

Targeting the adenosine A2b receptor in the tumor microenvironment overcomes local immunosuppression by myeloid-derived suppressor cells

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Keywords: A2bR, immunosuppression, immunotherapy, MDSCs, tumor microenvironment

Emerging evidence suggests that the adenosine A2b receptor (ADORA2B, also known as A2bR) plays a pivotal role in tumor progression. We have recently demonstrated that blocking A2bR stimulates T cell-mediated immunosurveillance in a melanoma model by impairing the influx of myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment. This results in robust antineoplastic effects, which can be abrogated by the adoptive transfer of MDSCs.

The adenosine A2b receptor (ADORA2B, best known as A2bR) critically influence tumor progression. We have recently shown that the selective A2bR agonist BAY 60–6583 enhances melanoma progression in mice, while the selective A2bR antagonist PSB1115 suppresses melanoma growth.¹ These results suggest that A2bR inhibitors may have therapeutic potential for the treatment of melanoma and perhaps other neoplasms.

The tumor-promoting activity of A2bR was first demonstrated in A2bR-deficient mice.² Tumor growth was indeed decreased in these mice as compared with their wild-type (WT) counterpart,² an effect that was associated with a significant decrease in the intratumoral levels of vascular endothelial growth factor (VEGF) and limited amounts of tumor-infiltrating CD11b⁺Gr1⁺ myeloid-derived suppressor cells (MDSCs).^{2,3} MDSCs are immunosuppressive cells that promote tumor progression by impairing antitumor T-cell responses and/or modulating angiogenesis (reviewed in

ref. 4). Studies by Rytzhov and colleagues indicate that A2bR promotes the expansion of MDSCs generated in vitro from mouse bone marrow hematopoietic progenitors.³ These data suggest that A2bR deficiency may promote cancer immunosurveillance by impairing the recruitment and/or accumulation of tumor-associated MDSCs.

However, A2bR deficiency in mice also modulates the intratumoral levels of paracrine factors that are critical for tumor infiltration by immune cells, including VEGF.² Various inflammatory mediators produced by malignant, stromal, and immune components of the neoplastic lesions, such as VEGF itself, multiple cytokines like interleukin (IL)-10, IL-1 β , and IL-6, chemokines and prostaglandin E₂ (PGE₂), inhibit the maturation of myeloid cell precursors into dendritic cells, macrophages or granulocytes, hence favoring the recruitment/accumulation into the tumor microenvironment of immunosuppressive MDSCs.⁵ Moreover, MDSCs can themselves produce immunosuppressive^{4,5} and

pro-angiogenic mediators, including VEGF.^{6,7} Our experiments show that the intratumoral administration of BAY 60–6583 causes a significant increase in tumor-infiltrating MDSCs (Fig. 1), without affecting neither their ability to suppress T-cell proliferation nor their degree of maturation.¹ We also found that BAY 60–6583 stimulates the production of IL-10 and chemokine (C-C motif) ligand 2 (CCL2, also known as MCP-1) in the tumor tissue (Fig. 1).¹ Conversely, A2bR blockade with PSB1115 turned out to promote immunosurveillance, as shown by increased amounts of tumor-infiltrating CD8⁺ T cells and natural killer T (NKT) cells coupled to decreased numbers of intratumoral MDSCs.¹ This was accompanied by reduced levels of IL-10 and MCP-1, as well as by an increase in T_H1 cytokines, such as interferon γ (IFN γ), and granzyme B.¹ The depletion of MDSCs completely reversed the tumor-promoting effect of BAY 60–6583, while the adoptive transfer of MDSCs abrogated the antitumor activity of PSB1115.¹ These data strongly support

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Submitted: 01/23/2014; Accepted: 01/24/2014; Published Online: 02/14/2014

Citation: Morello S, Miele L. Targeting the adenosine A2b receptor in the tumor microenvironment overcomes local immunosuppression by myeloid-derived suppressor cells. *Oncoimmunology* 2014; 3:e27989; <http://dx.doi.org/10.4161/onci.27989>

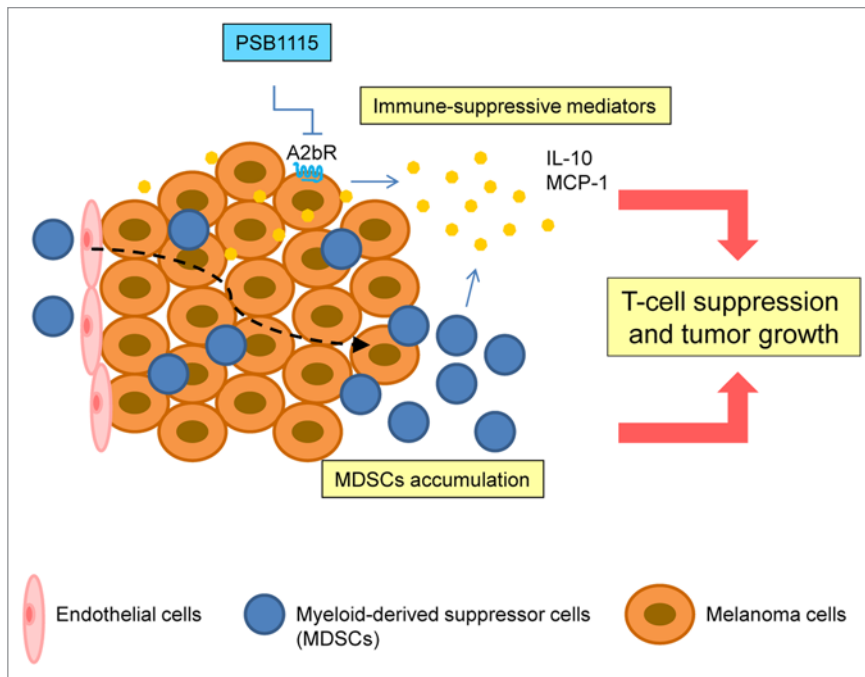


Figure 1. A2bR exerts robust immunosuppressive effects in the tumor microenvironment. Stimulation of adenosine A2b receptor (ADORA2B, also known as A2bR) with specific agonists promotes the growth of melanoma. This effect is associated with the accumulation of myeloid-derived suppressor cells (MDSCs) within neoplastic lesions and the production of immunosuppressive mediators, such as interleukin-10 (IL-10) and chemokine (C-C motif) ligand 2 (CCL2, also known as MCP-1), which can further stimulate the influx of MDSCs. Conversely, the pharmacological blockade of A2bR with the specific antagonist PSB1115 enhances T cell-dependent immunosurveillance by decreasing the amount of tumor-infiltrating MDSCs and the levels of immunosuppressive mediators released within the neoplastic tissue.

the hypothesis that MDSCs underlie the tumor-promoting activity of A2bR.

Blocking A2bR modulates the inflammatory response in the tumor microenvironment, hence impairing the accumulation of MDSCs in melanoma lesions (Fig. 1). Notably, PSB1115 failed to influence the levels of MDSCs in secondary lymphoid organs, consistent with a selective activity of this A2bR antagonist on the recruitment of MDSCs to neoplastic lesions

rather than with putative systemic effects.¹ It would be interesting to determine whether adenosine, the natural ligand of A2bR, might regulate the expression of chemokines and/or their receptors in the tumor microenvironment. Chemokines indeed play a crucial role in the recruitment of immunosuppressive cells, including MDSCs, to the tumor microenvironment. In support of this notion, it has been demonstrated that adenosine upregulates

chemokine (C-X-C motif) receptor 4 (CXCR4) via adenosine A2a receptor (ADORA2A, best known as A2aR) and A2bR, thus enhancing the proliferative and migratory responses of human malignant cells to chemokine (C-X-C motif) ligand 12 (CXCL12, best known SDF-1).⁸ Recent findings demonstrate that the CXCL12/CXCR4 signaling axis plays a critical role in attracting MDSCs into the tumor microenvironment.⁹ Future studies will provide an ever more detailed understanding of the A2bR-dependent effects of adenosine on various aspects of the MDSC biology, including their development, differentiation/maturation, immunosuppressive activity, and recruitment to tumor microenvironment.

Our working hypothesis is that adenosine, which is released in high amounts by hypoxic tumor tissues, stimulates immunosuppression via A2bR by modifying the tumor microenvironment and increasing the number of intratumoral MDSCs. Therefore, A2bR antagonists may be effective in delaying the growth of melanoma and perhaps other cancer as they improve local immunosurveillance. Consistent with this hypothesis, we observed that the combination of PSB1115 and dacarbazine, a chemotherapeutic agents commonly employed in melanoma patients, was more effective in suppressing tumor growth than either agent alone.¹ Our data may pave the way to clinical studies testing A2bR inhibitors alone or combined with other immunotherapeutic interventions, in melanoma patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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