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Teaser The crucial role of adenosine in modulating immune system activity indicates that adenosine and its receptors are potential drug targets for the development of novel anti-inflammatory agents.

Adenosine and inflammation: what's new on the horizon?

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Adenosine contributes to the maintenance of tissue integrity by modulating the immune system. Encouraging results have emerged with adenosine receptor ligands for the management of several inflammatory conditions in preclinical and clinical settings. However, therapeutic applications of these drugs are sometimes complicated by the occurrence of serious adverse effects. The scientific community is making intensive efforts to design novel adenosine receptor ligands endowed with greater selectivity or to develop innovative compounds acting as allosteric receptor modulators. In parallel, research is focusing on novel pharmacological entities (designated as adenosine-regulating agents) that can increase, in a site- and event-specific manner, adenosine concentrations at the inflammatory site, thereby minimizing the adverse systemic effects of adenosine.

Introduction

Over the years, advances in understanding the cellular and molecular mechanisms underlying the pathophysiology of inflammation have paved the way for the development of emerging classes of anti-inflammatory drugs, which, although improving patient quality of life, have limitations *in terms of efficacy and tolerability* [1,2]. *For these reasons*, the attention of the scientific community is constantly absorbed by the need for identifying novel molecular targets useful for developing innovative anti-inflammatory agents, endowed with more favorable pharmacodynamic/pharmacokinetic properties and an improved safety profile.

An increasing interest is currently being focused on the pharmacological manipulation of endogenous mediators, actively involved in the suppression and/or resolution of inflammation, as viable and innovative anti-inflammatory strategies [3]. Through these research efforts, several

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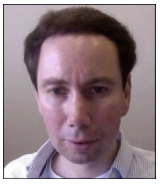

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novel anti-inflammatory and pro-resolutive mediators have been indeed identified. Among them, adenosine represents a powerful and evolutionarily selected modulating factor, which orchestrates the scope, duration and resolution of the inflammatory response through the activation of four specific receptors: classified as A_1, A_{2A}, A_{2B} and A_3, all of which are widely expressed in several immune cells [4–6].

Along these lines, several preclinical and clinical investigations have been designed and implemented to evaluate the potential beneficial effects of adenosine receptor ligands in the management of several inflammatory conditions [i.e. asthma, chronic obstructive pulmonary disorder (COPD), rheumatoid arthritis, psoriasis, sepsis, inflammatory bowel diseases (IBD)], and the results are encouraging [7–9]. However, the therapeutic application of these pharmacological entities remains hindered by the risk of serious cardiovascular adverse effects arising from the wide distribution of adenosine receptors [10,11]. For these reasons, intensive efforts are being currently dedicated to designing novel ligands endowed with greater selectivity as well as developing innovative allosteric modulatory compounds targeting adenosine receptors [12,13]. In parallel, the development of adenosine-regulating compounds that can increase, in a site- and event-specific manner, adenosine concentration within the inflammatory microenvironment represents another attractive field of active investigation [14–18]. This review is intended to discuss the potential therapeutic applications of adenosine receptor ligands and enzyme modulators in the management of inflammation, pointing out the novel perspectives in this field and highlighting possible future directions for the development of innovative drugs.

Adenosine signaling: a complex interplay between enzymes, transporters and receptors

Under basal conditions, nanomolar levels (ranging from 30 to 200 nM) of adenosine can be detected in the extracellular space [19]. From this basal level, the concentration of adenosine can increase, depending on the tissue metabolic demand or the onset of pathological conditions (i.e. inflammation, ischemia) through two mechanisms: (i) intracellular formation and export via nucleoside transporters; (ii) extracellular degradation of adenine nucleotides (ATP and/or ADP) released from several cells [19] (Fig. 1). The intracellular generation of adenosine is also regulated by the cytoplasmic enzyme S-adenosylhomocysteine hydrolase, which converts S-adenosylhomocysteine into adenosine. Once synthesized, adenosine can be delivered into the extracellular environment by means of nucleoside transporters [20] (Fig. 1). Alternatively, intracellular adenosine can undergo rapid deamination via adenosine deaminase or enter the purine nucleotide pool through the activity of adenosine kinase [20] (Fig. 1).

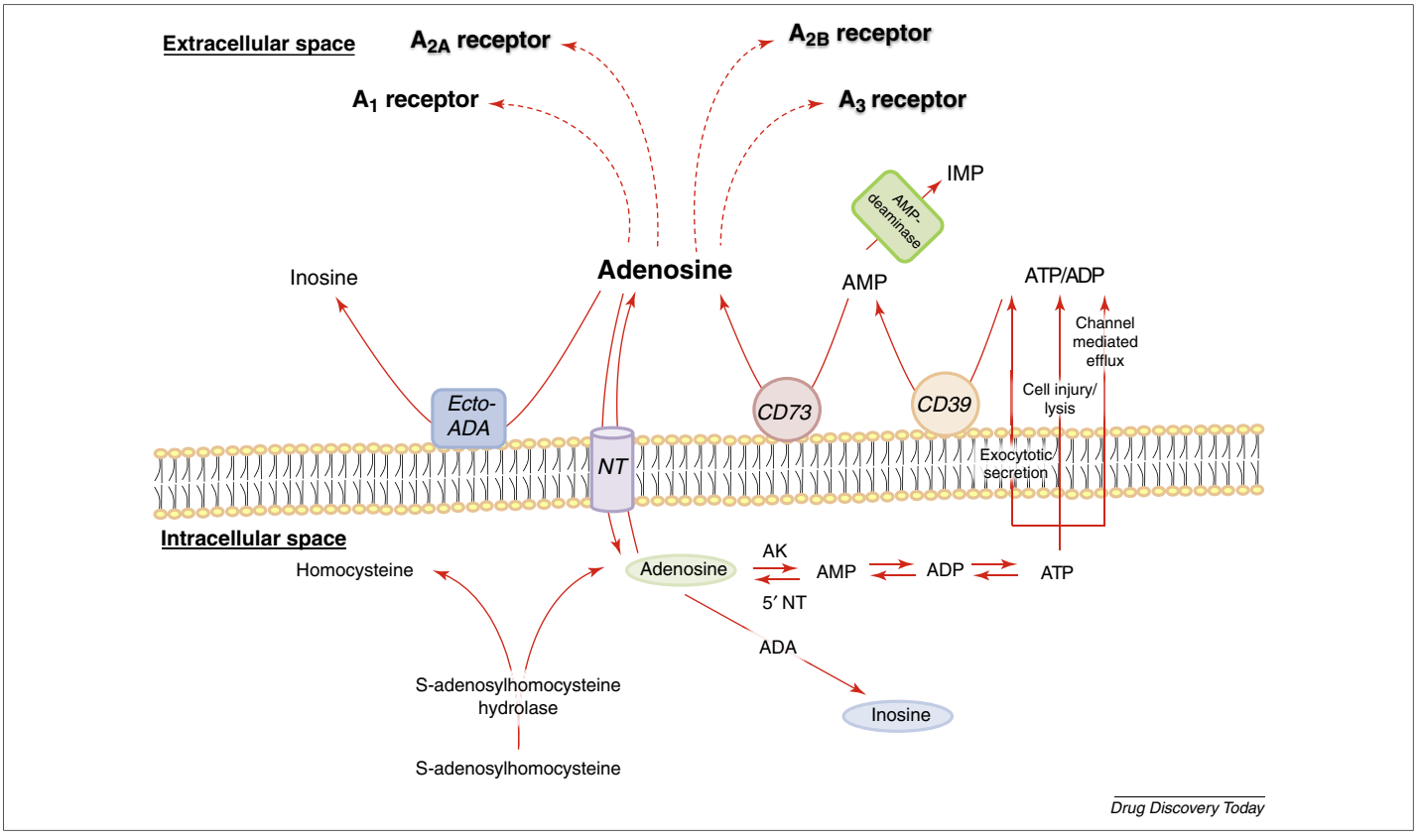

FIGURE 1

Schematic diagram showing the mechanisms that fine-tune the magnitude and/or duration of adenosinergic transmission. Once released into the extracellular environment, through channels, cell injury and/or lysis or other extrusion systems, ATP is degraded by ecto-ATPase (CD39) and ecto-5′-nucleotidase (CD73) into adenosine, which selectively interacts with A_1, A_{2A}, A_{2B} and A_3 receptors. Several cell types are endowed with nucleoside transporters (NT) or ecto adenosine deaminase (ecto-ADA), which operate the uptake or deamination of extracellular adenosine, respectively. After intracellular uptake, adenosine undergoes a rapid phosphorylation to AMP by adenosine kinase (AK), or deamination to inosine by adenosine deaminase (ADA). Abbreviations: ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monosphate; IMP, inosine monophosphate.

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