A2 Adenosine Receptors and Vascular Pathologies

Hillary A. Johnston-Cox, Milka Koupenova, Katya Ravid

Abstract— Cardiovascular disease, a leading cause of death and morbidity, is regulated, among various factors, by inflammation. The level of the metabolite adenosine is augmented under stress, including inflammatory, hypoxic, or injurious events. Adenosine has been shown to affect various physiological and pathological processes, largely through 1 or more of its 4 types of receptors: the A1 and A3 adenylyl cyclase inhibitory receptors and the A2A and A2B adenylyl cyclase stimulatory receptors. This article focuses on reviewing common and distinct effects of the 2 A2-type adenosine receptors on vascular disease and the mechanisms involved. Understanding the pathogenesis of vascular disease mediated by these receptors is important to the development of therapeutics and to the prevention and management of disease. (Arterioscler Thromb Vasc Biol. 2012;32:870-878.)

Key Words: macrophages ■ restenosis ■ signal transduction ■ thrombosis ■ adenosine

Coronary artery disease due to underlying atherosclerotic pathology is a leading cause of death and morbidity. Understanding the pathogenesis of vascular disease mediated by imbalanced lipid metabolism and maladaptive immune responses is a key to the development of therapeutics, prevention, and management of disease and its complications.

The pathobiology of atherosclerosis is characterized by an inflammatory-mediated response to vessel wall injury. Stages of atherosclerosis include endothelial activation and dysfunction, contributing to the loss of luminal elastin layer and exposure of proteoglycans, as proteoglycans facilitate the subendothelial. These particles are subjected to oxidative modification by reactive oxygen species or enzymes released from inflammatory cells. Ultimately, oxidized LDL signals to promote expression of adhesion molecules on the endothelial cell and secretion of chemokines, initiating immune cell infiltration of the intima. Fatty streaks consist of monocyte-derived macrophage foam cells and lymphocytes filled with lipids. Ultimately fatty streaks can progress to more advanced stages of atherosclerosis and a necrotic core develops from subsequent accumulation of apoptotic cells, debris and cholesterol crystals. A fibrous cap comprised of collagen and smooth muscle cells covers these fibroatheromatous plaques; inflamed caps contain macrophages that are thin and more prone to rupture of shoulder regions bearing maximal mechanical stress. Adventitial inflammation of advanced plaques is mediated by infiltrated T cells and mast cells that secrete proinflammatory cytokines and enzymes.1-4

Percutaneous coronary interventions are a huge component of the management of coronary artery disease. The mechanical and cellular consequences of percutaneous coronary interventions on atherosclerotic substrates generate a specific response to injury that can initiate and perpetuate restenosis.5 Unlike atherogenesis, restenosis is characterized by a rapid, although self-limiting vascular smooth muscle cell proliferation, remodeling of the vasculature, and luminal stenosis. In contrast, atherosclerosis is a chronic progression and depends on the composition and content of circulating lipids. Coronary intervention results in endothelial denudation, exposure of the subendothelium and its prothrombotic surface, thrombosis, and ensuing inflammation.6-9 The extent of vascular repair is determined by the initial degree of endothelial damage. Inflammatory response is characterized by initial change in expression of adhesion molecules, leukocyte adhesion, and recruitment following intimal injury.10,11 Exposure of the subendothelium also drives a thrombotic response mediated by platelet adhesion, activation, aggregation, and the formation of a thrombus. Aggregated, activated platelets secrete various vascular smooth muscle mitogens such as platelet-derived growth factor, which contributes to vascular smooth muscle cell migration and proliferation.12,13 Activated platelets also release thrombin, which serves as a direct activator of circulating platelets, a chemoattractant for monocytes, and stimulates vascular smooth muscle cell proliferation directly.14-16 Neointimal hyperplasia is a result of the vascular smooth muscle cell migration and proliferation and their production of excessive extracellular matrix.5,6,13,17

At sites of vascular injury, platelets are rapidly activated, which points to their potential as therapeutic targets to maintain hemostasis and in the context of the formation of an

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arterial thrombus. The rupture of an atherosclerotic plaque is followed by platelet adhesion and aggregation, which can contribute to thrombus formation and consequent coronary events, including acute coronary syndromes, stroke, and peripheral artery disease. Platelet activation also contributes to early atherogenic events. Briefly, platelet activation is induced by many platelet receptors and agonists, including the binding of ADP to P2Y1 or P2Y12 receptors, thromboxane A2 to TxA2 receptor, thrombin to PAR-1 and PAR-4 receptors, and collagen to GPVI and GPIbα21–25. Except for the glycoprotein receptor GPVI, the listed receptors are G-protein coupled receptors, and they signal through Gq to activate phospholipase C-β (PLC-β), excluding the P2Y12 receptor which couples to Gq resulting in the inhibition of cAMP levels. Phospholipase C is also activated by collagen, specifically phospholipase C-γ2. Subsequent downstream signaling26,27 lead to changes in activated platelet conformation and exposure of binding sites for fibrinogen,28–30 an important prerequisite for platelet aggregation. The binding of ligand to GPIbα results in a complex with filament and changes in the membrane cytoskeleton of platelet, important for adhesive events and the promotion of thrombus growth.31,32 Adenosine is an important metabolite that has been implicated in the regulation of vascular disease, including atherosclerosis, restenosis, and platelet activation.

### Adenosine Production and Metabolism

The metabolite adenosine is generated following an inflammatory, hypoxic, or injured event40–43 and is an important regulatory component of subsequent events, including increasing oxygen supply/demand ratio, angiogenesis, ischemic pre- and postconditioning, and anti-inflammatory actions.44,45 Adenosine is produced through the catabolism of ATP; the intracellular levels of ATP are normally in the millimolar range. Following insult to the membrane or pathology involving inflammation, hypoxia, or ischemia, there is a drastic elevation of extracellular ATP46. ATP can be released from cells through nerve stimulation,47 mechanical stress,48 and hypotonic stress49 and is rapidly degraded by membrane bound enzymes. The hydrolysis of nucleotides is achieved through the following families of enzymes: ectonucleoside triphosphate dephosphorylase, ectonucleotide pyrophosphatase/phosphodiesterase, ecto-5’-nucleotidase, and alkaline phosphatases (refer to Figure). Counteracting kinases can rephosphorylate adenosine, AMP and ADP to ATP including ecto-adenylate kinase (AK), and nucleoside diphosphate kinase (NDP) kinase. ATP is directly hydrolyzed to AMP by E-NPPs. Adenosine can be rescued by adenosine kinase to form AMP; AMP can be converted to ADP mediated by AK, and ADP conversion to ATP through ecto-NDP kinase.

### Adenosine Receptors: Classification and Distribution

Adenosine mediates its effects through the binding of 4 different G-protein coupled ARs, classified by their downstream activation or inhibition of adenyl cyclase.50 These receptor subtypes differ in their binding affinity for adenosine, coupling to different G-proteins and distinct downstream signaling, pharmacological profile, and sequence. The A1 AR can couple to inhibitory G-proteins, G or G, leading to a consequent reduction of 3’,5’-cAMP (cAMP) production or increased intracellular calcium levels determined by the effector pathway activated. A3AR can also couple to either inhibitor G-proteins G or G, with similar downstream ef-
The A2 subtype ARs, A2A and A2B, can both couple to Gαs, which results in downstream activation of adenylyl cyclase and elevation of cAMP levels. A2BAR can additionally couple to Gι0, with resulting alterations in intracellular calcium levels. The A2A, A1, and A3 ARs are classified by their high affinity for the adenosine ligand, where as the A2BAR is a low affinity receptor.62 A2BAR, A1AR, and CD39 are thought to associate with caveolae. This implicates close localization of adenosine-generating enzymes to ARs on the surface of the cell, mediating rapid binding of newly generated adenosine to its receptors.63–65

The tissue and cell distribution varies between the 4 subtypes of ARs. The A1AR is expressed significantly in the brain, heart, adipose tissue, stomach, vas deferens testis, spleen, kidney, aorta, eye, liver, and bladder.66 The A3AR is highly expressed in the lung and liver, with lower expression in the testis, kidney, placenta, brain, heart, spleen, bladder, uterus, jejunum, proximal colon, aorta, and eyes.67 The A2-type receptors also differ in their tissue distribution. A2AAR is highly expressed in the striatum, nucleus accumbens, and olfactory tubercle;66 it has also been demonstrated to be expressed in platelets,68,69 immune cells,70,71 lung,66 heart,72 and the vasculature.66,73 The A2BAR is predominantly expressed in the vasculature, retina, and brain, with lower levels of expression in various cells and tissues, including platelets at baseline.66,74 Numerous studies have demonstrated an upregulation of this receptor subtype with stress, including inflammation,75 hypoxia,76 and high fat diet.76 This review will focus on the A2-subtype ARs and their implication in vascular disease.

Effects on Inflammation

A2BAR

Early studies demonstrated the role of the A2BAR in the regulation of monocyte and macrophage function in the context of inflammatory cytokines. IFN-γ has been shown to upregulate macrophage A2BAR expression, which is postulated to be linked to macrophage deactivation.77 The activation of the A2BAR inhibits the production and release of proinflammatory cytokines, such as TNF-α and IL-1β from monocytes and macrophages,78–80 as well as stimulates the production of anti-inflammatory cytokines, such IL-10, from macrophages.81 Both effects thought to be modulated by downstream signaling of A2BAR’s activation of adenylyl cyclase and consequent increase in cAMP. A2BAR activation also inhibits macrophage proliferation postinflammatory stimulus.77,79,80 A2BAR stimulation upregulates alternative macrophage activation, which can have a regulatory role in vascular disease.82 These observations have been further confirmed by in vivo and in vitro studies in the A2BAR knockout (KO) mouse, at baseline and under vascular stress.

The generation and characterization of the A2BAR KO mouse provided in vivo evidence for a role of this receptor subtype in mediating anti-inflammatory events. The A2BAR KO mouse at baseline is modestly inflamed with elevated plasma TNF-α and IL-6; challenge with endotoxin, lipopolysaccharide, results in a consequent exaggerated production of TNF-α and IL-6. At baseline there is also an increased expression of vascular adhesion molecules thought to be mediated by the elevated levels of TNF-α and downregulation of ICAM-1.74 Transplantation experiments confirmed the role of A2BAR expression in bone marrow cells in the observed phenotype.74 Interestingly, another study described a role for A2BARs in controlling TNF-α level in macrophages, independent of receptor activation,83 suggesting other regulatory mechanisms, including potential control by yet to be identified binding proteins. Similarly, elevated TNF-α in A2BAR KO mice at baseline74 (with no receptor activation) could be co-led by such a regulatory pathway. Consistent results were demonstrated in another A2BAR KO mouse model where enhanced mast cell activation and increased sensitivity to IgE-mediated prophylaxis was found in the absence of this receptor, suggestive that the A2BAR is a necessary component of mast cell antigen induced proinflammatory cytokine production.84 Interestingly, however, there have been contradicting reports on the role of the A2BAR in controlling inflammation under conditions of acute bacterial pathogenesis, or following polymicrobial sepsis. In the former case, A2BAR deletion was protective,85 whereas in the latter case, A2BAR ablation led to excessive inflammation and increased mortality.86 Of note, different A2BAR KO mice were used in these studies.85,86 In another study, dextran sodium sulfate, 2,4,6-trinitrobenzene sulfonic acid, and Salmonella typhimurium were used to induce colitis in control and A2BAR KO mice. Colonic inflammation induced by these agents was attenuated in the KO mice compared with their wild-type counterparts.87 Thus, these studies highlight the importance of evaluating the duration, type of insult, and tissue involved in determining the final outcome of A2BAR activation or deletion under pathology. Indeed, in a recent report, emphasis was placed on the distinct roles the A2BAR plays in acute and chronic inflammation, using as model the different stages of bleomycin-induced lung injury.88

A2AAR

In vitro studies, involving activation of macrophage A2AAR indicated a role for this receptor in regulating the production of inflammatory cytokines.89–92 Via studies with A2AAR KO mice, it was concluded that the A2AAR is protective against inflammation induced by lipopolysaccharide, ie, the level of inflammatory cytokines was elevated in the KO mice.93 Bone marrow transplantation experiments did not demonstrate that expression of A2AAR in bone marrow cells mediated the observed phenotype. On the other hand, CD73 KO cells treated with A2AAR agonist ATL-460e led to a reversal of the upregulated VCAM-1 mRNA and protein expression and inhibited the arrest of monocytes. Continuous infusion of ATL-1460e in CD73 KO mice prevented neointima formation.94 Thus, this study presented evidence for the role of CD73 in endothelial cell activation and monocyte recruitment through generation of adenosine and subsequent activation of the A2AAR, providing further support for therapeutic use of this receptor subtype to modulate vascular inflammation.

Effects on Vascular Smooth Muscle Cell Proliferation and Restenosis

CD73/ecto-5′-nucleotidase, a significant generator of adenosine, is an important modulator of vasoprotection.95,96 CD73
KO mice have enhanced VCAM-1 in carotid arteries; in vitro and in vivo perfused carotid arteries lacking CD73 demonstrated increased monocyte arrest mediated by α5β1. Wild type mice postwire induced carotid injury had upregulation of CD73 expression; whereas CD73 KO mice postcarotid injury had increased neointimal plaque formation and macrophage content, elevated NF-KB activation, luminal expression of VCAM-1, and levels of soluble VCAM-1. This clearly suggested that CD73-dependent release of adenosine mediates such effects on neointimal hyperplasia. Here, the role of A2-type receptors is reviewed in this context.

The A2BAR
Vascular smooth muscle cell proliferation is an important component of vascular remodeling. Early studies identified adenosine as a candidate for a regulator of smooth muscle cell proliferation with suggested signaling through A2BAR. This was further confirmed by pharmacological approaches to demonstrate that activation of the A2BAR led to inhibition of vascular smooth muscle cell proliferation. Later in vitro studies demonstrated that A2BAR inhibits smooth muscle cell proliferation mediated by B-Myb regulation of the A2BAR. Arterial smooth muscle cell apoptosis is found in similar vascular diseases including arterial restenosis and atherosclerosis. Adenosine has been shown to dose-dependently trigger apoptosis of arterial smooth muscle cells through cAMP signaling which is inhibited by A2BAR antagonism; in advanced atherosclerosis the high rate of vascular smooth muscle cell apoptosis could potentially contribute to plaque instability and consequent rupture.

These studies support the therapeutic potential of this receptor in the prevention of vascular remodeling associated with various diseases, such as restenosis postangioplasty, atherosclerosis, and hypertension.

As to vascular restenosis, femoral artery injury in A2BAR KO mice was used to determine the role of the A2BAR in bone-marrow–derived macrophages and vascular smooth muscle cells in the context of vascular lesion formation. Consistent with earlier studies demonstrating a protective role of the A2BAR in modulating inflammation, bone-marrow–A2BAR was important for prevention of vascular lesion formation following injury. The authors demonstrated an upregulation of A2BAR in WT mice postwire-induced injury and that the level of TNF-α was regulated by A2BAR activity. In the absence of the A2BAR there were higher levels of TNF-α with correlated upregulation of CXCR4, a chemoattractant for progenitors during tissue regeneration, and greater proliferation of vascular smooth muscle cells. This increase of TNF-α and CXCR4 was dependent on A2BAR expression in bone marrow cells.

A2AAR
Early studies demonstrated a role for the A2AAR in the inflammatory response and endothelial activation following a vascular insult. Through the use of a carotid ligation model and the A2AAR selective agonist ATL-146e, it was demonstrated that A2AAR activation reduced early inflammatory processes that are pertinent to neointimal growth following vascular injury. The role of A2AAR signaling in leukocytes and their contribution to arterial neointimal formation was further investigated using a guide wire injury murine model. A2AAR, ApoE double knockout mice postarterial injury had larger neointima formation, consistent with the increased arterial neointima formation in chimeric mice that received A2AAR deficient bone-marrow–derived cells. These double knockout mice also demonstrated enhanced neutrophil rolling and adherence to injured arterial wall, correlated to the noted elevation in phosphorylation of MAPK, P-selectin glycoprotein ligand-1 clustering, and β-2 integrin affinity. Thus, the study demonstrated that in the absence of the A2AAR, there is an enhancement of leukocyte homing ability and of arterial neointima formation following injury. The pathological neointimal hyperplasia and the correlation of number of leukocytes in the neointima to the severity of restenosis are supportive of the therapeutic application of A2AAR antagonists on arterial restenosis following arterial angioplasty.

Influences on Atherosclerosis
A2BAR
Foam cell formation, a process that is mediated by LDL oxidation by macrophages, is a significant factor that contributes to the development of atherosclerosis. Hypoxia and hypoxia inducible factor 1 have significant roles in atherogenesis and promotion of intraplaque angiogenesis and foam cell formation, respectively. Adenosine under conditions of hypoxia stimulates the accumulation of hypoxia inducible factor-1α mediated by signaling through all AR subtypes. Gessi et al demonstrated through specific pharmacological ligands that adenosine-mediated stimulation of foam cell formation was inhibited by antagonism of A3AR and A2BAR, suggestive of a potential role for these receptors in the prevention of adenosine-mediated atherosclerotic plaque pathogenesis. Of note, however, A3AR KO mice on an apolipoprotein E (ApoE) null background, fed high-fat diet develop atherosclerosis to a similar degree as matching controls. A recent study by Koupenova et al demonstrated a significant role for the A2BAR in modulating atherosclerosis. Using a mouse model of atherosclerosis (ApoE deficient background) and a high-fat, high-cholesterol diet (HFD), the authors demonstrated that in the absence of the A2BAR there was a worse atherosclerotic profile. This aggravated phenotype in the A2BAR KO mice was not dependent on bone-marrow–derived signals. Interestingly, with high-fat, high-cholesterol diet, hepatic expression of A2BAR was significantly upregulated, along with plasma and hepatic levels of triglycerides and cholesterol and confirmed by pathology consistent with hepatic steatosis. Mechanistically, this was shown to be mediated by low levels of cAMP and consequent elevated expression of sterol regulatory element binding protein-1 and downstream targets that are regulators of lipogenesis. This was further confirmed by in vitro pharmacological treatments of primary hepatocytes with specific ligands for the A2BAR. Changes in cAMP mediated by A2BAR activation were found to regulate the transcriptionally active form of sterol regulatory element binding protein-1. The phenotype was ameliorated by adenoviral
restoration of the hepatic A2BAR in the knockout mice as well as through pharmacological activation of the A2BAR by BAY 60-6583. This in vivo data suggests the therapeutic potential of this receptor to modulate the pathogenesis of atherosclerosis.

**A2AAR**

The A2AAR has been demonstrated to have pro- as well as antiatherosclerotic properties. Studies based on a murine knockout model of the A2AAR on an ApoE null background concluded that the A2AAR is proatherosclerotic. These double KO mice displayed elevated cholesterol, proinflammatory cytokines, and increased inflammation status of atherosclerotic lesions; yet the lesions were smaller relative to control mice. Bone marrow transplantation experiments yielded similar results. Chimeric ApoE deficient mice transplanted with A2AAR-deficient bone marrow cells also had smaller atherosclerotic lesions. Macrophages from A2AAR-deficient mice and foam cells formed in vivo exhibited increased apoptosis, demonstrated to be a result of elevated p38 MAPK activity. This study suggested that perhaps inactivation of the A2AAR could be useful for the treatment of atherosclerosis.

Additional studies have focused on the role of the A2AAR in other aspects of the pathogenesis of atherosclerosis. Foam cell formation, a hallmark of atherosclerosis, is mediated by alterations in the transport of cholesterol out of macrophages; 2 important proteins that control cholesterol content are cholesterol 27-hydroxylation and adenosine 5'-triphosphate-binding cassette transporter A1. Cholesterol 27-hydroxylation has been shown to be downregulated by immune complexes and proinflammatory cytokines, leading to inhibition of macrophages efflux of cholesterol and consequent foam cell formation. Application of an A2AAR agonist CGS-21680 inhibited this foam cell formation in THP-1 human macrophages and in cultured peritoneal macrophages. Activation of the A2AAR led to an unregulation of cholesterol 27-hydroxylation and 5'-triphosphate-binding cassette transporter A1, indicating, in this case, antiatherosclerotic effects of A2AAR.

**Effects on Thrombosis**

**A2BAR**

As mentioned above, platelet activation and aggregation is an important component of both early atherosclerotic plaque formation as well as atherosclerotic plaque rupture and consequent coronary events. Early studies identified the A2AAR to be expressed on murine platelets as well as human platelets and to be the receptor through which adenosine mediated its inhibitory effects on platelet aggregation. This is achieved through inhibition of both the mobilization of internal stores of calcium and the influx of external calcium, both connected to activation of adenylyl cyclase. A2AAR-deficient mice demonstrate increased platelet aggregation; nonselective AR agonist, 5'-N-ethylcarboxamidoadenosine, inhibited platelet aggregation in wild type mice but had no effect in A2AAR null mice, indicating that A2AAR is a key mediator of the antiaggregatory effects of adenosine on platelets. Consistent with this observation, other groups have demonstrated in human platelets that the A2AAR mediates a 5'-N-ethyl-carboxamidoadenosine–stimulated elevation in cAMP levels, a key component of platelet activation. The use of a specific A2AAR agonist, 4'-[2-[[6-amino–9(N-ethyl-carboxamido)purin-2-yl]amino]ethyl]benzenepropanoic acid hydrochloride (CGS 21680), demonstrated a species-dependent platelet responsiveness to A2AAR agonism. Reactivity as well as aggregation of canine platelets was not inhibited by A2AAR agonism; whereas in a human recurrent thrombosis model, agonism of the A2AAR significantly inhibited platelet activation. In addition, in vitro, collagen-induced platelet aggregation was inhibited posttreatment with the A2AAR agonist CGS 21680, as well as an inhibition of the increase of platelet surface expression of P-selectin and inhibition of platelet-monocyte aggregation poststimulation with ADP and thromboxane agonist (U46619). This data supports the application of A2AAR agonists for clinical use when inhibition of platelet function is necessary.

**Other Cardiovascular Effects**

**A2BAR**

Uptregulation of A2BAR expression and functional activity is seen during hypoxic and ischemic conditions, ie, hypoxic human umbilical vein endothelial cells have increased A2BAR mRNA expression. Similar upregulation is found in human microvascular endothelial cells and T84 intestinal epithelial cells posthypoxia. The A2BAR gene promoter contains a functional hypoxia inducible factor 1-alpha binding site, a key transcriptional regulator necessary for adaptive response posthypoxia; disruption of this regulatory site results in the lack of A2BAR upregulation posthypoxic conditions. The A2BAR KO mice posthypoxia demonstrate increased vascular leakage as well as increased neutrophil influx into tissues. Bone marrow transplantation experiments showed this to be partially mediated by A2BAR expression in bone marrow cells. Pharmacological targeting of either A2AAR or A2BAR at reperfusion postischemic event provides cardioprotection evidenced by a reduced infarct size. These studies suggest the importance of A2AR in mediating an adaptive response postischemic insult. Aden-
Osine is also a stimulator of angiogenesis. Activation of A2BAR on endothelial cells or mast cells induces the release of angiogenic factors, such as vascular endothelial growth factor. Thus, the proangiogenic result of A2BAR activation suggests its clinical potential for regenerative processes, given the important role of angiogenesis in tissue repair.

A2AAR

Cardioprotection during a myocardial infarction or during reperfusion of the heart is achieved if treatments are applied prior to the onset of ischemia. Activation of the A2AAR at reperfusion reduced the infarct size in canine and rabbits, similar studies have demonstrated a therapeutic effect achieved by selectively activating the A2BAR, indicating that activation of the A2-subtype ARs mediates a protective postconditioning of the reperfused heart. A2AAR agonism has been postulated to provide protection through the ability of this receptor to increase coronary blood flow postcardiac ischemia, thought to be mediated by activation of K<sub>e</sub> and K<sub>ATP</sub> channels. A recent study demonstrated that for optimal adenosine-mediated cardioprotection there needs to be activation of multiple AR subtypes; through the use of pharmacological ligands and KO murine models, the authors demonstrated that for A1AR-mediated cardioprotection, A2AAR and A2BAR are required. Adenosine has an inhibitory effect on the release of thrombospondin 1, an antiangiogenic protein, with a consequent increase in vascular tube formation, suggested to be mediated by A2AAR agonism. Angiogenesis is an important component of tissue repair, thus activation of the A2AAR is of interest for regenerative-related clinical scenarios.

Conclusion

A2-subtype ARs mediate various biological processes that are pertinent to the pathogenesis of vascular disease; it is evident that they are key components of maintaining the balance of inflammatory responses following a stress or injury, as well as significant mediators of lipid metabolism and transport in different tissues and cell types. However, although both the A2BAR and A2AAR signal via cAMP, they also clearly differ in some physiological effects, such as the atherosclerotic response to high fat diet. This could be attributed to additional distinct signaling mediated by one of the receptors (e.g., Gq activation by the A2BAR), and/or owing to other regulatory proteins binding and affecting one or both receptors. Further studies that elucidate mechanism will be a key in the design of novel therapeutic applications geared toward cell and tissue specificity.

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Disclosures

None.

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