がん進展制御研究所セミナー

Purinergic signalling in cancer and inflammation

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Nucleosides and nucleotides are important extracellular signalling molecules that activate transmembrane purinergic receptors and play a key role in various pathophysiological conditions such as e.g. inflammation and cancer. The concentrations of extracellular nucleosides and nucleotides are tightly regulated by ecto-nucleotidases including ecto-nucleoside triphosphate diphosphohydrolases (ecto-NTPDases, CD39), ecto-nucleotide pyrophosphatases (ecto-NPPs, CD203a) and ecto-5'-nucleotidase (CD73). Therefore, purinergic receptor modulation via direct ligand-receptor interaction (agonism, antagonism) or throughout inhibition of ecto-nucleotidase activity is highly desirable.

The purinergic receptors are divided into two main receptor families: P1 and P2. Four P1 receptors (P1Rs), A1, A2A, A2B and A3, also named adenosine receptors upon their endogenous agonist, are G protein-coupled receptors (GPCRs). The second receptor family, P2 receptors, is further subdivided into G protein-coupled P2Y receptors (P2YRs), and ligand-gated ion channels (LGICs) P2X (P2XRs). Our group is interested in the development of subtype-selective agonists and antagonists for P1, P2Y1, P2Y6, P2Y14, P2X7 and P2X4 receptors, as well as CD73 inhibitors for the treatment of cancer and inflammation. Two projects focusing on the development of CD73 inhibitors and P2X7 receptor antagonists will be presented.

(I) Adenosine displays a strong immunosuppressant effect though adenosine receptor activation and is involved in the immune escape of cancer cells. CD73, overexpressed in the tumour microenvironment, is hydrolysing AMP to adenosine and thus promoting the immunosuppression. Herein, we will present the development of highly potent and selective CD73 inhibitors to circumvent the impact of CD73-generated adenosine and improve a tumour immune response.

(II) The P2X7 receptor (P2X7R) is emerging as a promising target for the treatment of breast cancer, pancreas cancer, colorectal cancer and inflammatory diseases. Herein we will present the development of potent and selective P2X7R ligands as innovative drugs for bioimaging and targeted drug delivery.

References;
Junker A. *et al*., ***J. Med. Chem***., 2016; 59: 6149-6168
Junker A. *et al*., U.S. Patent application No. US 62/233,162 filed September 25, 2015 'Triazole derivatives as P2Y14 receptor antagonists'; filed as PCT on September 26, 2016 HHS E-213-2015/0-PCT-02
Junker A. *et al*., U.S. Patent Application No. 62/719,492 filed August 17, 2018 'Purine and Pyrimidine Nucleotides as Ecto-5'-Nucleotidase Inhibitors'. HHS E-132-2018-0-US-01

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