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Mini-Review

Targeting adenosine or adenosine receptors as an approach to modulate pathogenic Th17 responses in autoimmune diseases

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ABSTRACT

T cell-mediated autoimmune diseases can be caused by Th1 and/or Th17-type pathogenic T cells. However, whether these two pathogenic T cell subsets are driven by distinctive pathogenic factors and whether treatments found effective for Th1 responses have a similar effect on the Th17 responses remain unknown. We made a systematic comparison of these two pathogenic responses by identifying factors that promote or inhibit either response and by determining the responses to such treatments. Our results demonstrate that the two types of pathogenic response differ fundamentally in pathological progressions and in their susceptibility to treatments. Extracellular adenosine is a critical pathogenic molecule involved in the pathogenicity of inflammation and T cell reactivity. Here we show that aberrant adenosine production plays a major role in augmented Th17 responses in the pathogenesis of autoimmune diseases. The possibility that the potential effect of targeting adenosine or adenosine receptors as an effective approach to modulate pathogenic Th17 responses in autoimmune disease is discussed.

KEYWORDS: autoimmunity, A2AR, adenosine 2A receptor, EAU, experimental autoimmune uveitis, γδ T cells, regulatory T cell, Th17, uveitis.

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INTRODUCTION

The extracellular level of adenosine increases greatly during inflammation, which modulates immune responses. Our recent studies showed that adenosine plays a critical role in the pathophysiological changes of disease, particularly inflammatory diseases. The discovery of the effect of adenosine on inflammation and immune responses has led to attempts to treat immune dysfunctions by targeting adenosine receptor (AR) signaling. In this review we discuss that targeting adenosine or adenosine receptors could be an effective approach to modulate pathogenic T cell responses in autoimmune diseases, particularly the Th17 responses.

Role of adenosine in inflammation

Among research approaches to resolve pathogenic mechanisms of T cell-mediated autoimmune diseases, our recent studies have focused on the role of adenosine. This focus was informed by previous findings that extracellular adenosine is a key regulator of inflammatory responses [1], which affects a wide range of immune cell functions, including lymphocytes [2-4], polymorphonuclear leukocytes [5, 6], NK cells [7], platelets [8], regulatory T cells [9-11] and macrophages/ dendritic cells (DCs) [2, 10, 12, 13]. Clinical trials have been launched manipulating adenosine generation/ binding to treat diseases [14-17].

Under physiological conditions, adenosine triphosphate (ATP) is predominantly an intracellular

molecule, present only at low concentrations in the extracellular space. Various pathological conditions dramatically change the extracellular ATP levels, however. Thus, ischemic conditions, including inflammation, facilitate ATP leakage from the intra- to the extracellular compartment. Here it is degraded to adenosine, under a cascade of enzymatic reactions catalyzed by ectonucleotides. These include CD39 (nucleoside triphosphate diphosphohydrolase-1) and CD73 (5′-ectonucleotidase) [18-20], which modulate immune responses [14, 21-23]. Indeed, many cell types are able to release ATP [24-27].

Although adenosine affects many immune responses [22, 28-30], its effect on the more recently identified Th17 responses has not been adequately examined. This includes the effect of adenosine on γδ T cells, which are important regulators of the Th17 responses [31-33]. We recently reported that adenosine is crucially involved in the function of γδ T cells that regulate Th17 responses, and that reciprocal interactions between adenosine- and γδ T-mediated regulation are important for experimental autoimmune uveitis (EAU) progression [31-33]. We therefore considered the possibility that adenosine might have a strong impact on Th17 responses. Better understanding the influence of adenosine on γδ T cells and their immune-regulatory activity should be helpful in unraveling the pathogenesis of autoimmune diseases and in improving adenosine- and γδ-based immunotherapies [34, 35].

Role of adenosine in Th1 and Th17 pathogenic T cell responses

Over the past three decades, substantial evidence has supported the notion that the major pathogenic T cell subset in autoimmune diseases produces IFN-γ. These cells were designated as Th1 pathogenic T cells [36-43]. Various studies have demonstrated that T cell subsets producing IL-17 are critically involved in disease pathogenesis as well [44-51]. Nevertheless, whether Th1 and Th17 pathogenic T cells are induced by different pathogenic/ environmental factors and whether they respond differently to the same treatment remain largely unknown. Clarification of these issues can be expected to improve the treatment of diseases caused by Th1 and/or Th17 pathogenic responses.

Studies examining the effect of adenosine on T cell responses have mainly focused on Th1 T cells. These studies have demonstrated that adenosine is inhibitory [9, 52]. To determine whether adenosine has a similar effect on Th17 T cells, we employed a well-established model of EAU and studied in parallel Th1 and Th17 responses, both *in vitro* and *in vivo*. Our experiments showed that the net effect of adenosine on Th17 responses is augmenting, in marked contrast to its inhibitory effect on Th1 responses [31, 53-55]. In particular, we assessed the effect of adenosine on T cell activation, under Th1 or Th17-polarizing conditions. We were surprised to observe that αβ and γδ T cells differ greatly in their responses to adenosine and that adenosine enhances γδ T cell activation but inhibits αβ T cell activation [31, 53-55].

Role of adenosine in γδ T cell-mediated immunoregulation

Avoiding autoimmunity and maintaining peripheral immune tolerance requires a functional balance between pathogenic T cells (Teff) and regulatory T cells (Treg) [56]. It is widely accepted that Treg cells promote self-tolerance by suppressing undesired immune responses [57-59]. Studies from mouse models revealed that mice expressing transgenic T cell receptors (TCRs) derived from autoreactive T cells nevertheless kept auto-aggression in check, even in the presence of huge numbers of auto-reactive cells [60, 61]. These data implied that effective albeit tightly controlled regulatory T cells are key to shaping desired immune responses, and that control of regulatory T cells can effectively manipulate autoimmunity. Accordingly, attempts were made to manipulate Treg populations in the treatment of various human pathologies.

Previous work on regulatory T cells has been focused on αβ TCR^+ Tregs [62, 63]. There is strong evidence that $Foxp3^+$ T cells are potent modulators of Th1 responses and that they are critical in maintaining peripheral tolerance [64-69]. The question of whether $Foxp3^+$ Treg cells are also effective regulators of Th17 responses remained unresolved; but the evidence suggests that Th17 responses may not be effectively suppressed by $Foxp3^+$ Treg cells [70-73]. Our previous studies on EAU demonstrated that the $Foxp3^+$ cells are

inhibitory for the Th1 response but have only a limited inhibitory effect on Th17 responses in EAU [70-73]. More recently, the regulatory effect of γδ T cells in autoimmune diseases has received greater attention. Studies from several laboratories [74-78], including ours [79-82], have demonstrated that γδ T cells have a substantial regulatory effect on autoimmune diseases [79-82]. Our investigations of the regulatory γδ T cells revealed that these cells exert a powerful regulatory influence on Th17 responses in EAU, whereas $Foxp3^+$ T cells exhibit only a weak regulatory effect [83].

Role of adenosine in γδ T cell activation

One of our major observations is that activated γδ T cells, but not resting γδ T cells, strongly promote the generation of uveitogenic T cells and the development of EAU [33, 80, 81, 84, 85]. In support of this conclusion we were able to demonstrate that Th17 responses are compromised under conditions in which γδ T cells are functionally defective (TCR-$\delta^{-/-}$ mouse); moreover, administration of activated, but not resting, γδ T cells to TCR-$\delta^{-/-}$ mice restored their disease susceptibility [31, 55, 79, 81, 85, 86]. Therefore, information about how γδ T cells are activated in pathogenic processes, and how this activation affects their pro- and anti-inflammatory activity, should help unravel the mechanism of autoimmune diseases, and particularly of Th17-dependent autoimmunity.

Studies have shown that many factors, including cytokines and Toll-like receptor (TLR) ligands, can activate γδ T cells in the absence of TCR ligation, and increase their proinflammatory effect [80, 85, 87-89]. We investigated the role of adenosine in γδ T cell-mediated immunoregulation [31-33, 55]. Our results show that adenosine is critical for γδ T cell activation and regulation [31, 55, 90]. In support of this, we were able to show that blockade of adenosine receptors on γδ T cells greatly reduced γδ activation and that γδ T cells obtained from A2AR-deficient mice could not be fully activated; so their enhancing effect on Th17 responses was much diminished.

Overall, the effect of adenosine receptor agonists on γδ T cells is stimulatory. In this indirect way, adenosine can augment Th17 responses, despite its propensity to directly inhibit αβ T cell activation. Since extracellular adenosine levels tend to be elevated under pathogenic conditions, we predict that during inflammation, high adenosine levels favor γδ T cell activation and that this effect can be synergistic with pro-inflammatory molecules like cytokines, which are γδ T cell stimulatory as well. However, when γδ T cell activation is prohibited, Th17 pathogenic responses are diminished and likely remain below dangerous levels. Our experiments clearly indicated that overproduction of adenosine is associated with augmented γδ T cell activation, which in turn can lead to augmented Th17 responses.

Reciprocal interactions between γδ T cells and adenosine metabolism

In addition to our observation that adenosine can enhance γδ T cell activation, we found that γδ T cells can enhance adenosine generation and that higher adenosine levels then further promote γδ T cell activation [87]. This ratcheting interaction appears to play an important role in augmented Th17 pathogenic responses.

γδ T cells play a major role in adenosine generation and ATP metabolism [31, 33, 54]. Adenosine is a major metabolite of ATP. A general scenario is that extracellular ATP tends to be proinflammatory; however, when ATP is degraded into adenosine, the suppressive effect of adenosine prevails [83, 91]. Inversely, a high ratio of ATP/adenosine favors enhancement of the immune response [92, 93]. The ecto-5-nucleotide enzyme CD73 is pivotal in the conversion of extracellular immunostimulatory ATP (eATP) into immunosuppressive adenosine [93, 94]. Although the mechanism remains unclear, we repeatedly showed that CD73 expressed on γδ T cells was functionally more active in ATP/adenosine conversion when compared to CD73 expressed by other immune cells, such as $Foxp3^+$ αβ T cells, other αβ T cells, and DCs [31, 33]. We have compared the conversion of adenosine monophosphate (AMP) to adenosine in the presence of various CD73-expressing immune cells, including γδ T cells, αβ T cells and DCs, using High performance liquid chromatography (HPLC) [33]. No adenosine was detectable in the supernatants of αβ or γδ T cells cultured in the absence of exogenously added AMP. However, after the addition of AMP, an adenosine peak was seen in the γδ T cell cultures, but not in the αβ T cell

cultures; this peak was diminished when the CD73 inhibitor α,β-methylene ADP (APCP) was added to the cultures. Since αβ and γδ T cells express comparable levels of CD73 [33], we conclude that CD73 on αβ T cells is less effective in the conversion of AMP into immunosuppressive adenosine.

Adenosine effect on DCs in balancing Th1 and Th17 responses

The adenosine–adenosine-receptor interaction exerts numerous effects on the differentiation, maturation and activation of cells of the mononuclear-phagocyte system [95-102]. Previous studies have shown that adenosine receptor signaling directly inhibits effector functions of T cells and macrophages/ DCs [2, 10, 13, 91, 103-106]. In contrast, our studies revealed that after treatment with adenosine, mouse bone marrow dendritic cells (BMDCs) were better able to promote Th17 autoreactive T cells, even though their ability to promote Th1 cells declined [32, 107]. Likewise, mouse bone marrow cells (BMCs), when cultured in GM-CSF-containing medium with adenosine receptor agonist, differentiated into a unique DC subset with greater Th17-stimulating activity [32]. Additionally, adenosine-treated DCs had a greater γδ T cell-stimulating effect, and thus activated γδ T cells further promoted Th17 responses. We were able to show that adenosine-treated DCs have an increased ability to stimulate γδ T cells; but the effect was only seen when DCs were dually treated with Toll ligands and adenosine, whereas adenosine alone appeared to be ineffective. After exposure to adenosine, the ability of DCs to produce IL-12 was decreased, but their ability to produce IL-23 was increased. Moreover, BMDCs derived from $A2AR^{-/-}$ mice did not show enhanced IL-23 production, indicating that adenosine receptors are important in regulating the capability of DCs to produce factors that promote Th1 or Th17 T cell responses.

Unique role of γδ T cells in adenosine-mediated immunoregulation

The regulatory effect of adenosine on immune responses has been well established [22, 28-30]. The effect of adenosine on many different cell types has been studied, including T cells [2, 3], macrophages/DCs [2, 10, 13], NK cells [7], neutrophils [6], platelets [8], and Tregs [9-11]. Our studies showed that activated γδ T cells have the strongest adenosine-binding capacity, even though adenosine can bind to many immune and non-immune cells [31]. Adenosine-binding tests revealed a hierarchical order of adenosine capture by immune cells with γδ T cells >> αβ T cells >> DCs. Importantly, γδ T cells showed much greater adenosine-binding than DCs or αβ T cells after their activation [108]. Upon activation, the ability of γδ T cells to bind adenosine increased >1000-fold [31], whereas activation of other immune cells, including αβ T and DCs, had little or no effect on their ability to bind adenosine. The increased adenosine binding of γδ T cells is associated with increased expression of adenosine receptor A2 (A2AR) [31]. The massive binding of adenosine to $A2AR^{high}$ activated γδ T cells reduced the availability of adenosine for αβ T cells, releasing them from adenosine suppression and leading to an augmented immune response. All the while, the binding of adenosine to γδ T cells promotes their activation and their ability to increase Th17 responses. In this way, once again, γδ T cell-activation plays an important role in the distribution of adenosine during disease pathogenesis.

Indeed, the enhancing effect of γδ T cells on Th17 responses is based on several pathways, all of which involve adenosine:

1. Adenosine enhances Th17 responses by promoting γδ T cell activation. Activated γδ T cells express at increased levels high-affinity adenosine receptors (A2AR), which can play the role of an "adenosine sink". The increased absorption of adenosine by γδ T cells enhances immune responses that are otherwise inhibited by adenosine, particularly Th17 responses.
2. Adenosine induces a functionally unique DC subset that preferentially activates Th17 cells. The influence of adenosine affects DC differentiation in favor of DCs capable of supporting $Th17^{+}$ pathogenic T cells, and therefore promotes Th17 responses, whereas Th1 responses are suppressed.
3. Adenosine-treated DCs produce more pro-Th17 cytokines and decreased amounts of Th1-promoting cytokines. Previous studies showed that adenosine-treated DCs have a decreased ability to produce IL-12, leading to reduced Th17 responses. However, we were able to show that while the adenosine-treated DCs

produced decreased amounts of IL-12, their production of IL-23 was significantly increased. As a result, the Th17 responses were enhanced. Moreover, adenosine can enhance γδ T cell activation, even though its direct effect on αβ T cells is inhibitory. Consistent activation of γδ T cells is an important step leading to higher Th17 responses.

4. Activated γδ T cells have the highest ability to bind adenosine, and their competition with αβ T cells for adenosine diminishes the effect of adenosine on αβ T cells.

Concluding remarks

Treatments targeting γδ T cells and adenosine/ adenosine receptors have been extensively tested in the laboratory and in clinical trials [14-17]. However, such studies mostly assessed Th1 responses, and have hardly tested Th17 responses. Our experiments showed that while adenosine inhibited Th1 responses, its overall effect on Th17 responses was enhancing [31, 55]. Defining how the inhibiting and enhancing effects of adenosine are generated and determining the mechanisms by which adenosine differentially affects Th1 and Th17 responses, should improve our understanding of disease pathogenesis and provide a solid basis for treating autoimmune diseases.

GRANT INFORMATION

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AUTHORS' CONTRIBUTION

Deming Sun: Formal analysis, Writing – original draft, formal analysis, performed the experiments and analyzed data. Hui Shao: designed research. HK designed research and wrote the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest pertaining to this work.

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