# Pharmacological blockade of A2B adenosine receptor reduces tumor angiogenesis and immunosuppression in a mouse model of melanoma

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Adenosine plays a pivotal role in endogenous immunosuppressive pathways in the tumor microenvironment. It is well known that adenosine inhibits T-cell proliferation and function of activated T-cells via A2A receptor subtype activation, protecting the tumour from immune-mediated destruction. Emerging evidence suggest that A2BR is also implicated in tumor progression in some murine tumor models. Recent studies demonstrate that A2BR contributes to the adenosine–mediated immunosuppressive effects, by regulating the accumulation of myeloid derived suppressor cells (MDSC) within tumor tissue. MDSCs are potent suppressor of T effector cells, and release angiogenic factors, including VEGF. In this study we investigated on the role of MDSCs in the pro-tumor effects of A2B receptor, focusing on both immunosuppressive and pro-angiogenic effects. Melanoma-bearing mice treated with Bay60-6583, a selective ligand of A2BR, showed accumulation of CD11b+Gr1+ cells, reduced number of T cells and enhanced VEGF-A expression and vessel density within tumor tissue. Depletion of MDSCs significantly reversed the effects mediated by Bay60-6583, suggesting that A2B-mediated accumulation of tumor myeloid cells contribute to the enhanced angiogenesis and immunosuppression in the tumor tissue. Endothelial cells, which express A2B receptors, play a critical role on the pro-angiogenic effects mediated by A2B receptor stimulation, while melanoma cells do not. Furthermore, we observed that the activation of signal transducer and activator of transcription (STAT) 3 enhanced in melanoma tissue of mice treated with Bay60-6583. Importantly, pharmacological blockade of A2BR with PSB1115 significantly reduced tumor growth. This effect was associated with reduced expression of VEGF and vessel density within melanoma sections and reduced presence of MDSC in the tumor, which critically contribute both to inhibit T cell response and release VEGF. These results support the therapeutic potential of A2B receptor antagonists as anti-cancer agents.