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Review

Adenosine receptors as potential targets in melanoma

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ABSTRACT

Melanoma is one of the most aggressive types of cancer, that is difficult to manage clinically. A major feature of melanoma cells is their ability to escape immune surveillance. Adenosine receptors play a pivotal role in host immune-surveillance. A2a (A2aR) and, partially, A2bR receptors mediate the adenosine-induced immune-suppression, which markedly facilitates tumor development/progression. On the contrary, A3R stimulation enhances the anti-tumor immune response and thus limits tumor growth. A3R also inhibits the proliferation of many cancer cells. Given that A2aR and A3R have profound effects on tumor growth and metastasis, they are attractive targets for novel therapeutic anti-cancer agents. Here, we review the role played by A2aR and A3R in regulating cancer pathogenesis, with a focus on melanoma, and the therapeutic potential of adenosine receptors pharmacological modulation.
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Contents

1. Introduction

Melanoma is a potentially lethal tumor, that arises from melanocytes present in the skin, mucosa or epithelial surfaces of the eyes and ears [1]. Melanoma cells have the potential to spread, and metastatic melanoma is highly resistant to conventional chemotherapy. Currently, dacarbazine is the chemotherapeutic drug of choice used for treating metastatic melanoma, despite the low response rate contributing only 8 months median survival [2]. Recently, it has been demonstrated that some cytotoxic agents, including dacarbazine, have also immune-stimulatory effects [3]. It is well known that melanoma is one of the most immunogenic types of cancer. Melanoma cells express a variety of melanoma-associated antigens (MAAs), which are recognized by T lymphocytes. These antigens belong to three main groups: tumor-associated testis-specific antigens (MAGE, BAGE, GAGE and PRAME), melanocyte differentiation antigens (tyrosinase, Melan-A/MART-1, gp100, TRP-1 and TRP-2) and mutated or aberrantly expressed antigens (MUM-1, CDK4, β-catenin, gp100-in4, p15 and N-acetylglucosaminyltransferase V) [4–10]. In a few cases, patients with established melanoma can have spontaneous tumor

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regression, suggesting that the induction of a specific anti-tumor immune response, which is mediated by T cells, can indeed be achieved [11–13].

Some clinical protocols directed to maintain pre-existing or adoptively transferred melanoma-specific T cells are currently used. Interleukin (IL)-2 treatment, which has an unbiased response rate of 15–20%, has been approved by the Food and Drug Administration (FDA) [14,15]. Further, the adoptive transfer of autologous tumor-infiltrating lymphocytes (TILs) is a promising anti-tumor therapy in patients with melanoma [16–18]. TIL therapy has shown a clinical response in 49–72% of patients with metastatic melanoma and a long lasting complete response rate of 40% [19–21]. However, numerous strategies to treat melanoma with immunotherapy have been only partially successful [22]. Various mechanisms have been implicated in the escaping of an anti-tumor immune response *in vivo*. Melanoma cells evade T-cell-immune-mediated destruction by down-regulating the expression of class I Human Leukocyte Antigen (HLA) of the MAAs and the production of multiple immunosuppressive factors that cause the generation of a chronic inflammatory microenvironment [23–25]. During chronic inflammation, several inflammatory factors are released including cytokines, chemokines, growth factors, reactive oxygen and nitrogen species as well as prostaglandins from the surrounding tissue and/or tumor cells [26–28]. Inflammatory factors, which were present in the melanoma microenvironment, consist of chemokines (CC-chemokine ligand 2, CCL2; CCL5; CXC-chemokine ligand 1, CXCL1; CXCL2; CXCL3; CXCL5; CXCL6; CXCL7; CXCL8; CXCL10 and CXCL12), as well as growth factors (granulocyte macrophage-colony stimulating factor, GM-CSF; vascular endothelial growth factor, VEGF; transforming growth factor-β, TGF-β) and cytokines (tumor necrosis factor, TNF, IL-1, IL-4, IL-5, IL-6, IL-10 and IL-13) [25,29]. These factors, produced by tumor, stroma and immune cells, promote melanoma growth and progression. They can drive the recruitment and activation of many immunosuppressive cells in the tumor environment, including T regulatory cells (Tregs) [30] myeloid-derived suppressor cells (MDSCs) [31] and tumor-associated macrophages (TAMs) [32]. Both inflammatory factors and immunosuppressive cells play a critical role in limiting the effectiveness of anti-tumor immunotherapy [29,30].

The first successful attempt to abolish immune-suppression in melanoma treatment has been achieved with the use of the recently FDA-approved monoclonal antibody (mAb) ipilimumab. Ipilimumab binds to the cytotoxic T lymphocyte antigen-4 (CTLA-4) [33–36], which is expressed on activated $CD4^+$ T cells and $CD8^+$ T cells. Its interaction with members of the B7 family on antigen-presenting cells (APCs) inhibits T-cell activation. Ipilimumab competes successfully for B7 binding with the co-stimulatory receptor CD28. Ipilimumab therapy improves the overall survival rate in patients with metastatic melanoma determining a 32% reduction in the risk of death compared to the control group [37].

Taken together, these findings emphasize the great potential of immune-active therapies against melanoma and the importance of investigating novel therapeutic strategies aimed at the inhibition of cancer-induced immune-suppression, that in turn may restore an efficient anti-tumor immune response.

2. Adenosine: a critical modulator of immune response in the tumor environment

Numerous evidences suggest that adenosine plays a pivotal role in endogenous immunosuppressive pathways which regulate immune responses in the tumor microenvironment [38,39]. Adenosine is an adenosine triphosphate (ATP)-derived molecule, whose effects are mediated by four different membrane-spanning G-protein-coupled receptors (GPCRs): A1R, A2aR, A2bR and A3R [40] (Fig. 1). A2a and A2b are Gs-coupled receptors, that by increasing intracellular cyclic AMP (cAMP) levels (Fig. 1), mediate the immune suppressive effects of adenosine. In contrast, A1 and A3 receptors are Gi/o-coupled receptors, that by inhibiting adenylate cyclase (AC), lower intracellular cAMP levels (Fig. 1) and thus activate immune cells. Metabolic stress and cell damage caused by ischemia, hypoxia and inflammation lead to an enhanced hydrolysis of ATP into adenosine via two cell-surface ectonucleotidases, CD39 and CD73 (Fig. 1) [38,41]. Up-regulation of A2a and A2b receptors expression also occurs under hypoxic conditions [42]. In inflammatory-associated conditions, adenosine typically induces an attenuation of the inflammatory response [43]. Ohta and Sitkovsky [44] have shown for the first time that A2aR-deficient mice are unable to control inflammation and exhibit an amplified immune responses which can trigger extensive tissue disruption with subsequent cell death. Adenosine via A2aR on immune cells induces a wide range of remarkable immunosuppressive responses which regulate the uncontrolled inflammation to harmful insults [43,45–47].

In the cancerous lesions, adenosine, either produced by tumor cells and/or by immune suppressive cells including Tregs and MDSCs [48–50], accumulates in the tissue. Here, adenosine favors the immune escape from immune surveillance with the consequence of tumor progression, in an A2aR-dependent manner [38,51]. A2aR activation leads to the inhibition of T cell receptor (TCR)-triggered effector functions, including proliferation, expansion and secretion of important cytokines such as interferon (IFN)-γ, TNF-α, and IL-2 via cAMP/protein kinase cAMP-dependent (PKA) pathways. This phenomenon was described for both naïve $CD4^+$ T cells and polarized T helper (Th) type 1 and Th2 cells [52–54]. Furthermore, A2aR stimulation reduces the expression of CD25 and CD40 ligand (CD40L) and increases the expression of programmed death-1 (PD-1) and CTLA-4 on T cells [55]. A2aR activation suppresses $CD8^+$ T cell cytolytic activity [56], and promotes peripheral tolerance by inducing T-cell anergy [57]. These results show the critical role of A2aR in the modulation of immune cell function in inflammatory conditions, including those associated with cancer pathogenesis.

Therefore, inhibition of A2aR by pharmacological drugs or reduction of adenosine generation in the tumor tissue, by inhibiting CD73, have been shown to be beneficial in restoring the anti-tumor immune response in different mouse tumor models, including melanoma [51,58–62]. Although it has been clearly demonstrated that adenosine reduces the immune response upon A2aR ligation, stimulation of different adenosine receptor subtypes, such as A3R, may be associated with opposite outcomes on tumor growth. These findings have encouraged the scientific and clinical community to further study the role of A3R in cancer progression. Selective A3R agonists, such as 1-Deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9*H*-purin-9-yl]-*N*-methyl-β-D-ribofuranuronamide (IB-MECA, also designed CF101) and 1-[2-Chloro-6-[[(3-iodophenyl)methyl]amino]-9*H*-purin-9-yl]-1-deoxy-*N*-methyl-β-D-ribofuranuronamide (Cl-IB-MECA, also designed CF102), are able to suppress the proliferation of several human cancer cells *in vitro* and in some murine tumor models [reviewed in Ref. [63]]. This effect is related to the cell cycle arrest at G1 phase, at least in part by the inhibition of cyclin D1 and E2 expression, and by de-phosphorylation of ERK1/2. Cl-IB-MECA also enhances TNF-related apoptosis inducing ligand (TRAIL)-induced apoptosis in human thyroid cancer cells [63–65]. It worth stressing that both, IB-MECA and Cl-IB-MECA lose their selectivity for A3R at μM concentrations, but nevertheless induce death of tumor cells in an A3R-independent manner [64,66]. A3R is expressed in several tumor cell lines [63] and it is up-regulated both in human cancer and peripheral blood mononuclear cells (PBMCs) of hepatocellular carcinoma patients,

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