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RESEARCH HIGHLIGHT

CD73 in autoimmune arthritis

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Adenosine is a potent anti-inflammatory molecule that plays an important role in many diseases. Extracellular levels of adenosine are determined by a combination of membrane transporters and ecto-nucleotidases such as CD73. Therapeutic targeting of the adenosinergic pathway, such as administration of adenosine receptor agonists, could be a valuable approach in the treatment of rheumatoid arthritis (RA). Until recently, the role of CD73 in RA pathogenesis had not been established. Using CD73-deficient gene-targeted mice, we demonstrated that CD73 plays a critical protective role in collagen-induced arthritis (CIA) in mice. Our findings, together with the results of recently published human studies, thus suggests that enhancement of CD73 activity may be a novel therapeutic approach in RA

Keywords: CD73; adenosine; rheumatoid arthritis; collagen induced arthritis

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Rheumatoid arthritis is a chronic, progressive autoimmune inflammatory disease which can have debilitating effects for affected patients and is associated with a decrease in life-expectancy. Many patients at the moment fail to be adequately managed by currently used treatments, which are also associated with significant side effects [1, 2]. Therefore introduction of improved therapeutic regimen is warranted. In this regard, modulation of the adenosinergic system including CD73 may be a novel useful therapeutic approach.

The adenosinergic system is a complex of multiple enzymes, receptors and transporters which regulate the homeostasis of adenosine and its metabolites. Extracellular adenosine is either released from cells or is a product of ATP conversion by two membrane bound or soluble enzymes working in tandem; CD39 (ENTPD1, converting ATP or ADP into AMP) and CD73 (5'-ectonucleotidase, converting AMP into adenosine). CD73 and CD39 have a wide pattern of distribution, with expression detected also on immune cells, endothelial cells, and synovial mesenchymal cells and their expression is upregulated by hypoxia and by pro-inflammatory cytokines [3].

CD73 generated adenosine has been shown to play an important role in the biology of multiple organ systems and in the pathogenesis of multiple diseases, including cancer, infection, autoimmunity and ischemia-reperfusion injury [3, 4, 5]. A key function of adenosine is in the suppression of inflammation. In this context, CD73 and CD39 act as molecular switches, converting a pro-inflammatory ATP rich environment into an anti-inflammatory adenosine rich one.

Adenosine signals through specific G-protein coupled adenosine receptors (A1, A2A, A2B, or A3). The important role of the adenosine mediated A2A receptor signaling in the down-modulation in inflammation has been revealed in A2A receptor knockout mice [6, 7]. The adenosinergic system plays an important role in the regulation of innate immune as well as adaptive immune responses. CD73-generated adenosine negatively regulates T cell responses, essentially through the

A2A receptor on the surface of T cells. CD73-generated adenosine is also important for suppressive activity of regulatory T cells (T-reg) [8]. CD73 further plays a role in leukocyte trafficking across vascular endothelium and its absence results in increased adhesion of leukocytes to endothelium [9].

The therapeutic potential of targeting of the adenosinergic pathway has been assessed in the collagen induced arthritis (CIA) mouse model, a preclinical model which shares many similarities with RA [10]. Administration of A2A and A3 agonists demonstrated benefit [11, 12] in preclinical models and an A3 agonist has been tried in a Phase 2 clinical study, also showing benefit, although not statistically significant [13].

An alternative therapeutic strategy in RA could be to pharmacologically enhance CD73 activity. Increased expression of CD73 on cells from murine arthritic joint cells was therapeutically utilized in a preclinical study in which a CD73-dependent pro-drug demonstrated therapeutic benefit [14]. However, very little has been known about the exact role and importance of CD73 in RA. In order to investigate this question we decided to assess development of CIA in CD73 deficient mice. CD73 deficient mice developed a worse form of the disease, associated with an enhanced Th1 response and enhanced articular inflammation demonstrating that CD73 plays a protective role in CIA [15]. Because this phenotype could be reversed by the administration of a selective A2A receptor agonist, these data suggest that extracellular CD73 enzymatic activity is important to protect against CIA development.

In agreement with this conclusion, in juvenile rheumatoid arthritis a decrease of CD73 on synovial lymphocytes was found, with a more pronounced decrease in patients with more extensive disease [16, 17]. These data indicate that adenosine generation locally in the joint of these patients is compromised and suggest a protective role of CD73 in RA. In our study, we also constructed bone marrow transplantation chimeras in order to assess the role of CD73 on hematopoietic cells versus non-hematopoietic cells in disease development. We observed that CD73 on non-hematopoietic host cells conferred the protective anti-arthritic effect. This phenotype could be a consequence of increased extravasation of leukocytes into tissues in CD73 deficient mice, as has been documented previously [18]. Alternatively, it is possible that CD73 on the surface of non-hematopoietic cells in the joint exerts a protective effect. A possible candidate population in our opinion is synovial mesenchymal stem cells (MSCs). The synovium is a key organ in RA pathogenesis and MSCs have been documented to express very high levels of CD73 [15]. Furthermore, administration of MSCs in multiple, although not all, studies led to amelioration of CIA, and one such a study described that this protective effect is a consequence of CD39 and CD73 activity on these cells [19, 20, 21].

CD73 has previously been shown to regulate the anti-inflammatory effects of methotrexate (MTX), a key RA drug, in a carrageenan air pouch inflammation model [22]. The observations that CD73 adenosine regulates the severity of CIA, and that low levels on joint lymphocytes are associated with more severe form of juvenile RA, raises the question if CD73 is also important for patient clinical response to MTX. A recent publication reported that lack of response to MTX in RA patients is associated with and can even be predicted by decreased levels of CD39 on blood $CD4^+CD25^+$ T-reg cells [23]. Although CD73 levels on these cells were not different between responding and unresponsive patients in this study, this data strongly points to the importance of a functional extracellular adenosine generating pathway for the therapeutic effect of MTX, and establishes CD39 as a biomarker. In view of the low levels of CD73 in the joint of juvenile RA patients, and in view of the fact that more than 35% of these patients fail to respond to MTX, it is possible that downregulation of CD73 at least in this group of patients contributes to the low therapeutic efficacy of MTX.

Taken together, the results of our study combined with observations by others suggest a protective role of CD73 in RA and argue for enhancement of the extracellular adenosinergic pathway, including enhancement of CD73 activity as a novel therapeutic strategy in RA patients.

Conflicting interests

The authors have declared that no competing interests exist.

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Abbreviations

RA: rheumatoid arthritis; CIA: collagen induced arthritis; ATP: adenosine triphosphate; ADP: adenosine diphosphate; AMP: adenosine monophosphate; T-reg: regulatory T cell.

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