascular endothelial cell VEGF production; Khoa et al. 2003; Montesinos et al. 1997) and indirectly via promotion of VEGF production by macrophages (Leibovich et al. 2002). Desai and colleagues (Desai et al. 2005) have also reported evidence to indicate that A_{2A}AR occupancy suppresses the production of thrombospondin I, a potent inhibitor of angiogenesis, and this inhibition is responsible for enhanced vascular tube formation in vitro. Thus, there is growing evidence that A_{2A}ARs play an important role in skin neovascularization, and particularly during wound healing.

2.2 Regulation of Neovascularization in the Heart and Skeletal Muscles

Many studies have demonstrated that chronic elevation of tissue adenosine concentrations induced by the adenosine reuptake blocker dipyridamole (Adolfsson et al. 1981, 1982; Adolfsson 1986a, b; Belardinelli et al. 2001; Mall et al. 1987; Mattfeldt and Mall 1983; Symons et al. 1993; Tornling et al. 1978, 1980a, b; Tornling 1982a, b; Torry et al. 1992), or long-term administration of adenosine and its analogs (Hudlicka et al. 1986; Wothe et al. 2002; Ziada et al. 1984), promotes capillary proliferation in the heart and skeletal muscles. Antagonism of ARs with caffeine abrogated VEGF upregulation in skeletal muscles induced by local injection of adenosine 5′-*N*-ethyluronamide (NECA) into the mouse hind limb and produced a 46% reduction in neovascularization in a mouse ischemic hind limb model (Ryzhov et al. 2007). In the isolated heart model, adenosine but not selective A_{2A} or A_3 AR agonists increased retention of embryonic endothelial progenitors to microvascular endothelium, suggesting that A_1 and A_{2B}ARs may play an important role in the initial phase of vasculogenesis, promoting homing of endothelial progenitor cells to the site of ischemic injury (Ryzhov et al. 2008b). Indeed, endothelial progenitor cells and cardiac microvascular endothelial cells preferentially express functional A_1 and A_{2B}ARs, respectively, and both subtypes are involved in the regulation of the adhesion of endothelial progenitors to microvascular endothelial cells in the heart. Moreover, the interaction between P-selectin and its ligand PSGL-1 plays an important role in these process, and stimulation of A_{2B}ARs in cardiac microvascular endothelial cells induces rapid cell surface expression of P-selectin (Ryzhov et al. 2008b). These findings suggested a role for A_1 and A_{2B}ARs in myocardial vasculogenesis, and provided a rationale for the potential use of adenosine to stimulate engraftment in cell-based therapies.

2.3 Regulation of Neovascularization in the Lung

Angiogenesis is a feature of chronic lung diseases such as asthma and pulmonary fibrosis. Studies in adenosine deaminase (ADA)-deficient mice, characterized by elevated lung tissue levels of adenosine, strongly suggest a causal association between adenosine and an inflammatory phenotype (Blackburn et al. 2000; Blackburn 2003). These mice exhibit a lung phenotype with features of lung inflammation, bronchial hyperresponsiveness, enhanced mucus secretion, increased IgE synthesis, and elevated levels of proinflammatory cytokines and angiogenic factors that could be reversed by lowering adenosine levels with exogenous ADA (Blackburn et al. 2000). In particular, levels of the angiogenic chemokine CXCL1 (mouse functional homolog of human IL-8) are significantly elevated in an adenosine-dependent manner in the lungs of ADA-deficient mice, leading to substantial angiogenesis in the tracheas (Mohsenin et al. 2007a). The A_{2B}AR subtype appears to play an important role in this model, because pharmacological inhibition of A_{2B}ARs significantly reduced elevations in proinflammatory cytokines as well as mediators of airway remodeling induced by high adenosine levels in the lungs of ADA-deficient mice (Sun et al. 2006). In contrast, genetic removal of the A_{2A}AR enhances pulmonary inflammation, mucin production, and angiogenesis in ADA-deficient mice (Mohsenin et al. 2007b).

2.4 Regulation of Neovascularization in Tumors

Metabolically active solid tumors grow rapidly and routinely experience severe hypoxia and necrosis, which causes adenine nucleotide degradation and adenosine release. Expression of A_{2B}ARs was documented in various cancerous cells (Feoktistov and Biaggioni 1993, 1995; Panjehpour et al. 2005; Phelps et al. 2006; Rodrigues et al. 2007; Zeng et al. 2003), and analysis of gene expression in primary human tumors uncovered overexpression of A_{2B}ARs, suggesting their potential role in cancer biology (Li et al. 2005). Studies from different laboratories demonstrate that stimulation of A_{2B}ARs in cancer cell lines upregulates the production of angiogenic factors, suggesting that tumor A_{2B}ARs may promote neovascularization (Feoktistov et al. 2003; Merighi et al. 2007; Zeng et al. 2003). A_3ARs

expressed in some tumor cell lines may also complement these A_{2B}AR-mediated effects by up-regulating other proangiogenic factors (Feoktistov et al. 2003; Merighi et al. 2005, 2007). In addition, host tumor-infiltrating immune cells can also play an important role in tumor angiogenesis, since Lewis lung carcinoma isografts in A_{2B}AR knockout mice contained lower VEGF levels and exhibited lower vessel density compared to tumors grafted in wild-type mice (Ryzhov et al. 2008a). Furthermore, treatment with A_{2A}/A_{2B}AR antagonists inhibited neovascularization of CL8-1 melanoma in mice (Ohta et al. 2006). Thus, there is growing evidence that adenosine acting via A_{2B} and possibly A_3 or A_{2A}ARs can promote tumor neovascularization. Involvement of different AR subtypes in the regulation of neovascularization is not surprising due to the multifaceted mechanism of blood vessel development.

3 Role of Adenosine in Fibrosis

3.1 A_{2A} Adenosine Receptor Agonists Promote Wound Healing

Recent reports indicate that topical application of an A_{2A}AR agonist increases the rate at which wounds close (Montesinos et al. 1997). That A_{2A}ARs were involved in this pharmacologic effect was demonstrated by the observation that a specific A_{2A}AR antagonist, but not antagonists at other ARs, reversed the effect of the selective A_{2A}AR agonist CGS21680 on wound healing. Treatment of wounds with this AR agonist promoted fibroblast migration in vitro, and in the AR agonist-treated mice there was an increase in matrix and fibroblast infiltration into the wounds (Montesinos et al. 1997). More recent studies demonstrate that a more highly selective A_{2A}AR agonist, sonedenoson, is a more potent promoter of wound healing than recombinant platelet derived growth factor (becaplermin) (Victor-Vega et al. 2002). The role of A_{2A}ARs in the promotion of wound healing was more fully confirmed by the observation that a selective A_{2A}AR agonist promotes wound healing in wild-type but not A_{2A}AR knockout mice (Montesinos et al. 2002; Victor-Vega et al. 2002). In these studies, there was a marked increase in the number of blood vessels in the healing wounds of wild-type mice treated with the A_{2A}AR agonist as compared to untreated controls. Absence of A_{2A}ARs was associated with disorganized granulation tissue although re-epithelialization was not delayed in the knockout mice. In contrast to this study, Sun and colleagues observed that N_6-cyclopentyladenosine, a relatively selective A_1AR agonist, promotes wound healing (Sun et al. 1999). In this study, there was no confirmation that the high concentrations of the agonist used were indeed selective for A_1ARs or whether the phenomenon could be mediated by A_{2A}ARs. These findings indicate that A_{2A}ARs stimulate wound healing by modulating inflammatory cell, endothelial cell and fibroblast functions that promote wound healing. A topical A_{2A}AR agonist, sonedenoson, is currently undergoing testing in Phase II clinical trials for the treatment of diabetic foot ulcers.

3.2 A_{2A} Adenosine Receptor Occupancy Stimulates Fibroblast Matrix Production

Replacement of the collagenous matrix of the skin and other tissues is an integral part of wound healing. Once the debris and destroyed matrix at the site of injury are eliminated, fibroblasts lay down a new matrix. This matrix may be remodeled over a longer period of time and the wound develops the characteristic appearance of a scar. A_{2A}AR occupancy stimulates fibroblasts to synthesize type I and III collagen at an increased level, similar to that induced by the growth factor transforming growth factor (TGF)-β, and downregulates matrix metalloproteinase (MMP) 9 but not MMP2 (Chan et al. 2006a).

The observation that adenosine, acting at A_{2A}ARs, stimulates the formation of matrix suggests the possibility that adenosine A_{2A}ARs play a role in fibrosing conditions and scarring, a hypothesis confirmed by in vivo experiments. Animals lacking A_{2A}ARs or

treated with an A_{2A}AR antagonist were protected from developing diffuse dermal fibrosis in response to bleomycin (Chan et al. 2006a). The role of A_{2A}ARs in fibrosis in tissues outside of the skin is less clear. Prior studies have demonstrated that A_{2B}ARs regulate production of collagen in pulmonary and cardiac fibroblasts (Chen et al. 2004; Dubey et al. 2000, 2001), but other studies have demonstrated that A_{2A}ARs regulate collagen I and III production by hepatic stellate cells (Che et al. 2007), the fibroblasts of the liver, and A_{2A}AR knockout mice are protected from developing hepatic fibrosis following treatment with either CCl_4 or thioacetamide (Chan et al. 2006b). These observations help to explain the protection against death from liver disease provided by coffee drinking (Corrao et al. 1994, 2001; Gallus et al. 2002; Klatsky et al. 1993, 2006; Klatsky and Armstrong 1992; Ruhl et al. 2005; Sharp et al. 1999; Tverdal and Skurtveit 2003), since caffeine is a relatively weak and nonselective AR antagonist which offers some protection (although not complete) from the development of hepatic fibrosis in murine models (Chan et al. 2006b).

In a murine model of diffuse dermal fibrosis resembling scleroderma, we have also found that A_{2A}ARs play a central role in the development of fibrosis. A_{2A}ARs are present on human dermal fibroblasts and, when occupied, regulate collagen production by these cells (Chan et al. 2006a). Mice treated with subcutaneous bleomycin develop diffuse dermal fibrosis and we found that both A_{2A}AR knockout mice and mice treated with a selective A_{2A}AR antagonist were protected from the development of bleomycin-induced dermal fibrosis (Chan et al. 2006a). These results are consistent with the hypothesis that A_{2A}ARs play a role in organ and tissue fibrosis and that blockade or elimination of these receptors can prevent fibrosis.

Recently published indirect evidence provides further support for a role for adenosine and its receptors in dermal fibrosis. Imiquimod is an immune modulator that promotes a shift from Th2- to Th1-type immune responses (reviewed in Schon and Schon 2007) by mechanisms that have not been fully evaluated. Studies in inflammatory cells indicate that imiquimod, at pharmacologically relevant concentrations, is an A_{2A}AR antagonist, and that this may account for its immunological effects (Schon et al. 2006). Imiquimod, applied topically, has been used to treat morphea, a skin disease characterized by localized fibrosis, and its use has been advocated for the treatment of Dupuytren's contracture, another fibrosing disease (Dytoc et al. 2005; Man and Dytoc 2004; Namazi 2006; Schon et al. 2006). While intriguing (and supporting the clinical relevance of this work), we do realize the anecdotal nature of these reports.

3.3 A_{2B} Adenosine Receptor Occupancy Regulates Fibroblast Collagen Production and Fibrosis

As described above, a number of recent studies have demonstrated that cardiac and pulmonary fibroblasts express A_{2B}ARs that regulate their production of collagen (Chen et al. 2004; Dubey et al. 1997, 1998; Zhong et al. 2005). Stimulation of A_{2B}ARs in cardiac fibroblasts inhibited their proliferation, protein synthesis and collagen production (Chen et al. 2004; Dubey et al. 1997, 1998). Furthermore, it has been demonstrated in vivo that long-term stimulation of A_{2B}ARs after myocardial infarction prevents cardiac remodeling (Wakeno et al. 2006). In contrast, studies in ADA-deficient mice indicate that these animals develop pulmonary inflammation and pulmonary fibrosis that appear to be mediated by A_{2B}ARs (Sun et al. 2006), thus suggesting a role for A_{2B}ARs in pulmonary fibrosis. Based on these studies and the results described above, it is reasonable to conclude that adenosine can either inhibit (heart) or stimulate (skin, liver, lungs) fibrosis, and that adenosine-regulated fibrosis is mediated by different receptors depending on which organ is studied (skin and liver vs. heart and lungs).

3.4 A_1 Adenosine Receptors Play a Role in Cardiac and Vascular Fibrosis

Recently, Kalk and coworkers reported that SLV320 (Solvay Pharmaceuticals), a highly selective A_1AR antagonist, reduced myocardial fibrosis in a model of uremic cardiomyopathy (Kalk et al. 2007). In this model, partially (5/6) nephrectomized rats were treated with SLV320 or vehicle and myocardial fibrosis was markedly reduced, as was albuminuria, without any change in blood pressure or other factors that might have accounted for the change. Another problem associated with fibrosis and abnormal “wound” healing that may be mediated by A_1ARs is intimal hyperplasia and stenosis following stent placement, and recent studies suggest that an A_1AR antagonist diminishes both intimal hyperplasia and smooth muscle proliferation in a model of stent stenosis (Edwards et al. 2008) Thus, A_1ARs may also play a role in fibrosis, although their role seems to be confined to the cardiovascular system.

4 Conclusion

Adenosine and its receptors play important roles in both matrix production and neovascularization, processes that are critical for wound healing and tissue repair. Moreover, adenosine and its receptors play a direct role in stimulating fibrosis in the skin, lungs and liver, but inhibiting fibrosis in the heart. Adenosine and its receptors may also play an important role in physiologic and pathologic angiogenesis. Targeting of ARs to promote wound healing and neovascularization of ischemic tissues or to diminish pathologic fibrosis and angiogenesis is currently underway.

Abbreviations

ADA	Adenosine deaminase
AR	Adenosine receptor
bFGF	Basic fibroblast growth factor
IFN	Interferon
IL	Interleukin
MMP	Matrix metalloproteinase
NECA	Adenosine 5′-*N*-ethyluronamide
TGF	Transforming growth factor
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor

References

Adair TH, Montani JP, Strick DM, Guyton AC. Vascular development in chick embryos: a possible role for adenosine. Am J Physiol. 1989; 256:H240–H246. [PubMed: 2463773]

Adolfsson J. The time dependence of training-induced increase in skeletal muscle capillarization and the spatial capillary to fibre relationship in normal and neovascularized skeletal muscle of rats. Acta Physiol Scand. 1986a; 128:259–266. [PubMed: 2430430]

Adolfsson J. Time dependence of dipyridamole-induced increase in skeletal muscle capillarization. Arzneimittel-Forschung. 1986b; 36:1768–1769. [PubMed: 3566837]

Adolfsson J, Ljungqvist A, Tornling G, Unge G. Capillary increase in the skeletal muscle of trained young and adult rats. J Physiol. 1981; 310:529–532. [PubMed: 7230047]

Adolfsson J, Tornling G, Unge G, Ljungqvist A. The prophylactic effect of dipyridamole on the size of myocardial infarction following coronary artery occlusion. Acta Pathol Microbiol Immunol Scand A Pathol. 1982; 90:273–275.

Afzal A, Shaw LC, Caballero S, Spoerri PE, Lewin AS, Zeng D, Belardinelli L, Grant MB. Reduction in preretinal neovascularization by ribozymes that cleave the A_{2B} adenosine receptor mRNA. Circ Res. 2003; 93:500–506. [PubMed: 12919950]

Belardinelli R, Belardinelli L, Shryock JC. Effects of dipyridamole on coronary collateralization and myocardial perfusion in patients with ischaemic cardiomyopathy. Eur Heart J. 2001; 22:1205–1213. [PubMed: 11440493]

Blackburn MR. Too much of a good thing: adenosine overload in adenosine-deaminase-deficient mice. Trends Pharmacol Sci. 2003; 24:66–70. [PubMed: 12559769]

Blackburn MR, Volmer JB, Thrasher JL, Zhong H, Crosby JR, Lee JJ, Kellems RE. Metabolic consequences of adenosine deaminase deficiency in mice are associated with defects in alveogenesis, pulmonary inflammation, and airway obstruction. J Exp Med. 2000; 192:159–170. [PubMed: 10899903]

Bshesh K, Zhao B, Spight D, Biaggioni I, Feoktistov I, Denenberg A, Wong HR, Shanley TP. The A_{2A} receptor mediates an endogenous regulatory pathway of cytokine expression in THP-1 cells. J Leukoc Biol. 2002; 72:1027–1036. [PubMed: 12429726]

Chan ES, Fernandez P, Merchant AA, Montesinos MC, Trzaska S, Desai A, Tung CF, Khoa DN, Pillinger MH, Reiss AB, Tomic-Canic M, Chen JF, Schwarzschild MA, Cronstein BN. Adenosine A_{2A} receptors in diffuse dermal fibrosis: pathogenic role in human dermal fibroblasts and in a murine model of scleroderma. Arthritis Rheum. 2006a; 54:2632–2642. [PubMed: 16871530]

Chan ES, Montesinos MC, Fernandez P, Desai A, Delano DL, Yee H, Reiss AB, Pillinger MH, Chen JF, Schwarzschild MA, Friedman SL, Cronstein BN. Adenosine A_{2A} receptors play a role in the pathogenesis of hepatic cirrhosis. Br J Pharmacol. 2006b; 148:1144–1155. [PubMed: 16783407]

Che J, Chan ES, Cronstein BN. Adenosine A_{2A} receptor occupancy stimulates collagen expression by hepatic stellate cells via pathways involving protein kinase A, Src, and extra-cellular signal-regulated kinases 1/2 signaling cascade or p38 mitogen-activated protein kinase signaling pathway. Mol Pharmacol. 2007; 72:1626–1636. [PubMed: 17872970]

Chen Y, Epperson S, Makhsudova L, Ito B, Suarez J, Dillmann W, Villarreal F. Functional effects of enhancing or silencing adenosine A_{2B} receptors in cardiac fibroblasts. Am J Physiol. 2004; 287:H2478–H2486.

Clark AN, Youkey R, Liu X, Jia L, Blatt R, Day YJ, Sullivan GW, Linden J, Tucker AL. A_1 adenosine receptor activation promotes angiogenesis and release of VEGF from monocytes. Circ Res. 2007; 101:1130–1138. [PubMed: 17901362]

Corrao G, Lepore AR, Torchio P, Valenti M, Galatola G, D'Amicis A, Arico S, di Orio F. The effect of drinking coffee and smoking cigarettes on the risk of cirrhosis associated with alcohol consumption. A case–control study. Provincial Group for the Study of Chronic Liver Disease. Eur J Epidemiol. 1994; 10:657–664. [PubMed: 7672043]

Corrao G, Zambon A, Bagnardi V, D'Amicis A, Klatsky A. Collaborative SIDECIR Group. Coffee, caffeine, and the risk of liver cirrhosis. Ann Epidemiol. 2001; 11:458–465. [PubMed: 11557177]

Cronstein BN, Levin RI, Philips M, Hirschhorn R, Abramson SB, Weissmann G. Neutrophil adherence to endothelium is enhanced via adenosine A_1 receptors and inhibited via adenosine A_2 receptors. J Immunol. 1992; 92:2201–2206. [PubMed: 1347551]

Desai A, Victor-Vega C, Gadangi S, Montesinos MC, Chu CC, Cronstein BN. Adenosine A_{2A} receptor stimulation increases angiogenesis by down-regulating production of the antiangiogenic matrix protein thrombospondin 1. Mol Pharmacol. 2005; 67:1406–1413. [PubMed: 15673602]

Dubey RK, Gillespie DG, Mi Z, Jackson EK. Exogenous and endogenous adenosine inhibits fetal calf serum-induced growth of rat cardiac fibroblasts: role of A_{2B} receptors. Circulation. 1997; 96:2656–2666. [PubMed: 9355907]

Dubey RK, Gillespie DG, Jackson EK. Adenosine inhibits collagen and protein synthesis in cardiac fibroblasts: role of A_{2B} receptors. Hypertension. 1998; 31:943–948. [PubMed: 9535419]

Dubey RK, Gillespie DG, Shue H, Jackson EK. A_{2B} receptors mediate antimitogenesis in vascular smooth muscle cells. Hypertension. 2000; 35:267–272. [PubMed: 10642309]

Dubey RK, Gillespie DG, Zacharia LC, Mi Z, Jackson EK. A_{2B} receptors mediate the antimitogenic effects of adenosine in cardiac fibroblasts. Hypertension. 2001; 37:716–721. [PubMed: 11230362]

Dubey RK, Gillespie DG, Jackson EK. A_{2B} adenosine receptors stimulate growth of porcine and rat arterial endothelial cells. Hypertension. 2002; 39:530–535. [PubMed: 11882603]

Dusseau JW, Hutchins PM. Hypoxia-induced angiogenesis in chick chorioallantoic membranes: a role for adenosine. Respir Physiol. 1988; 71:33–44. [PubMed: 2448857]

Dusseau JW, Hutchins PM, Malbasa DS. Stimulation of angiogenesis by adenosine on the chick chorioallantoic membrane. Circ Res. 1986; 59:163–170. [PubMed: 2427248]

Dytoc M, Ting PT, Man J, Sawyer D, Fiorillo L. First case series on the use of imiquimod for morphoea. Br J Dermatol. 2005; 153:815–820. [PubMed: 16181467]

Edwards JM, Alloosh MA, Long XL, Dick GM, Lloyd PG, Mokelke EA, Sturek M. Adenosine A_1 receptors in neointimal hyperplasia and in-stent stenosis in Ossabaw miniature swine. Coronary Artery Dis. 2008; 19:27–31.

Eltzschig HK, Ibla JC, Furuta GT, Leonard MO, Jacobson KA, Enjyoji K, Robson SC, Colgan SP. Coordinated adenine nucleotide phosphohydrolysis and nucleoside signaling in posthypoxic endothelium: role of ectonucleotidases and adenosine A_{2B} receptors. J Exp Med. 2003; 198:783–796. [PubMed: 12939345]

Ethier MF, Dobson JG Jr. Adenosine stimulation of DNA synthesis in human endothelial cells. Am J Physiol. 1997; 272:H1470–H1479. [PubMed: 9087626]

Ethier MF, Chander V, Dobson JG. Adenosine stimulates proliferation of human endothelial cells in culture. Am J Physiol. 1993; 265:H131–H138. [PubMed: 8342624]

Feoktistov I, Biaggioni I. Characterization of adenosine receptors in human erythroleukemia cells. Further evidence for heterogeneity of adenosine A_2 receptors. Mol Pharmacol. 1993; 43:909–914. [PubMed: 8391117]

Feoktistov I, Biaggioni I. Adenosine A_{2B} receptors evoke interleukin-8 secretion in human mast cells. An enprofylline-sensitive mechanism with implications for asthma. J Clin Invest. 1995; 96:1979–1986. [PubMed: 7560091]

Feoktistov I, Goldstein AE, Ryzhov S, Zeng D, Belardinelli L, Voyno-Yasenetskaya T, Biaggioni I. Differential expression of adenosine receptors in human endothelial cells: role of A_{2B} receptors in angiogenic factor regulation. Circ Res. 2002; 90:531–538. [PubMed: 11909816]

Feoktistov I, Ryzhov S, Goldstein AE, Biaggioni I. Mast cell-mediated stimulation of angiogenesis: cooperative interaction between A_{2B} and A_3 adenosine receptors. Circ Res. 2003; 92:485–492. [PubMed: 12600879]

Feoktistov I, Ryzhov S, Zhong H, Goldstein AE, Matafonov A, Zeng D, Biaggioni I. Hypoxia modulates adenosine receptors in human endothelial and smooth muscle cells toward an A_{2B} angiogenic phenotype. Hypertension. 2004; 44:649–654. [PubMed: 15452028]

Fischer S, Sharma HS, Karliczek GF, Schaper W. Expression of vascular permeability factor/vascular endothelial growth factor in pig cerebral microvascular endothelial cells and its upregulation by adenosine. Brain Res Mol Brain Res. 1995; 28:141–148. [PubMed: 7707868]

Fischer S, Knoll R, Renz D, Karliczek GF, Schaper W. Role of adenosine in the hypoxic induction of vascular endothelial growth factor in porcine brain derived microvascular endothelial cells. Endothelium. 1997; 5:155–165. [PubMed: 9272379]

Fredholm BB, Irenius E, Kull B, Schulte G. Comparison of the potency of adenosine as an agonist at human adenosine receptors expressed in Chinese hamster ovary cells. Biochem Pharmacol. 2001; 61:443–448. [PubMed: 11226378]

Gallus S, Tavani A, Negri E, La Vecchia C. Does coffee protect against liver cirrhosis? Ann Epidemiol. 2002; 12:202–205. [PubMed: 11897178]

Grant MB, Tarnuzzer RW, Caballero S, Ozeck MJ, Davis MI, Spoerri PE, Feoktistov I, Biaggioni I, Shryock JC, Belardinelli L. Adenosine receptor activation induces vascular endothelial growth factor in human retinal endothelial cells. Circ Res. 1999; 85:699–706. [PubMed: 10521243]

Grant MB, Davis MI, Caballero S, Feoktistov I, Biaggioni I, Belardinelli L. Proliferation, migration, and ERK activation in human retinal endothelial cells through A_{2B} adenosine receptor stimulation. Investig Ophthalmol Vis Sci. 2001; 42:2068–2073. [PubMed: 11481274]

Gu JW, Brady AL, Anand V, Moore MC, Kelly WC, Adair TH. Adenosine upregulates VEGF expression in cultured myocardial vascular smooth muscle cells. Am J Physiol. 1999; 277:H595–H602. [PubMed: 10444484]

Gu JW, Ito BR, Sartin A, Frascogna N, Moore M, Adair TH. Inhibition of adenosine kinase induces expression of VEGF mRNA and protein in myocardial myoblasts. Am J Physiol. 2000; 279:H2116–H2123.

Hashimoto E, Kage K, Ogita T, Nakaoka T, Matsuoka R, Kira Y. Adenosine as an endogenous mediator of hypoxia for induction of vascular endothelial growth factor mRNA in U-937 cells. Biochem Biophys Res Commun. 1994; 204:318–324. [PubMed: 7945378]

Hudlicka O, Wright AJ, Ziada AM. Angiogenesis in the heart and skeletal muscle. Can J Cardiol. 1986; 2:120–123. [PubMed: 2423212]

Jen SC, Rovainen CM. An adenosine agonist increases blood flow and density of capillary branches in the optic tectum of *Xenopus laevis* tadpoles. Microcirculation. 1994; 1:59–66. [PubMed: 8790578]

Kalk P, Eggert B, Relle K, Godes M, Heiden S, Sharkovska Y, Fischer Y, Ziegler D, Bielenberg GW, Hocher B. The adenosine A_1 receptor antagonist SLV320 reduces myocardial fibrosis in rats with 5/6 nephrectomy without affecting blood pressure. Br J Pharmacol. 2007; 151:1025–1032. [PubMed: 17558436]

Khoa ND, Montesinos MC, Williams AJ, Kelly M, Cronstein BN. Th1 cytokines regulate adenosine receptors and their downstream signaling elements in human microvascular endothelial cells. J Immunol. 2003; 171:3991–3998. [PubMed: 14530318]

Klatsky AL, Armstrong MA. Alcohol, smoking, coffee, and cirrhosis. Am J Epidemiol. 1992; 136:1248–1257. [PubMed: 1476147]

Klatsky AL, Armstrong MA, Friedman GD. Coffee, tea, and mortality. Ann Epidemiol. 1993; 3:375–381. [PubMed: 8275213]

Klatsky AL, Morton C, Udaltsova N, Friedman GD. Coffee, cirrhosis, and transaminase enzymes. Arch Intern Med. 2006; 166:1190–1195. [PubMed: 16772246]

Kong T, Westerman KA, Faigle M, Eltzschig HK, Colgan SP. HIF-dependent induction of adenosine A_{2B} receptor in hypoxia. FASEB J. 2006; 20:2242–2250. [PubMed: 17077301]

Leibovich SJ, Chen JF, Pinhal-Enfield G, Belem PC, Elson G, Rosania A, Ramanathan M, Montesinos C, Jacobson M, Schwarzschild MA, Fink JS, Cronstein B. Synergistic up-regulation of vascular endothelial growth factor expression in murine macrophages by adenosine A_{2A} receptor agonists and endotoxin. Am J Pathol. 2002; 160:2231–2244. [PubMed: 12057925]

Li S, Huang S, Peng SB. Overexpression of G protein-coupled receptors in cancer cells: involvement in tumor progression. Int J Oncol. 2005; 27:1329–1339. [PubMed: 16211229]

Lutty GA, Mathews MK, Merges C, McLeod DS. Adenosine stimulates canine retinal microvascular endothelial cell migration and tube formation. Curr Eye Res. 1998; 17:594–607. [PubMed: 9663849]

Mall G, Schikora I, Mattfeldt T, Bodle R. Dipyridamole-induced neoformation of capillaries in the rat heart. Quantitative stereological study on papillary muscles. Lab Invest. 1987; 57:86–93. [PubMed: 2439774]

Man J, Dytoc MT. Use of imiquimod cream 5% in the treatment of localized morphea. J Cutan Med Surg. 2004; 8:166–169. [PubMed: 15129316]

Mattfeldt T, Mall G. Dipyridamole-induced capillary endothelial cell proliferation in the rat heart: a morphometric investigation. Cardiovasc Res. 1983; 17:229–237. [PubMed: 6871913]

Meininger CJ, Granger HJ. Mechanisms leading to adenosine-stimulated proliferation of microvascular endothelial cells. Am J Physiol. 1990; 258:H198–H206. [PubMed: 2154131]

Meininger CJ, Schelling ME, Granger HJ. Adenosine and hypoxia stimulate proliferation and migration of endothelial cells. Am J Physiol. 1988; 255:H554–H562. [PubMed: 3414822]

Merighi S, Benini A, Mirandola P, Gessi S, Varani K, Leung E, Maclennan S, Baraldi PG, Borea PA. A_3 adenosine receptors modulate hypoxia-inducible factor-1alpha expression in human a375 melanoma cells. Neoplasia. 2005; 7:894–903. [PubMed: 16242072]

Merighi S, Benini A, Mirandola P, Gessi S, Varani K, Simioni C, Leung E, Maclennan S, Baraldi PG, Borea PA. Caffeine inhibits adenosine-induced accumulation of hypoxiainducible factor-1a,

vascular endothelial growth factor, and interleukin-8 expression in hypoxic human colon cancer cells. Mol Pharmacol. 2007; 72:395–406. [PubMed: 17488804]

Mino RP, Spoerri PE, Caballero S, Player D, Belardinelli L, Biaggioni I, Grant MB. Adenosine receptor antagonists and retinal neovascularization in vivo. Invest Ophthalmol Vis Sci. 2001; 42:3320–3324. [PubMed: 11726639]

Mohsenin A, Burdick MD, Molina JG, Keane MP, Blackburn MR. Enhanced CXCL1 production and angiogenesis in adenosine-mediated lung disease. FASEB J. 2007a; 21:1026–1036. [PubMed: 17227950]

Mohsenin A, Mi T, Xia Y, Kellems RE, Chen JF, Blackburn MR. Genetic removal of the A_{2A} adenosine receptor enhances pulmonary inflammation, mucin production, and angiogenesis in adenosine deaminase-deficient mice. Am J Physiol. 2007b; 293:L753–L761.

Montesinos MC, Gadangi P, Longaker M, Sung J, Levine J, Nilsen D, Reibman J, Li M, Jiang CK, Hirschhorn R, Recht PA, Ostad E, Levin RI, Cronstein BN. Wound healing is accelerated by agonists of adenosine A_2 (Gas-linked) receptors. J Exp Med. 1997; 186:1615–1620. [PubMed: 9348321]

Montesinos MC, Desai A, Chen JF, Yee H, Schwarzschild MA, Fink JS, Cronstein BN. Adenosine promotes wound healing and mediates angiogenesis in response to tissue injury via occupancy of A_{2A} receptors. Am J Pathol. 2002; 160:2009–2018. [PubMed: 12057906]

Montesinos MC, Shaw JP, Yee H, Shamamian P, Cronstein BN. Adenosine A_{2A} receptor activation promotes wound neovascularization by stimulating angiogenesis and vasculogenesis. Am J Pathol. 2004; 164:1887–1892. [PubMed: 15161625]

Namazi H. Imiquimod: a potential weapon against Dupuytren contracture. Med Hypotheses. 2006; 66:991–992. [PubMed: 16368197]

Ohta A, Gorelik E, Prasad SJ, Ronchese F, Lukashev D, Wong MK, Huang X, Caldwell S, Liu K, Smith P, Chen JF, Jackson EK, Apasov S, Abrams S, Sitkovsky M. A_{2A} adenosine receptor protects tumors from antitumor T cells. Proc Natl Acad Sci USA. 2006; 103:13132–13137. [PubMed: 16916931]

Olah ME, Roudabush FL. Down-regulation of vascular endothelial growth factor expression after A_{2A} adenosine receptor activation in PC12 pheochromocytoma cells. J Pharmacol Exp Ther. 2000; 293:779–787. [PubMed: 10869376]

Panjehpour M, Castro M, Klotz KN. Human breast cancer cell line MDA-MB-231 expresses endogenous A_{2B} adenosine receptors mediating a Ca^{2+} signal. Br J Pharmacol. 2005; 145:211–218. [PubMed: 15753948]

Phelps PT, Anthes JC, Correll CC. Characterization of adenosine receptors in the human bladder carcinoma T24 cell line. Eur J Pharmacol. 2006; 536:28–37. [PubMed: 16581066]

Pinhal-Enfield G, Ramanathan M, Hasko G, Vogel SN, Salzman AL, Boons GJ, Leibovich SJ. An angiogenic switch in macrophages involving synergy between Toll-like receptors 2, 4, 7, and 9 and adenosine A_{2A} receptors. Am J Pathol. 2003; 163:711–721. [PubMed: 12875990]

Pueyo ME, Chen Y, D'Angelo G, Michel JB. Regulation of vascular endothelial growth factor expression by cAMP in rat aortic smooth muscle cells. Exp Cell Res. 1998; 238:354–358. [PubMed: 9473343]

Rodrigues S, De Wever O, Bruyneel E, Rooney RJ, Gespach C. Opposing roles of netrin-1 and the dependence receptor DCC in cancer cell invasion, tumor growth and metastasis. Oncogene. 2007; 26:5615–5625. [PubMed: 17334389]

Ruhl CE, Everhart JE, Ruhl CE, Everhart JE. Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. Gastroenterology. 2005; 129:1928–1936. [PubMed: 16344061]

Ryzhov S, McCaleb JL, Goldstein AE, Biaggioni I, Feoktistov I. Role of adenosine receptors in the regulation of angiogenic factors and neovascularization in hypoxia. J Pharmacol Exp Ther. 2007; 382:565–572. [PubMed: 17132813]

Ryzhov S, Novitskiy SV, Zaynagetdinov R, Goldstein AE, Biaggioni I, Carbone DC, Dikov MM, Feoktistov I. Host A2B adenosine receptors promote carcinoma growth. Neoplasia. 2008a; 10:987–995. [PubMed: 18714400]

Ryzhov S, Solenkova NV, Goldstein AE, Lamparter M, Fleenor T, Young PP, Greelish JP, Byrne JG, Vaughan DE, Biaggioni I, Hatzopoulos AK, Feoktistov I. Adenosine receptor-mediated adhesion of endothelial progenitors to cardiac microvascular endothelial cells. Circ Res. 2008b; 102:356–363. [PubMed: 18032734]

Schon M, Schon MP. The antitumoral mode of action of imiquimod and other imidazoquinolines. Curr Med Chem. 2007; 14:681–687. [PubMed: 17346155]

Schon MP, Schon M, Klotz KN. The small antitumoral immune response modifier imiquimod interacts with adenosine receptor signaling in a TLR7- and TLR8-independent fashion. J Invest Dermatol. 2006; 126:1338–1347. [PubMed: 16575388]

Sexl V, Mancusi G, Baumgartner-Parzer S, Schutz W, Freissmuth M. Stimulation of human umbilical vein endothelial cell proliferation by A_2-adenosine and β_2-adrenoceptors. Br J Pharmacol. 1995; 114:1577–1586. [PubMed: 7599925]

Sharp DS, Everhart JE, Benowitz NL. Coffee, alcohol, and the liver. Ann Epidemiol. 1999; 9:391–393. [PubMed: 10501405]

Sun LL, Xu LL, Nielsen TB, Rhee P, Burris D. Cyclopentyladenosine improves cell proliferation, wound healing, and hair growth. J Surg Res. 1999; 87:14–24. [PubMed: 10527699]

Sun CX, Zhong H, Mohsenin A, Morschl E, Chunn JL, Molina JG, Belardinelli L, Zeng D, Blackburn MR. Role of A_{2B} adenosine receptor signaling in adenosine-dependent pulmonary inflammation and injury. J Clin Invest. 2006; 116:2173–2182. [PubMed: 16841096]

Symons JD, Firoozmand E, Longhurst JC. Repeated dipyridamole administration enhances collateral-dependent flow and regional function during exercise. A role for adenosine. Circ Res. 1993; 73:503–513. [PubMed: 8348693]

Takagi H, King GL, Robinson GS, Ferrara N, Aiello LP. Adenosine mediates hypoxic induction of vascular endothelial growth factor in retinal pericytes and endothelial cells. Invest Ophthalmol Vis Sci. 1996; 37:2165–2176. [PubMed: 8843903]

Teuscher E, Weidlich V. Adenosine nucleotides, adenosine and adenine as angiogenesis factors. Biomed Biochim Acta. 1985; 44:493–495. [PubMed: 4004845]

Tornling G, Unge G, Ljungqvist A, Carlsson S. Dipyridamole and capillary proliferation. A preliminary report. Acta Pathol Microbiol Scand A Pathol. 1978; 86:82.

Tornling G, Adolfsson J, Unge G, Ljungqvist A. Capillary neoformation in skeletal muscle of dipyridamole-treated rats. Arzneimittel-Forschung. 1980a; 30:791–792. [PubMed: 6156689]

Tornling G, Unge G, Adolfsson J, Ljungqvist A, Carlsson S. Proliferative activity of capillary wall cells in skeletal muscle of rats during long-term treatment with dipyridamole. Arzneimittel-Forschung. 1980b; 30:622–623. [PubMed: 7190403]

Tornling G. Capillary neoformation in the heart and skeletal muscle during dipyridamole: treatment and exercise. Acta Pathol Microbiol Immunol Scand. 1982a; 278(Suppl):1–63.

Tornling G. Capillary neoformation in the heart of dipyridamole-treated rats. Acta Pathol Microbiol Immunol Scand A Pathol. 1982b; 90:269–271.

Torry RJ, O'Brien DM, Connell PM, Tomanek RJ. Dipyridamole-induced capillary growth in normal and hypertrophic hearts. Am J Physiol. 1992; 262:H980–H986. [PubMed: 1373575]

Tverdal A, Skurtveit S. Coffee intake and mortality from liver cirrhosis. Ann Epidemiol. 2003; 13:419–423. [PubMed: 12875799]

Van Daele P, Van Coevorden A, Roger PP, Boeynaems JM. Effects of adenine nucleotides on the proliferation of aortic endothelial cells. Circ Res. 1992; 70:82–90. [PubMed: 1727689]

Victor-Vega C, Desai A, Montesinos MC, Cronstein BN. Adenosine A_{2A} receptor agonists promote more rapid wound healing than recombinant human platelet-derived growth factor (becaplermin gel). Inflammation. 2002; 26:19–24. [PubMed: 11936752]

100. Wakai A, Wang JH, Winter DC, Street JT, O'Sullivan RG, Redmond HP. Adenosine inhibits neutrophil vascular endothelial growth factor release and transendothelial migration via A_{2B} receptor activation. Shock. 2001; 15:297–301. [PubMed: 11303729]

101. Wakeno M, Minamino T, Seguchi O, Okazaki H, Tsukamoto O, Okada K, Hirata A, Fujita M, Asanuma H, Kim J, Komamura K, Takashima S, Mochizuki N, Kitakaze M. Long-term stimulation of adenosine A_{2B} receptors begun after myocardial infarction prevents cardiac remodeling in rats. Circulation. 2006; 114:1923–1932. [PubMed: 17043167]

102. Wothe D, Hohimer A, Morton M, Thornburg K, Giraud G, Davis L. Increased coronary blood flow signals growth of coronary resistance vessels in near-term ovine fetuses. Am J Physiol. 2002; 282:R295–R302.

103. Zeng D, Maa T, Wang U, Feoktistov I, Biaggioni I, Belardinelli L. Expression and function of A_{2B} adenosine receptors in the U87MG tumor cells. Drug Dev Res. 2003; 58:405–411.

104. Zhong H, Belardinelli L, Maa T, Zeng D. Synergy between A_{2B} adenosine receptors and hypoxia in activating human lung fibroblasts. Am J Respir Cell Mol Biol. 2005; 32:2–8. [PubMed: 15472138]

105. Zhou AM, Li WB, Li QJ, Liu HQ, Feng RF, Zhao HG. A short cerebral ischemic preconditioning up-regulates adenosine receptors in the hippocampal CA1 region of rats. Neurosci Res. 2004; 48:397–404. [PubMed: 15041193]

106. Ziada AM, Hudlicka O, Tyler KR, Wright AJ. The effect of long-term vasodilatation on capillary growth and performance in rabbit heart and skeletal muscle. Cardiovasc Res. 1984; 18:724–732. [PubMed: 6518456]