New insights into the regulation of inflammation by adenosine

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Adenosine, long known as a regulator of cardiovascular function, has recently been identified as a significant paracrine inhibitor of inflammation that acts primarily by activation of A2A adenosine receptors (A2ARs) on lymphoid or myeloid cells. In this issue of the JCI, Yang et al. describe a proinflammatory phenotype resulting from deletion of the gene encoding the A2B adenosine receptor (A2BAR) in the mouse, suggesting that activation of the A2BAR can also have antiinflammatory effects (see the related article beginning on page 1913). Nevertheless, the role of the A2BAR remains enigmatic since its activation can either stimulate or inhibit the release of proinflammatory cytokines in different cells and tissues.

There is growing interest in elucidating the mechanisms by which adenosine inhibits the immune system, since these inhibitory adenosine receptors and their downstream signaling pathways are promising targets for new antiinflammatory therapies. By signaling through the A2A adenosine receptor (A2AR), adenosine suppresses the immune system, primarily by inhibiting lymphoid or myeloid cells including neutrophils (1), macrophages (2), lymphocytes (3, 4), and platelets (5). These responses are amplified by rapid induction of A2AR mRNA in macrophages and T lymphocytes in response to inflammatory or ischemic stimuli (2, 3, 6, 7). The A2B adenosine receptor (A2BAR) also appears to mediate antiinflammatory effects in macrophages by inhibiting the production of TNF-α and IL-1β, stimulating IL-10 and inhibiting macrophage proliferation (8–11) (Figure 1A). Macrophage A2BAR signaling increases during

Nonstandard abbreviations used: A2AR, A2A adenosine receptor; A2BAR, A2B adenosine receptor.

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References


inflammation, as the macrophage-activating cytokine IFN-γ causes induction of macrophage A2B AR mRNA (12). However, the A2B AR is somewhat unusual in that it is dually coupled to the generally antiinflammatory G protein Gq and the generally proinflammatory G protein Gs (13); in addition, numerous proinflammatory effects mediated by activation of the A2B AR have also been described (Table 1).

**Inflamed phenotype of the A2B AR knockout mouse**

Given the opposing cellular effects mediated by A2B AR activation, the phenotype that would result from deletion of the gene encoding A2B AR was uncertain. In this issue of the JCI, Yang and coworkers use a receptor knockout/reporter gene knock-in approach to confirm the expected expression pattern of the A2B AR transcript, noting high levels in monocytes/macrophages and the vasculature (14). Interestingly, they report a moderately inflamed phenotype in the A2B AR knockout mouse at baseline, including elevated adhesion molecule expression on vascular endothelial cells and elevated cytokine production. The inflammatory phenotype is exaggerated in mice given endotoxin. The baseline response to A2B AR knockout is surprising since the A2B AR is recognized to have a low affinity for adenosine, yet the data imply that baseline adenosine levels are high enough to produce some activation of the A2B AR. A well-recognized limitation of the global knockout approach is that the resulting phenotype may reflect a developmental adaptation to the gene knockout and not an acute direct consequence of deleting the gene product.

In order to address this possibility, Yang et al. examined the effect of deleting the gene that codes for A2B AR on mRNA levels of the other adenosine receptor subtypes and found no changes. However, other possible adaptations have yet to be examined. It has recently been demonstrated that hypoxia triggers coordinate upregulation on endothelial cells of mRNA for the A2B AR and ectoenzymes involved in the conversion of extracellular adenine nucleotides to adenosine (15) (Figure 1B). In addition, the release of adenine nucleotides from various cells, including neutrophils and endothelial cells, is a regulated process (16). It will be of interest in future studies to determine whether deletion of the gene encoding A2B AR influences either nucleotide release or extracellular nucleotide metabolism. Such effects could indirectly influence inflammation by altering the availability of adenosine to other adenosine receptor subtypes, particularly the A2A AR. Deletion of either the ecto-apyrase CD39 (also known as NTPDase1; ref. 17) or the ecto-5’-nucleotidase (also known as CD73; refs. 18, 19) results in a proinflammatory phenotype.

**Future questions**

It will also be of interest in future studies to examine the response of the A2B AR to hypoxia.

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**Table 1**

Proinflammatory effects of activating A2B AR

<table>
<thead>
<tr>
<th>Cell</th>
<th>Response</th>
<th>References</th>
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<tr>
<td>Mast cell</td>
<td>Degranulation, IL-8 release</td>
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<td>IL-6 and MCP-1 release</td>
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<td>Pituitary folliculostellate cell</td>
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<td>32</td>
</tr>
<tr>
<td>Airway epithelial cell</td>
<td>Prostenoid release</td>
<td>33</td>
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</tbody>
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MCP-1, monocyte chemoattractant protein 1.

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**Figure 1**

Anti- and proinflammatory effects mediated by activation of the A2B AR. (A) In macrophages, the release of TNF-α and other proinflammatory cytokines is inhibited as a result of activating either the A2A AR or the A2B AR. These effects are amplified if TNF-α production is stimulated by LPS, which signals through TLR4 and other Toll-like receptors. Activation of the A2B AR also stimulates production of the antiinflammatory cytokine IL-10. (B) In endothelial cells and other cells noted in Table 1, activation of the A2B AR stimulates IL-6 and other proinflammatory cytokines. Hypoxia increases the intracellular production of adenosine, which is transported outside the cell by nucleoside transport proteins. Hypoxia and possibly activation of the A2B AR stimulate the release of ATP and the production of the A2B AR and ectoenzymes (CD39 and CD73) that convert ATP to adenosine. Vasodilation in response to A2B AR activation may increase shear stress to stimulate ATP release.
knockout mouse in the setting of hypoxia or ischemia, which elicits the accumulation of large levels of adenosine. A selective A2B receptor antagonist blocks myocardial preconditioning when applied to the isolated rabbit heart after ischemia (20). This could occur either because A2B receptors on the heart mediate cardioprotection or, as discussed above, because A2BAR activation facilitates the release and/or metabolism of adenosine nucleotides to indirectly enhance adenosine production. The latter scheme is consistent with the observation that myocardial preconditioning has a remote adenosine-mediated effect on platelet function (21).

In conclusion, the study by Yang et al. (14) bolsters the conclusion that activation of A2BARs on certain cells, particularly macrophages, inhibits inflammation. A proinflammatory phenotype noted at rest is somewhat unexpected, and the mechanism underlying this inflammation is not yet known. In view of a number of previous reports indicating that A2BAR activation can be proinflammatory (Table 1), it will be of interest to use the newly available A2B knockout mouse in order to determine whether A2BAR activation on different cells can elicit both pro- and antiinflammatory responses.

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