Infarct-Sparing Effect of A2A-Adenosine Receptor Activation Is Due Primarily to Its Action on Lymphocytes

Zequan Yang, MD, PhD; Yuan-Ji Day, MD, PhD; Marie-Claire Toufektsian, PhD; Susan I. Ramos, BS; Melissa Marshall, BS; Xin-Qun Wang, MS; Brent A. French, PhD; Joel Linden, PhD

Background—A2A-adenosine receptor (A2AAR) activation on reperfusion after ischemia reduces the size of myocardial infarction, but the mechanism of action has not been fully defined.

Methods and Results—We created chimeric mice by bone marrow transplantation from A2AAR-knockout or green fluorescent donor mice to irradiated congenic C57BL/6 (B6) recipients. In the GFP chimeras, we were unable to detect green fluorescent–producing cells in the vascular endothelium, indicating that bone marrow–derived cells were not recruited to endothelium at appreciable levels after bone marrow transplantation and/or acute myocardial infarction. Injection of 5 or 10 µg/kg of a potent and selective agonist of A2AAR, ATL146e, had no effect on hemodynamic parameters but reduced infarct size in B6 mice after 45 minutes of left anterior descending artery occlusion followed by 24 hours of reperfusion to 42.5±3.0% and 39.3±4.7% of risk region, respectively, compared with 61.0±2.3% in vehicle-treated B6 mice (P<0.05). Myocardial myeloperoxidase activity in the risk region measured at 4 hours after reperfusion was significantly reduced by ATL146e. The salutary effects of ATL146e were absent in A2AAR-knockout mice or in mice treated with a selective A2AAR antagonist, ZM241385. ATL146e also reduced infarct size and myeloperoxidase in B6/B6 (donor/recipient) chimeras (P<0.05) but not in A2AAR-knockout/B6 chimeras. In immunocompromised Rag-1–KO mice, infarct size was significantly reduced compared with B6 mice but was not further reduced by ATL146e.

Conclusions—The results indicate that A2AAR activation on bone marrow–derived cells, specifically T or B lymphocytes, is responsible for the infarct-sparing and antiinflammatory effects of ATL146e administered at the time of reperfusion after coronary occlusion. (Circulation. 2005;111:2190-2197.)

Key Words: adenosine ■ chimera ■ lymphocytes ■ myocardial infarction ■ receptors

Multiple lines of evidence have suggested that the A2A adenosine receptor (A2AAR) is critical for adenosine-mediated protection against ischemia-reperfusion injury. A2AAR-mediated inhibition of tissue ischemia-reperfusion injury has been documented in various organs, including liver, lung, kidney, and heart1–5; however, the precise mechanisms responsible for A2AAR-mediated tissue protection remain unknown. A2AAR is widely distributed and mediates a variety of physiological responses in mammalian organisms. A2AARs couple to Gs proteins and activate adenyl cyclase, leading to an increase in cellular cAMP levels.6,7 The mechanisms of protection mediated by A2AAR activation may include inhibition of leukocyte-mediated inflammatory response,7,8 vasodilation,9,10 and direct effects on organ parenchymal cells.3,6,11

The salutary effect of A2AAR activation against myocardial ischemia-reperfusion injury has been reported in intact animal models2–4 and in several ex vivo experiments.11–13 However, other ex vivo studies showed that activation of A2AARs exerts no protective effects to the myocardium during postischemic reperfusion.14,15 The conflicting findings in these experiments may be attributed to an important role for blood-borne leukocytes that are absent in exsanguinous hearts and/or variations in A2AAR distribution or function in different animal species. Although in vivo experiments have shown the cardioprotective effect of A2AAR activation during reperfusion, these experiments have not identified the major cellular target (myocytes, endothelium, or blood-borne cells) responsible for the salutary effect of A2AAR activation.

In the present study, we used a potent and selective A2AAR agonist, ATL146e,14 at a dose without significant hemodynamic effects in an intact mouse model of myocardial ischemia-reperfusion injury. By using Rag-1– and A2AAR-knockout (KO) mice in combination with bone marrow transplantation (BMT) to create chimeric mice, we demonstrate a predominant role of A2AAR activation on bone marrow–derived cells, specifically T or B lymphocytes, in protecting the heart against ischemia-reperfusion injury.
TABLE 1. Animal Groups and Protocols

<table>
<thead>
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<th>Protocol, min/h</th>
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<td>1+2</td>
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<tr>
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<td>MPO</td>
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<tr>
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<td>MPO</td>
<td>6</td>
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<tr>
<td>ATL+ZM I/R, 45/4</td>
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<td>A2AAR KO</td>
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<td>11</td>
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<td>1+1</td>
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<tr>
<td>Chimera (BMT)</td>
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<td>5</td>
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<tr>
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</tr>
<tr>
<td>Total</td>
<td></td>
<td>140</td>
<td>5+7</td>
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I/R indicates ischemia/reperfusion; IF, infarct size. ATL146e was administered at a dose of 10 µg/kg, except in the group with 5 µg/kg.

Methods

This study, which conformed to the Guide for the Care and Use of Laboratory Animals published by the National Institute of Health (NIH publication No. 85-23, revised 1985), was conducted under protocols approved by the Institutional Animal Care and Use Committee.

Animals

One hundred forty 8- to 14-week-old male C57BL/6 (B6) mice, A2AAR-KO mice, and Rag-1–KO mice were assigned to 17 different groups (see Table 1). Another 4 B6 mice were used for hemodynamic studies. An additional group of green fluorescent (GFP) transgenic mice was used to create chimeras of GFP/B6. B6 mice were purchased from Hilltop Laboratory Animals (Scottsdale, Pa); Rag-1–KO (B6.129S7-Rag1tm1Mom) and GFP mice were obtained from Jackson Laboratory (Bar Harbor, Maine). A2AAR-KO mice, congenic to B6 mice, were derived from breeders supplied by Dr Jiang-Fan Chen (Harvard University, Boston, Mass).

Chimeras were produced using standard techniques as described previously. Briefly, donor mice (age, 8 to 10 weeks; weight, 24 to 26 g) were anesthetized with Nembutal (0.02 mg/g) and euthanized by cervical dislocation. The bone marrow from the tibia and femur was harvested under sterile conditions, yielding ~50 million nucleated bone marrow cells per mouse. Recipient mice (age, 7 to 8 weeks; weight, 22 to 25 g) were irradiated with 2 doses of 6.00 Gy each 4 hours apart. Immediately after irradiation, 2 x 10⁶ to 4 x 10⁶ bone marrow cells were infused intravenously via the external jugular vein under general anesthesia plus local injection of bupivacaine. During each irradiation, 2 control mice did not receive BMT.

Irradiated/transplanted mice were housed in microisolators for ≥8 weeks before experimentation.

A2AAR Agonist and Antagonist

ATL146e (Adenosine Therapeutics, LLC) was injected intraperitoneally at a dose of either 5 or 10 µg/kg 2 minutes before reperfusion. ZM241385, a selective A2AAR antagonist, was administered intraperitoneally immediately before ATL146e at a dose of 6.9 µg/kg (equimolar with ATL146e). ZM241385 was a gift from AstraZeneca Pharmaceuticals, Cheshire, UK.

Hemodynamic Study

The effect of ATL146e at a dose of 10 µg/kg on hemodynamics was studied in 4 B6 mice. Mice were anesthetized with 1% (vol) isoflurane. The right common carotid artery was exposed and cannulated with a 1.4F Millar microtip catheter (Millar Instruments, Inc). After peripheral arterial blood pressures were acquired, the catheter tip was advanced into the left ventricular (LV) chamber. After bolus injection of ATL146e through an intraperitoneal line, LV pressures (end-systolic and end-diastolic pressures) and developed pressures (dP/dt+ and dP/dt−) were recorded for 20 minutes.

Myocardial Ischemia-Reperfusion

Mice were subjected to 45 minutes of coronary occlusion, followed by either 4 or 24 hours of reperfusion, and then euthanized. Hearts were removed to determine myocardial myeloperoxidase (MPO) activity or to evaluate infarct size (Table 1). A standard protocol was used, as detailed previously. Briefly, mice were anesthetized with sodium pentobarbital (100 mg/kg IP) and orally intubated. Artificial respiration was maintained with a FiO2 of 0.80, 100 strokes per minute, and a 2- to 3-mL stroke volume. The heart was exposed through a left thoracotomy, and coronary artery occlusion was achieved by passing a suture beneath the left anterior descending coronary artery (LAD) and tightening over a piece of PE-60 tubing for 45 minutes. Reperfusion was induced by removal of the PE-60 tubing.

Myocardial Infarct Size Measurement

The mice were euthanized 24 hours after reperfusion, and the hearts were cannulated through the ascending aorta for sequential perfusion with 3 to 4 mL of 1.0% TTC and 10% Phthalo blue. The LAD was reocluded with the same suture used for coronary occlusion before Phthalo blue perfusion to determine risk region (RR). The LV was cut into 5 to 7 transverse slices that were weighed and digitally photographed to determine infarct size as a percent of RR as described previously.

Tissue MPO Activity Measurement

Parallel groups of B6 and BMT chimeras were studied to determine neutrophil infiltration into the heart at 4 hours after reperfusion. After the heart was harvested, the right ventricle and atria were removed. The LV was separated into 3 pieces: ischemic (there was a clear-cut border between previously ischemic and nonischemic regions), adjacent (1- to 1.5-mm thickness of peri-ischemic region), and remote regions. Each part was homogenized in a solution containing 0.5% hexadecyltrimethylammonium bromide dissolved in 10 mmol/L potassium phosphate buffer (pH 7) and centrifuged for 30 minutes at 20,000g at 4°C. An aliquot of the supernatant was allowed to react with a solution of tetramethylbenzidine (1.6 mmol/L) and 0.1 mmol/L H2O2. The rate of the change in absorbance was measured with a spectrophotometer at 650 nm.

Immunohistochemistry of GFP-Producing Cells, Neutrophils, and CD3+ T Cell

The hearts were harvested, cut into 3 short-axis slices, and immediately fixed in 4% paraformaldehyde in PBS (pH 7.4) for paraffin embedding. Paraffin-embedded sections (5 µm) were rehydrated and incubated with 1% hydrogen peroxide. After being rinsed in PBS, the sections were incubated with 10% blocking serum. Immunostaining
TABLE 2. Hemodynamics Before and After A2AAR Activation

<table>
<thead>
<tr>
<th>Time After ATL146e Injection (10 μg/kg IP, min)</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
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<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>438±18</td>
<td>450±12</td>
<td>438±19</td>
<td>463±8</td>
<td>469±7</td>
<td>463±8</td>
<td>455±22</td>
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<tr>
<td>ABP, mm Hg</td>
<td>84±1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>86±2</td>
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<tr>
<td>Systolic</td>
<td>60±4</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>54±6</td>
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<td>92±3</td>
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<td>92±1</td>
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<tr>
<td>LVBP, mm Hg</td>
<td>7593±206</td>
<td>7782±209</td>
<td>7436±209</td>
<td>7687±403</td>
<td>7724±648</td>
<td>7958±599</td>
<td>8152±695</td>
</tr>
<tr>
<td>dP/dt+, mm Hg/s</td>
<td>8127±430</td>
<td>7429±582</td>
<td>7378±451</td>
<td>7316±588</td>
<td>6675±452</td>
<td>6556±404</td>
<td>6962±237</td>
</tr>
</tbody>
</table>

ABP indicates arterial blood pressure; LVBP, LV blood pressure; ESP, end-systolic pressure; and EDP, end-diastolic pressure. n=4.

Results

Exclusion and Mortality

Of the 140 mice that underwent myocardial ischemia-reperfusion injury, 5 died during early reperfusion (2 ATL-treated B6 mice, 1 ATL-treated A2AAR-KO mouse, 2 Rag-1–KO mice). Seven mice were excluded because of either inordinately small RRs (<25% of LV mass) or technical failures during the TTC-blue staining procedure (Table 1).

Effect of A2AAR Activation on Hemodynamics

Table 2 shows LV hemodynamic parameters before and after administration of ATL146e. There were no significant alterations in heart rate, arterial pressure, or LV pressure within 20 minutes after the administration of ATL146e at a dose of 10 μg/kg.

Role of A2AAR Activation in Wild-Type and KO Mice

Myocardial infarct size was evaluated in 4 groups of B6 mice and 2 groups of A2AAR-KO mice at 24 hours after reperfusion. There were no statistical differences in RR. Both low- (5 μg/kg) and high- (10 μg/kg) dose ATL146e treatment significantly reduced infarct size (percent of RR) in B6 mice (42.5±3.0% and 39.3±4.7% versus 61.0±2.3% for vehicle-treated B6 controls; P<0.05). However, the salutary effect of ATL was completely blocked by cotreatment with ZM241385 (Figures 1 and 2). Neutrophil infiltration into the ischemic zone was significantly reduced in ATL146e-treated mice but not in ZM-pretreated mice (Figure 3). In parallel groups of mice, myocardial MPO activity measured 4 hours after reperfusion was significantly increased in the RR than in the remote region in vehicle-treated or ZM-pretreated B6 mice. MPO activity in the RR was significantly reduced in A2AAR-KO mice but not in ZM-pretreated mice (Figure 3A). In A2AAR-KO mice, no difference in infarct size was found between A2AAR-KO and B6 mice (59.7±2.7% versus 61.0±2.3%; P<0.05). Infarct size was not significantly changed by ATL146e in A2AAR-KO mice compared with B6 or A2AAR-KO control mice (Figures 1 and 2). Immunohistochemistry showed that in A2AAR-KO mice, ATL146e lost its ability to inhibit neutrophil infiltration (Figure 3).
Absence of Bone Marrow–Derived Cells in the Endothelium After Transplantation

In GFP/B6 (donor/recipient) chimeras, GFP-producing cells derived from donor marrow were not found in the vascular endothelium, indicating that hematopoietic cells were not recruited to endothelial tissue at appreciable levels after BMT and/or acutely after myocardial infarction (MI) (Figure 5).

Role of A2AAR Activation in Chimeras

B6/B6 chimeras were prepared to control for possible effects of BMT on the response of the heart to ischemia-reperfusion injury. These chimeras were found to respond much like wild-type animals. ATL146e dramatically reduced infarct size in B6/B6 chimeras from 58.4 ± 1.9% to 33.5 ± 2.2% (P < 0.05) 24 hours after reperfusion. In A2AAR-KO/B6 chimeras, the infarct-sparing effect of ATL146e disappeared, and infarct size (50.9 ± 4.1%) was similar to that observed in vehicle-treated B6/B6 chimeras (Figure 6). ATL146e significantly reduced the infiltration of neutrophils in B6/B6 chimeras but not in A2AAR-KO/B6 chimeras (Figure 3). In parallel groups of mice, RR myocardial MPO activity measured 4 hours after reperfusion was significantly reduced by ATL146e in B6/B6 but not in A2AAR-KO/B6 chimeras (Figure 4B).

Role of Lymphocytes in Mediating Myocardial Ischemia-Reperfusion Injury

Rag-1–KO mice (B6.129S7-RAG-1 tm1Mom) are completely deficient in mature T and B lymphocytes and are congenic to B6 wild-type mice. There were no statistical differences in RR (percent of LV) between mice in any of the 4 groups...
Infarct size in B6 control mice was 61.0 ± 2.3% of RR. In Rag-1–KO mice, infarct size was significantly reduced to 40.5 ± 3.3% (P < 0.05 versus B6 control), which was no different from that of ATL-treated B6 mice (39.3 ± 4.7%; P = NS). Treatment with ATL146e exerted no further reduction in infarct size in Rag-1–KO mice (Figure 7, bottom). Significant CD3+ T-lymphocyte and neutrophil infiltration after 45 minutes of LAD occlusion and 24 hours of reperfusion was detected in the hearts of B6 mice (Figures 6 and 7, top) and was reduced by ATL146e treatment. CD3+ T lymphocytes were not found in the hearts of Rag-1–KO mice, but neutrophil infiltration was similarly reduced in both treated and untreated Rag-1–KO mice (Figure 7, top).

Discussion
By using a highly selective A2AAR agonist (ATL146e), a selective antagonist (ZM241385), and chimeric mice, we have identified bone marrow–derived cells as the cells primarily responsible for myocardial protection by A2AAR receptor activation during reperfusion after ischemia. In wild-type mice, ATL146e was found to significantly reduce myocardial infarct size, and the salutary effect was totally blocked by ZM241385, indicating that stimulation of the A2AARs mediates the effect of ATL146e in reducing post-ischemic myocardial injury. The specificity of A2AAR activation was further confirmed in A2AAR-KO mice, in which the cardioprotective effect of ATL146e disappeared. In A2AAR-KO/B6 chimera mice, which lack the A2AAR only in bone marrow–derived cells, the protective effect of ATL146e was also abolished. The dose of AT146e used in this study had no effect on heart rate, peripheral arterial pressure, or LV pressures (Table 2), consistent with the conclusion that cardioprotection is not due to effects on the vasculature. The finding that ATL146e protects the heart by binding to receptors on bone marrow–derived cells indicates that the mechanism of the protection is due to inhibition of inflam-
Immunostaining showed that CD3+ T lymphocytes and neutrophils infiltrated into the postischemic myocardium and that infiltration was reduced by A2AAR activation. These investigations were then extended by using immunocompromised Rag-1–KO mice to interrogate the role of a particularly important subpopulation of bone marrow–derived cells (i.e., lymphocytes). Rag-1–KO mice were found to have reduced infarct size, similar to that of ATL146e-treated B6 mice. Administration of ATL146e provided no further reduction in infarct size in Rag-1–KO mice. Taken together, the results of these studies strongly indicate that lymphocytes, logically T lymphocytes, play a critical role in mediating myocardial ischemia-reperfusion injury and that the infarct-sparing effect of ATL146e is due primarily to its action on lymphocytes.

A2AARs are widely distributed in both vascular and hematopoietic cells.7,8,21,22 The identity of the cell type(s) responsible for mediating the cardioprotective effects of A2AAR activation is largely unknown. Studies using in vivo animal models have shown that A2AAR activation achieved by applying CGS-21680 during reperfusion significantly reduces myocardial infarction.2,3,23 This infarct-limiting effect was correlated with a reduction in neutrophil infiltration.2,23 Similar cardioprotective effects also have been reported in exsanguinous isolated heart models.11–13 Hence, the attenuation of postischemic myocardial injury by A2AAR agonists has been attributed to their actions on the vasculature (or myocytes) under certain conditions.11,24 Several other studies using isolated heart models revealed that A2AAR activation does not alter ventricular myocyte cAMP levels and exerts no protective effect against myocardial ischemia-reperfusion injury.14,15,21 suggesting that A2AARs either were expressed at low levels or were not functionally significant in cardiomyocytes. Reconciliation of the inconsistent effects of A2AAR agonists in protecting the heart against ischemia-reperfusion injury was difficult without an understanding of which cell type mediated protection by A2AAR activation. By using bone marrow chimeras and a highly selective A2AAR agonist at a dose free from hemodynamic effects, we have now established a primary role for A2AARs on bone marrow–derived cells in mediating cardioprotection against ischemia-reperfusion injury.

The BMT technique provides for the creation of chimeric mice. All irradiated control mice that did not undergo BMT died within 2 weeks of irradiation. Our previous studies showed that in bone marrow chimeras, 98% of CD11b+ cells, 84% of CD4+ cells, and 85% of CD8+ cells are derived from donor mice.17 Eight weeks after BMT, peripheral blood analysis by HEMAVET (CDC Technologies)
showed that the numbers of red blood cells, white blood cells, and platelets in chimeric mice were comparable to preirradiation levels. To exclude the possibility that donor bone marrow cells might engraft in the endothelium of recipient mice, we created GFP/B6 chimeras and found GFP in circulating cells and in leukocytes infiltrating the myocardium after MI but not in the endothelium. It has been reported that bone marrow–derived stem cells can form endothelium during neovascularization after tissue injury, but this apparently cannot occur during the short time frame of our experiments (24 hours after reperfusion). No GFP-positive cells were detected in the endothelium before or after MI (Figure 5). Thus, in A2AAR-KO/B6 chimeras, the bone marrow–derived cell lineages (but not endothelial cells) are replaced by cells derived from A2AAR-KO bone marrow, enabling us to investigate the role of A2AARs on bone marrow–derived cells without interference from A2AARs on endothelial cells.

Compelling evidence from both animal and clinical studies has indicated that lymphocytes are the principal effector cells of reperfusion injury. Reperfusion induces a vigorous inflammatory response and a dramatic increase in neutrophil adherence to the reperfused endothelium, which leads to capillary plugging, edema, and a reduction in coronary blood flow. A2AARs are widely expressed on blood-borne cells (including T lymphocytes, monocytes, neutrophils, and platelets). Stimulation of A2AARs on bone marrow–derived cells mediates immunosuppression and inhibits neutrophil oxidative activity by a Gs protein-cAMP–dependent pathway. A2AARs therefore play a critical role in inhibiting proinflammatory responses and reducing neutrophil accumulation. The present study clearly demonstrates that neutrophil infiltration to the previously ischemic zone is significantly reduced by ATL146e in B6 and chimeric B6/B6 mice but not in A2AAR-KO/B6 mice (Figures 3 and 4), indicating that A2AARs on bone marrow–derived cells mediate the attenuation of neutrophil infiltration independently of A2AARs on endothelial cells. Furthermore, CD3+ T lymphocytes were also found infiltrating into previously ischemic regions. This infiltration was reduced by ATL146e, indicating that T lymphocytes may also be involved in the posts ischemic inflammatory response. To confirm the role of lymphocytes in mediating myocardial ischemia–reperfusion injury, we used Rag-1–KO mice in which the loss of the normal V(D)J recombination activating (rag) gene causes reduced lymphoid organ size and a complete lack of mature B or T lymphocytes. Rag-1 mice were found to have significantly smaller organ size and a complete lack of mature B or T lymphocytes. However, the expression of A2AARs on B lymphocytes has not been fully defined. More CD4+ than CD8+ T lymphocytes express A2AARs, and activation of T lymphocytes increases A2AAR expression, primarily in CD8+ T lymphocytes. Studies of T helper cell subsets (Th1 and Th2) reveal that lymphokine-producing cells are much more likely to express A2AARs than cells that do not produce lymphokines. A2AARs have a nonredundant role in the attenuation of inflammation and tissue damage in vivo and are a critical part of the physiological negative feedback mechanism for the limitation and termination of both tissue-specific and systemic inflammatory responses.

Stimulation of A2AARs mediates immunosuppression by inhibiting the activation of virtually all tested functions of T cells and inhibits neutrophil oxidative activity by a Gs protein-cAMP–dependent pathway. The immunosuppressive effect of A2AAR activation is further confirmed by studies showing that genetic inactivation of A2AAR increases the intensity and prolongs the duration of T-cell–dependent proinflammatory cytokine accumulation and tissue damage.

It remains unclear how T lymphocytes become activated during myocardial ischemia–reperfusion injury and how activated T lymphocytes stimulate reperfusion-induced inflammatory responses. In particular, the functional relationships between lymphocytes and other leukocyte subtypes remain unclear. The fact that A2AAR activation fails to provide any additional cardioprotection in Rag-1–KO mice further suggests that ATL146e reduces myocardial ischemia–reperfusion injury by inhibiting lymphocytes. Although reduced, neutrophil infiltration into the RR still existed and was comparable between vehicle and ATL-treated groups, indicating that the neutrophils in Rag-1–KO mice are functionally intact and can home independently of A2AAR stimulation. Lymphocyte-mediated inflammatory response appears to be lethal to ischemically injured myocytes early during reperfusion, whereas subsequent neutrophil infiltration (24 hours after reperfusion) is essentially reparative because the amount of neutrophil infiltration into the RR is directly proportional to the size of myocardial infarction (Figures 1 through 4). The fact that A2AAR activation fails to further reduce neutrophil infiltration into the myocardium in Rag-1 mice indicates that a brief period of A2AAR stimulation during reperfusion is sufficient to reduce lethal myocardial damage without compromising the subsequent reparative functions of blood-borne cells. Furthermore, our results indicate that lymphocytes, probably T lymphocytes, play a central role in regulating other effector leukocytes (ie, monocytes and neutrophils) during the inflammatory responses initiated by posts ischemic reperfusion. Thus, the cardioprotective effect of A2AAR activation is mediated through inhibition of T lymphocytes rather than directly through the inhibition of neutrophils or monocytes.

In summary, by testing the effect of a highly selective A2AAR agonist, ATL-146e, in wild-type, A2AAR-knockout, Rag-1–knockout, and chimeric mice specifically lacking A2AAR on bone marrow–derived cells, we found that A2AARs play a critical role in downregulating proinflammatory responses and mediating cardioprotection against ischemia–reperfusion injury. The infarct-sparing effect of A2AAR activation is due primarily to its action on bone marrow–derived cells, probably T lymphocytes. We speculate that myocardial protection occurs because A2AAR agonists inhibit T-lymphocyte activation, which in turn inhibits inflammation...
and/or promotes the survival of cardiomyocytes in the border area after ischemia-reperfusion injury.

Acknowledgments

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References

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