Review

CD73: a potent suppressor of antitumor immune responses

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Tumors use several strategies to evade immunosurveillance. One such mechanism is the generation of adenosine within the tumor microenvironment, which potently suppresses antitumor T cell responses. Adenosine within the tumor is generated by CD73, a membrane-bound nucleotidase that is expressed by tumor cells, suppressive immune subsets such as T regulatory cells (Tregs) and myeloid-derived suppressor cells and endothelial cells. Recent evidence suggests that targeted inhibition of CD73 has the potential to reduce tumorigenesis and metastasis, as well as enhancing the potency of T-cell-directed therapies. This review outlines the impact of adenosine on suppressing the antitumor response and the evidence supporting the rationale for CD73 targeting in the treatment of cancer.

Tumor immunosuppression and progression of cancer

It is now accepted that the immune system is fundamental in suppressing both the initiation of malignant neoplasms and the progression of established tumors. In immunological terms, these are respectively known as the elimination and equilibrium stages of cancer. In the third stage termed 'escape', the tumor adapts in ways that allow it to avoid immunosurveillance [1,2]. Tumors use several mechanisms that facilitate immune escape and prevent tumor elimination including anti-inflammatory cytokine production, recruitment of regulatory immune subsets comprising Tregs and myeloid-derived suppressor cells (MDSCs), negative co-stimulation of effector T cells and the production of immunosuppressive metabolites [3]. Significant therapeutic opportunity exists in targeting these pathways and thus modifying the tumor environment from immunosuppressive to immune-activating. The potential of this strategy is underlined by the recent FDA approval of ipilimumab, an anti-cytotoxic T lymphocyte antigen (CTLA)-4 monoclonal antibody (mAb), to treat metastatic melanoma. This therapy is effective because it prevents the negative signaling induced in T cells following CTLA-4 ligation [4]. Furthermore, it is now clear that conventional cancer treatments such as some chemotherapeutic agents and radiation therapy are efficacious, in part, due to their induction of antitumor immune responses [5]. Thus, immunotherapies that act to harness both endogenous and therapeutically induced antitumor immune responses are currently being actively pursued. One such therapeutic target is CD73, an ectoenzyme that catalyzes the generation of adenosine; a potently immunosuppressive host nucleoside. CD73 is expressed on lymphocytes, endothelial and epithelial cells and plays a physiological role in ion transport, maintaining barrier function, endothelial homeostasis and cardioprotection in response to ischemia [6,7] (reviewed in [8]). The focus of this review is the impact of CD73 on suppressing immune responses and its potential as a therapeutic target in cancer.

CD73 is pivotal in the conversion of immunostimulatory ATP into immunosuppressive adenosine

The metabolism of ATP into its metabolites ADP, AMP and adenosine is a tightly regulated process, due to the important role of ATP in cellular metabolism, signaling and immune homeostasis. AMP is generated by the stepwise catabolism of ATP into AMP via the intermediate ADP and is subsequently converted to adenosine (Figure 1). These reactions are carried out by ectoenzymes of the NTPDase family (eight have been identified in humans) and tissue-non-specific alkaline phosphatases. The conversion of ATP into AMP is predominantly catalyzed by CD39 (NTPDase-1) with only trace amounts of ADP being released [9], whereas CD73 (ecto-5′-nucleotidase) catalyses the conversion of AMP to adenosine. Thus CD73 and CD39 act in concert to convert ATP into adenosine. The conversion of ATP to AMP by CD39 is reversible by the actions of the extracellularly located kinases NDP kinase (ATP>ADP) and adenylate kinase (AMP>ADP). By contrast, the conversion of AMP into adenosine by CD73 is reversible only following intracellular transport of adenosine where it can be converted to AMP by adenosine kinase. This places CD73 at a crucial checkpoint in the conversion of immune-activating ATP into immunosuppressive adenosine. Although CD73 is required for the conversion of AMP into adenosine in physiological conditions, loss of function mutations in the CD73 gene lead to an increase in the expression of tissue-non-specific alkaline phosphatases [7]. Thus, at least to a certain extent, alkaline phosphatases have the capacity to compensate for lack of CD73 function, which may be important in maintaining homeostasis under such conditions. Whilst inhibitors for CD73 (APCP)

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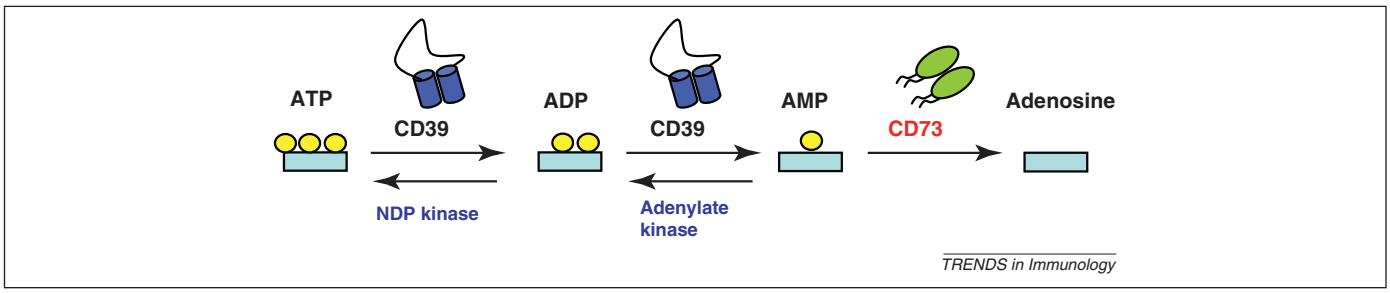

Figure 1. Ectoenzymes and extracellular kinases involved in the generation of adenosine. ATP is converted to immunosuppressive adenosine via the intermediates ADP and AMP by the ectoenzymes CD39 and CD73. Catabolism of ATP to AMP can be reversed by adenylate kinase and NDP kinase, whereas conversion of AMP to adenosine is reversible only by intracellularly expressed adenosine kinase.

and CD39 (ARL67156) exist for preclinical investigations, there are no known modulators of this pathway being developed for clinical use.

The balance between adenosine and ATP is crucial in immune homeostasis because ATP is a danger signal released by damaged and dying cells that acts to prime immune responses through the ligation of P_2X and P_2Y purinoreceptors. Thus ATP, via the activation of the P_2X_7– NACHT, LRR and PYD domains-containing protein 3 (NALP3) inflammasome pathway, is vital for the activation of dendritic cells (DCs) and the secretion of interleukin (IL)-1β and IL-18 (Figure 2) [10]. Indeed, mice deficient for P_2X_7 receptors or the NALP3 inflammasome elicit impaired antitumor T cell responses and less efficacious responses to chemotherapy [11]. By contrast, adenosine suppresses immune responses through the activation of G-protein-coupled

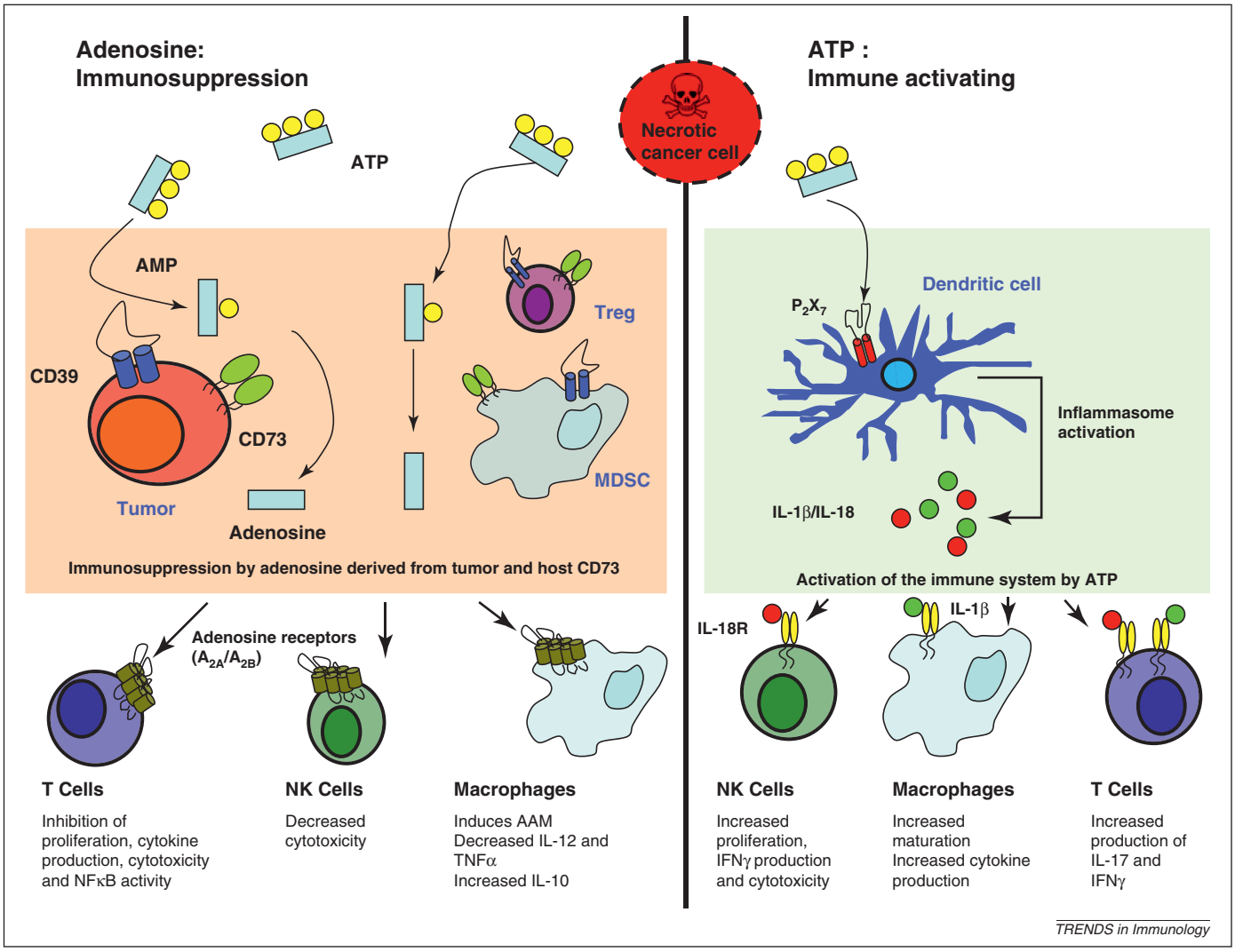

Figure 2. Immunosuppression induced by the conversion of ATP into adenosine by tumor cells and suppressive immune subsets. ATP released by dying cells can activate the immune system via the stimulation of P_2X_7 receptors on DCs. This results in the activation of the NALP3 inflammasome and consequently the production of IL-1β and IL-18. These proinflammatory cytokines stimulate antitumor immunity through activation of immune cells including NK cells, T cells and macrophages. Ectoenzymes CD73 and CD39, expressed on host suppressive cells and tumor cells, convert ATP into adenosine. Adenosine consequently suppresses antitumor immunity through activation of adenosine receptors on multiple immune subsets including T cells, NK cells and macrophages.