Regulation of Foam Cells by Adenosine

Allison B. Reiss, Bruce N. Cronstein

Abstract—Macrophages rely on reverse cholesterol transport mechanisms to rid themselves of excess cholesterol. By reducing accumulation of cholesterol in the artery wall, reverse cholesterol transport slows or prevents development of atherosclerosis. In stable macrophages, efflux mechanisms balance influx mechanisms, and accumulating lipids do not overwhelm the cell. Under atherogenic conditions, inflow of cholesterol exceeds outflow, and the cell is ultimately transformed into a foam cell, the prototypical cell in the atherosclerotic plaque. Adenosine is an endogenous purine nucleoside released from metabolically active cells by facilitated diffusion and generated extracellularly from adenine nucleotides. Under stress conditions, such as hypoxia, a depressed cellular energy state leads to an acute increase in the extracellular concentration of adenosine. Extracellular adenosine interacts with 1 or more of a family of G protein–coupled receptors (A1, A2A, A2B, and A3) to modulate the function of nearly all cells and tissues. Modulation of adenosine signaling participates in regulation of reverse cholesterol transport. Of particular note for the development of atherosclerosis, activation of A2A receptors dramatically inhibits inflammation and protects against tissue injury. Potent antiatherosclerotic effects of A2A receptor stimulation include inhibition of macrophage foam cell transformation and upregulation of the reverse cholesterol transport proteins cholesterol 27-hydroxylase and ATP binding cassette transporter A1. Thus, A2A receptor agonists may correct or prevent the adverse effects of inflammatory processes on cellular cholesterol homeostasis. This review focuses on the importance of extracellular adenosine acting at specific receptors as a regulatory mechanism to control the formation of foam cells under conditions of lipid loading. (Arterioscler Thromb Vasc Biol. 2012;32:879-886.)

Key Words: ABC transporter ■ foam cells ■ macrophages ■ adenosine receptor

Adenosine, a purine nucleoside normally found at low concentrations in human tissues, is released into the extracellular space in response to metabolic stress such as that encountered during inflammatory events or during tissue hypoxia or ischemia. During ischemia, adenosine is endogenously produced in the heart as a result of ATP catabolism.1 It is well established that adenosine exerts multiple potent cardioprotective effects on the ischemic/reperfused heart, attenuating reversible and irreversible myocardial injury.2 Adenosine acts as an immunomodulator with anti-inflammatory properties and has antplatelet effects, all of which can be atheroprotective. It downregulates proinflammatory cytokine production by macrophages.3 Adenosine suppresses macrophage activation by interferon (IFN)-γ, a cytokine centrally involved in promoting atherosclerosis.4,5

In evaluating the impact of adenosine on cardiovascular function, recent studies have focused on aspects of the atherosclerotic process. Atherosclerosis involves both lipid accumulation and activation of inflammatory pathways in multiple cell types and, perhaps most importantly, in macrophages.6 This review discusses the influence of activation of specific adenosine receptors on cell types present in the vessel wall that contribute to atherosclerosis or its prevention. These cell types include endothelium and monocytes/macrophages. Special attention is given to adenosine effects on macrophage transformation into foam cells during the atherosclerotic process. The therapeutic significance of adenosine-mediated effects is highlighted.

Adenosine Receptors

Adenosine is an endogenous purine nucleoside signaling molecule that is constitutively present at low levels in the extracellular space. Adenosine concentrations dramatically increase following metabolic stress conditions at sites of tissue injury and inflammation such as those induced by hypoxia or ischemia.7-9 Adenosine is a regulatory metabolite, and the biological activities of adenosine are mediated through interaction with 4 distinct G protein–coupled cell surface receptors classified by molecular, biochemical, and pharmacological data into 4 subtypes: A1, A2A, A2B, and A3.10,11 The A1 and A3 receptors couple with inhibitory G proteins and inhibit adenylate cyclase, diminishing cellular

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cAMP levels. In contrast, A2a and A2b receptors couple to stimulatory Gs proteins and activate adenylate cyclase, leading to an increase in intracellular cAMP levels. These subtypes elicit unique and sometimes opposing effects.

Atherosclerotic Plaque and Foam Cells

The development of an atherosclerotic plaque begins with the recruitment of blood-borne inflammatory monocytes to activated vascular endothelium at sites of lipid deposition or arterial injury.12–14 Circulating monocytes adhere to the endothelial layer and then, in response to locally produced chemoattractant molecules, transmigrate across the endothelium into the intima, where they differentiate into macrophages.15 These macrophages then express scavenger receptors that bind and facilitate uptake of modified lipoproteins. Through the ingestion of these subendothelial lipoproteins, the macrophages hoard large amounts of intracellular cholesterol and thereby form foam cells. Accumulation of foam cells leads to the fatty streak—the first macroscopically recognizable lesion of atherosclerosis.16 The fatty streak progressively evolves to an advanced plaque with characteristic architecture and complex cellular composition. The plaque generally consists of a lipid-rich necrotic core bordered by a rim of lipid-laden macrophages and covered by a fibrous cap composed of smooth muscle cells and collagen.17

Cholesterol Transport Disruption and Macrophage Cholesterol Overload

Formation of foam cells by cholesterol accumulation in arterial wall macrophages is a crucial first step in atherogenesis. A number of critical proteins are involved in maintaining a balance between influx and efflux of lipids from macrophages. This balance depends on limiting cholesterol inflow through scavenger receptors, as well as maintaining outflow through reverse cholesterol transport—the transport of excess cholesterol from peripheral tissues, including cholesterol-laden macrophages in vessel walls, to the liver for excretion.18,19 A number of cellular proteins work in a coordinated fashion to accomplish reverse cholesterol transport. These include cytochrome P450 cholesterol 27-hydroxylase, ATP binding cassette transporters (ABC) A1 and ABCG1, and liver X receptors (LXRs) and LXRβ.20–22

Low-density lipoprotein (LDL) is poorly taken up by macrophages unless it has been modified, because macrophages contain only 1 native LDL receptor that is subject to feedback mechanisms. However, macrophages express a number of scavenger receptors. The scavenger receptor family proteins are defined by their ability to bind and internalize modified lipoproteins, primarily oxidized LDL, contributing to foam cell formation. Once oxidized, LDL particles lose their affinity for the LDL receptor but gain affinity for scavenger receptors and can then be taken up by intimal macrophages. The class B scavenger receptor CD36 is a glycoprotein that mediates the uptake of oxidized LDL particles by macrophages.23 The class A scavenger receptors (SR-A) are widely expressed on macrophages but can also be detected on endothelial and smooth muscle tissues. The SR-A1 and SR-AII isoforms recognize a wide variety of polyanionic ligands. They can bind modified LDL, both acetylated and oxidized, as well as polynucleic acids, phosphatidylserine, and bacterial components.24 In human atherosclerotic lesions, SR-A is expressed on the cell surface of macrophages and macrophage-derived foam cells. SR-A deficient mice crossbred onto an apolipoprotein E (apoE) knockout background exhibit a 60% reduction in atherosclerosis in the aortic root.25 In hyperlipidemic adult mice, RNA interference–mediated silencing of either SR-A or CD36 reduces atherosclerotic lesion size.26

Homeostatic atheroprotective mechanisms that orchestrate cholesterol balance in the vessel wall involve reverse cholesterol transport from arterial wall to liver. Cholesterol 27-hydroxylase enzyme activity is crucial in this pathway responsible for efflux of cholesterol from cells. This enzyme constitutes one of the first lines of defense in the prevention of atherosclerosis.22 Cholesterol 27-hydroxylase catalyzes the initial step in the oxidation of the side chain of sterol intermediates in the bile acid synthesis pathway: 27-hydroxylation of cholesterol to form 27-hydroxycholesterol.27 27-Hydroxycholesterol, the most abundant oxysterol in human circulation (0.4 μM/L in normal serum), is a component of the major circulating lipoproteins. It is transported out of cells through lipid membranes orders of magnitude faster than cholesterol.27 Cholesterol 27-hydroxylase activity in arterial endothelium and macrophages provides a pathway for elimination of intracellular cholesterol by conversion to more polar metabolites, including 27-hydroxycholesterol, that are transported to the liver for excretion.28 27-Hydroxycholesterol behaves as a statin, potently inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase while also suppressing smooth muscle cell proliferation and diminishing macrophage foam cell formation.22,29

ABCA1 plays an essential role in the prevention of foam cell formation in macrophages by mediating the active export of cellular cholesterol and phospholipids to apoA1, the major lipoprotein in high-density lipoprotein.30,31 ABCA1 thus functions as a regulator of high-density lipoprotein plasma concentration.32 Under conditions where expression levels of reverse cholesterol transport genes are low, macrophages display a reduced capacity to handle and efflux cellular cholesterol. In atherosclerosis-prone mice, either apoE-deficient or LDL receptor–deficient, selective inactivation of ABCA1 in monocytes/macrophages markedly increased atherosclerosis and foam cell accumulation.33,34

Macrophage cholesterol efflux mechanisms and expression of a number of ABC transporters lie under the transcriptional control of LXRs.35 LXRs function as sterol sensors by responding to increases in oxysterols with upregulated transcription of gene products that control cholesterol catabolism and efflux.36 Activation of LXRs by endogenous oxysterol ligands induces transcription of ABCA1 and ABCG1.37 Oxysterols bind directly to the ligand binding domain of LXRs.38 27-Hydroxycholesterol, the most abundant enzymatically generated oxysterol in human atheroma, is an endogenous LXR ligand. Thus, 27-hydroxycholesterol not only represents a cholesterol efflux pathway from macrophages but also induces ABC transporter expression and subsequent high-density lipoprotein–dependent efflux via the activation of LXR (Figure 1).
Adenosine Effects on Cholesterol Efflux Pathways

Recently, considerable progress has been made in understanding the molecular basis of lipoprotein metabolism, including the influence of adenosine. Knowledge of adenosine effects began with the observation that methotrexate, an effective treatment for patients with rheumatoid arthritis (RA) and other forms of inflammatory arthritis, increases extracellular adenosine concentrations. Autoimmune disorders such as RA accelerate the progression of atherosclerosis. Methotrexate may provide a substantial survival benefit in RA, largely by reducing cardiovascular mortality. Many of the anti-inflammatory effects of methotrexate are attributed to adenosine release. Antiatherogenic effects of methotrexate may be mediated through adenosine as well. Adenosine acts as an anti-inflammatory agent, suppressing expression of inflammatory cytokines. Anti-inflammatory effects of adenosine on leukocytes and endothelial cells are mediated through its A2A receptor. Studies have suggested that occupancy of the anti-inflammatory adenosine A2A receptor minimizes early atherosclerotic changes in arteries following injury.

Monocytes/macrophages have recently emerged as prime targets of the immunomodulatory impact of adenosine. Our laboratory has determined that A2A receptor occupancy affects expression of proteins involved in cholesterol flux in monocytes/macrophages and, consequently, provides a defense against lipid overload-induced macrophage foam cell formation. In BALB/c murine macrophages, a selective A2A receptor agonist increases 27-hydroxylase message by 47%. In murine macrophages lipid-loaded with acetylated LDL, A2A receptor occupancy modulates foam cell formation stimulated by either immune complexes (bovine serum albumin, rabbit anti-bovine serum albumin) or the cytokine IFN-γ. Macrophages are activated by IFN-γ, a proinflammatory and proatherogenic cytokine. The selective adenosine A2A receptor agonist CGS-21680 completely abrogates immune complex–induced foam cell transformation in BALB/c peritoneal macrophages. Preincubation with the A2A receptor antagonist ZM-241385 reverses this effect, allowing foam cell formation to proceed as if no agonist were present. Similar results are observed in murine peritoneal macrophages from A1 receptor knockout mice and their respective wild-type controls. In contrast, CGS-21680 fails to affect immune complex–stimulated foam cell transformation in peritoneal macrophages from A2A receptor knockout mice. This shows a direct physiological link between macrophage A2A receptor ligation and the ability of the cells to defend against cholesterol overload.

Based on the observations in murine cells, our group proceeded to establish the same effect in THP-1 human monocyteid cells. THP-1 cells display macrophage-like differentiation in response to phorbol esters and are a frequently used model system for macrophage behavior in atherosclero-
six. THP-1 cells express adenosine receptors, including the A2A receptor, and incubation of lipid-loaded THP-1 macrophages with CGS-21680 (1 μmol/L) diminishes foam cell transformation stimulated by IFN-γ by 30% and reduces immune complex–stimulated foam cell transformation by approximately 40%. In THP-1 monocytes, A2A receptor ligation with CGS-21680 increases cholesterol 27-hydroxylation and ABCA1 mRNA expression levels in concert (Figure 1). When exposed to CGS-21680 in the presence and absence of the antagonist ZM-241385, both cholesterol 27-hydroxylase and ABCA1 message levels fail to rise. Similarly, in THP-1 macrophages exposed to IFN-γ, addition of CGS-21680 increases ABCA1 protein levels. As might be expected, in THP-1-derived macrophages subjected to small interfering RNA for knockdown of ABCA1, A2A receptor activation has no effect on ABCA1 protein levels. Furthermore, CGS-21680 fails to decrease foam cell formation in IFN-γ-treated THP-1 macrophages with silencing of ABCA1. In parallel experiments with ABCG1, A2A receptor activation does not alter expression or function of this transporter. Thus, A2A–induced effects on macrophage foam cell transformation can be attributed to a mechanism that involves ABCA1.

Our group then went on to demonstrate the in vitro ability of methotrexate to prevent IFN-γ–induced transformation of lipid-laden macrophages into foam cells, an effect mediated by promotion of reverse cholesterol transport by methotrexate.

To make certain that THP-1 results accurately represent primary human monocyte behavior, peripheral blood mononuclear cells were isolated from healthy human donors and incubated for 24 hours in media with and without the addition of methotrexate (5 μmol/L). Methotrexate exposure resulted in a nearly fourfold increase in 27-hydroxylase mRNA as assessed by quantitative reverse transcription–polymerase chain reaction. This atheroprotective effect of methotrexate, mediated by adenosine acting through A2A receptor activation, may account for the beneficial effects of methotrexate therapy in the prevention of atherosclerotic cardiovascular disease in RA.

Adenosine Effects on Lectin-Like Oxidized LDL Receptor-1

Studies in animals and humans have shown that maintenance of the functional integrity of the endothelium exerts potent antiatherosclerotic and antithrombotic effects. Hypercholesterolemia causes focal activation of endothelium in large and medium-sized arteries. Atherosclerosis is initiated by dysfunction of endothelial cells at lesion-prone sites in the walls of arteries. The endothelium becomes activated and leaky, which results in extravasation of plasma molecules and lipoprotein particles, as well as monocyte infiltration into the arterial intima. The endothelial receptor for oxidized LDL, called the lectin-like oxidized LDL receptor-1 (LOX-1), is a membrane-bound receptor that is found at high concentrations in human atherosclerotic lesions. LOX-1, a member of the scavenger receptor family, is expressed in vivo in vascular endothelium, macrophages, and smooth muscle cells. It acts as a cell surface endocytosis receptor. It binds, internalizes, and degrades oxidized LDL but not native LDL or acetylated LDL. LOX-1 mRNA is expressed in atheromatous lesions. This receptor is involved in the pathobiological proatherogenic actions of oxidized LDL in the endothelium, such as induction of adhesion molecules, monocyte chemotactic protein-1, and growth factors, and activation of transcription factor nuclear factor-kB. LOX-1 gene expression in endothelial cells and macrophages is upregulated markedly by tumor necrosis factor-α. The LOX-1 receptor may play an important role in oxidized LDL uptake and subsequent foam cell formation in macrophages. Activation of LOX-1 elicits rapid generation of reactive oxygen species and decreases nitric oxide release from endothelial cells, both of which contribute to endothelial dysfunction and vascular damage. Recent studies in our laboratory have demonstrated downregulation of LOX-1 in both cultured human arterial endothelium and THP-1 macrophages upon adenosine A2A receptor ligation. The effect is completely abolished by pretreatment with an A2A receptor antagonist (unpublished results).

Hypoxia-Inducible Factor-1

Hypoxia-inducible factor-1 (HIF-1) is a principal transcriptional regulator of angiogenesis and is also involved in inflammatory reactions. HIF-1 is a heterodimeric transcription factor composed of α and β subunits. Constitutively expressed in many cell types, HIF-1α is undetectable under normoxia because rapid proteasomal degradation renders it highly labile. However, under hypoxic conditions, it is stabilized because of the inhibition of proline hydroxylation and subsequent decreases in ubiquitination and degradation. Hypoxia has been detected in human atherosclerotic lesions, and HIF-1 colocalizes with macrophages in areas of hypoxia, where it has been shown to promote intraplaque angiogenesis and foam cell development. In the human monoblastic cell line U937, transfection of HIF-1α–small interfering RNA inhibits foam cell formation in the presence of oxidized LDL. Under conditions of normal oxygen tension, adenosine induces HIF-1 and the expression of HIF-1 target genes in macrophages via activation of the adenosine A2A receptor. HIF-1 activation occurs through the protein kinase C and phosphatidylinositol 3-kinase/Akt pathways. Under hypoxic conditions, adenosine increases accumulation of HIF-1 in U937 cells, human macrophages, and lipid-loaded foam cells. This effect is not due to changes in HIF-1 transcription or stability but is likely a result of increased translation. Blockade of each specific adenosine receptor (selective for A1, A2A, A2B, and A3) individually or silencing of each receptor reduces HIF-1α protein accumulation in the presence of adenosine. Simultaneous silencing of all 4 adenosine receptors eliminates the adenosine effect, whereas high-affinity agonists for individual adenosine receptors increase HIF-1 protein. This suggests that all adenosine receptors contribute to HIF-1 enhancement by adenosine. HIF-1 modulation involves extracellular signal–regulated kinase 1/2, p38 mitogen-activated protein kinase, and protein kinase B (Akt) phosphorylation in the case of A1, A2A, and A2B receptors and extracellular signal–regulated kinase 1/2 phosphorylation in the case of A3 receptor. In this study, foam cell formation was enhanced by adenosine through activation.
of A2B and A3 subtypes. The authors posit that A3, A2B, or mixed A1/A2A antagonists may provide potential therapeutic approaches for blocking important steps in atherosclerotic plaque development.

**Adenosine Counters Atherogenic Effects of Cyclooxygenase Inhibitors**

Cyclooxygenase (COX), a key enzyme required for the synthesis of prostaglandins, plays an important role in inflammatory processes (Figure 2). COX exists in 2 distinct isoforms, COX1 (constitutive form, present in stomach, intestines, kidneys, and platelets) and COX2 (inducible form, expressed under pathological conditions, such as inflammation). Inhibitors of COX, such as traditional nonsteroidal anti-inflammatory drugs inhibit both COX1 and COX2, whereas selective COX2 inhibitors, or coxibs, have good tolerability and therapeutic activity but may contribute to or promote cardiovascular toxicity.72 The cardiovascular risk of coxibs has led to withdrawal from the market of a number of the drugs in this class. Only celecoxib is available for clinical use at this time. The precise mechanisms by which COX inhibitors amplify cardiovascular risk are unclear. A recently uncovered biological rationale for this problem is the discovery that COX inhibition promotes atherogenesis by both compromising cholesterol outflow and enhancing cholesterol uptake in macrophages.74,75 Inhibition of COX activity in human monocytes/macrophages interferes with cellular defense against cholesterol overload by diminishing expression of cholesterol 27-hydroxylase and ABCA1, proteins responsible for reverse cholesterol transport out of the cell to the circulation for ultimate excretion.76 COX inhibition also triggers overexpression of scavenger receptors CD36 and SR-A, leading to uncontrolled uptake of modified cholesterol. The result is excessive macrophage foam cell transformation.

Activation of the adenosine A2A receptor by either the disease-modifying antirheumatic drug methotrexate or an A2A-specific agonist counters the effect of COX inhibition. The specific A2A agonist CGS-21680 overcomes the reduction in both 27-hydroxylase and ABCA1 expression induced by the COX2 inhibitor NS398. Addition of CGS-21680 to NS398 (50 μmol/L)-treated THP-1 cells gives rise to a 184% increase in 27-hydroxylase and a 141% increase in ABCA1 expression.

In THP-1 cells, methotrexate (5 μmol/L, 18 hours) increases 27-hydroxylase mRNA expression and completely blocks NS398 (50 μmol/L)-induced downregulation of 27-hydroxylase enzyme expression. Methotrexate also prevents NS398 and IFN-γ (500 U/mL) from increasing transformation of lipid-loaded THP-1 macrophages into foam cells. Our results suggest that methotrexate reduces death rates due to atherosclerotic cardiovascular disease, at least in part, by favorably altering cholesterol homeostasis.52

**Other Actions Relevant to Atherosclerosis**

Although adenosine A2A receptor ligation has a suppressive effect on inflammation and foam cell formation, multiple other factors are involved in atherosclerotic lesion development, and several of these may be affected by adenosine. For example, adenosine may modify vascular tone and play a role in vasculogenesis/angiogenesis and vascular remodeling.77,78 Adenosine A2A receptor activation stimulates production of angiogenic factors, such as vascular endothelial growth factor, while also inhibiting production of thrombospordin 1, an antiangiogenic protein.79 The building of new blood vessels may be a reparative mechanism to restore blood flow and oxygen to affected tissue. The A2A receptor exerts potent coronary vasodilatory effects, and the A2A receptor may also be vasodilatory to a lesser extent.80-82 Adenosine may promote tumor survival by stimulating angiogenesis.83 Another mechanism by which adenosine encourages tumor growth is through inhibition of antitumor T cells via the A2A receptor.84

In addition to anti-inflammatory effects of the A2A receptor, the A2B receptor also influences inflammatory processes. In mice with targeted deletion of the A2B gene, expression of cytokines is elevated, and leukocyte adhesion to the vasculature is significantly increased.85

The A2A receptor subtype is of critical importance in stroke. Inactivation of this receptor or administration of antagonists has been shown to offer robust protection against brain injury in models of stroke in gerbils and rats.86,87 Adenosine can also be neuroprotective in ischemic and hypoxic brain injury, primarily by acting through A1 receptors.88

In the murine heart, A1 receptor activation improves postischemic contractile recovery.89 Studies performed in animal models indicate that adenosine receptor activation is involved in the cardioprotection conferred by postconditioning (repetitive interruptions in blood flow applied early in reperfusion).90 The protective effects are blocked by A2A and A3 selective antagonists given before postconditioning. Intravenous adenosine has been used as a postconditioning drug to protect the human heart and minimize infarct size during acute myocardial infarct reperfusion therapy.91

**Atherosclerosis in A2A Receptor–Deficient Atherosclerosis-Prone Mice**

Wang et al92 crossed the well-described apoE knockout mouse (a hypercholesterolemic mouse that develops complex atherosclerotic lesions) with an adenosine A2A receptor knockout mouse to generate the double knockout. Unexpectedly, suppression of atherosclerosis was observed in this double knockout with a reduced number of macrophages in the atherosclerotic lesions compared with the apoE-deficient single-knockout mice. This was attributed to apoptosis of macrophages and foam cells due to increased p38 mitogen-activated protein kinase activity in the A2A receptor knockout mice. This study stands in contrast to multiple findings consistent with atheroprotective effects of the A2A receptor and may represent an artifact of the extreme inability to export cholesterol from macrophages in this double-knockout mouse.

Firm conclusions cannot be drawn regarding a definitive role for adenosine in atherosclerosis at this time, even through a suppressive effect of adenosine on inflammation and foam cell formation has been observed.

**Conclusions**

The transformation of macrophages to foam cells is a critical component of atherosclerotic lesion formation.93 Reverse
cholesterol transport proteins work in a coordinated fashion to export excess lipid from macrophages, limiting foam cell formation.

The endogenous purine nucleoside adenosine is widely thought to elicit coronary vasodilation and attenuate smooth muscle cell proliferation, thereby providing cardioprotection.

Adenosine released into the extracellular space during tissue stress and injury can regulate macrophage inflammatory and atherogenic functions through ligation of 1 or more plasmalemmal adenosine receptor subtypes.

Potent antiatherosclerotic effects of A2A receptor stimulation include inhibition of macrophage foam cell transformation and upregulation of the reverse cholesterol transport proteins cholesterol 27-hydroxylase and ABCA1. Cross-talk among adenosine receptors has been documented. In nerve terminals of young adult rats, activation of adenosine A2A receptors decreases presynaptic adenosine A1 receptor binding.94 Adenosine receptor subtype interactions may also occur in the heart. Cardiac adenosine A2A receptors influence the adenosine A1 receptor antiadenergenic effect.95,96 Additional studies are needed to establish whether interaction among adenosine receptor subtypes plays a role in determining extent of foam cell formation.

Future research may reveal new pathways involved in cholesterol transport and should provide novel therapeutic agents for cardiovascular disease. Thus, adenosine and some of its analogs that bind to the A2A receptor on monocytes/macrophages may offer an alternative therapeutic approach to lower risk of atherosclerotic cardiovascular disease.

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None.

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