Adenosine and Adenosine Receptors in the Immunopathogenesis and Treatment of Cancers

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Identification of the precise mechanisms behind the robust immunosuppression exerted by tumor cells can help us to design new therapeutic approaches for cancer therapy. The generation of adenosine is one of the main immunosuppressive mechanisms by which tumor cells not only inhibit anti-tumor responses, but also induce suppressive cells such as regulatory T cells (Treg). Two cell surface expressed molecules including CD73 and CD39 catalyze the generation of adenosine from adenosine triphosphate (ATP). The generation of adenosine can be enhanced under metabolic stress like tumor hypoxic conditions. Adenosine exerts its immunoregulatory functions through four identified adenosine receptors (ARs) including A1, A2A, A2B and A3 which are expressed on various immune cells. So, blocking the adenosine generating enzymes or ARs can be considered as an important therapeutic approach for cancer therapy. It is demonstrated that signalling of A2A receptor (A2AR) and A2BR in the tumor microenvironment can lead to induction and expansion of immunosuppressive cells such as Treg and MDSC. On the other hand, reports regarding the effect of A1R and A3R signalling in tumor biology are controversial. It seems that tumor promoting or tumor limiting effects of these two receptors depend on the tumor type and tumor condition. Several ARs directed agonists and antagonists have been developed and used for treatment of various tumors. We think the use of these agents as monotherapy or in combination with other conventional cancer drugs may lead to promising outcome in near future.

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