

Abstract

Tools and Drugs for Purine-Binding Targets—Important Players in Inflammation and Cancer [†]

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Abstract: Purine and pyrimidine derivatives, such as the nucleotides ATP, ADP, UTP, and UDP, the nucleoside adenosine, and the nucleobase adenine, are important signaling molecules which activate membrane receptors termed P0 (adenine receptors), P1 (adenosine receptors), P2Y, and P2X (nucleotide receptors). P0, P1, and P2Y receptors are G protein-coupled, while P2X receptors are ATP-gated ion channels. There is a metabolic link between P1 and P2 receptor agonists, since the nucleotides ATP and ADP (P2 agonists) are hydrolyzed by various ectonucleotidases, producing the P1 agonist adenosine. While ATP is a danger signal mediating pro-inflammatory effects, adenosine acts as a stop signal inducing anti-inflammatory and immunosuppressive activities. Despite decades of research, only few drugs have been approved that interact with purine receptors. Recently, new hopes and hopes have been created in the field, mainly due to the gold rush fever in immuno-oncology. Adenosine is one of the strongest immunosuppressant agents of the innate immune system. Cancer cells and tissues can release large amounts of ATP, which is immediately hydrolyzed by ectonucleotidases. These ecto-enzymes, including ectonucleotide pyrophosphatase/phosphodiesterase 1 (NPP1, CD203a), ectonucleoside diphospho-hydrolase 1 (NTPDase1, CD39), and ecto-5'-nucleotidase (CD73), are upregulated on many cancer cells, leading to the production of adenosine. The cloud of adenosine formed around cancer tissues contributes to immune escape by interacting with adenosine A_{2A} and A_{2B} receptor subtypes (A_{2A}AR, A_{2B}AR) on immune cells. In addition, activation of A_{2B}ARs by adenosine enhances cancer cell proliferation, metastasis, and angiogenesis. Blockade of A_{2A} and A_{2B} adenosine receptors and/or inhibition of adenosine formation by blocking ectonucleotidases are being pursued as novel principles that activate the immune system to defeat cancer. Recent progress in the development of adenosine receptor antagonists and ectonucleotidase inhibitors will be presented and discussed.

Keywords: adenosine; ATP; CD73; ectonucleotidases; immuno-oncology; inhibitors; NPP1; purine receptors



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