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Connection between γδ T-cell– and Adenosine-Mediated Immune Regulation in the Pathogenesis of Experimental Autoimmune Uveitis

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Abstract

Regulatory effects of γδ T-cells on immune responses have been studied for years. We have investigated the regulatory effect of γδ T-cells on Th1 and Th17 autoimmune responses, and have studied molecular and cellular mechanisms by which γδ T-cells enhance or inhibit immune responses, exploiting a well-characterized murine model of experimental autoimmune uveitis (EAU). Our results show that (1) aberrant γδ T-cell activation is an important pathogenic event in EAU; (2) γδ T-cells have a unique regulatory effect on Th17 autoimmune responses, which is shaped by the activation status of γδ T-cells; and (3) γδ-mediated immunoregulation is closely linked with the extracellular adenosine metabolism. Reciprocal interactions between γδ T-cells and extracellular adenosine partially determine the development of EAU.

Keywords

adenosine deaminase (ADA); autoimmunity; adenosine receptors; experimental autoimmune uveitis; Foxp3; γδ T-cell; regulatory T-cell; Th17; uveitis

I. INNATE IMMUNITY IN AUTOIMMUNE DEVELOPMENT

Recent studies have shown that an effective immune response requires a coordinated interaction between innate and adaptive immunity.[1–6] A rapid innate immune response not only fills the gap in immunologic defense before a fully effective adaptive response is generated; it also determines the pattern and intensity of the subsequent adaptive responses.[5–7]

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γδ T-cells as cellular elements of innate immunity constitute less than 1% of the total lymphocytes in the periphery, but during infection or inflammation their numbers rapidly and dramatically expand within a few days.[8] In mice induced for experimental autoimmune uveitis (EAU), a large portion (> 60%) of peripheral γδ T-cells became activated in early preclinical phases of the disease (one week before its clinical appearance) and subsequently became a strong driving force of induced mouse EAU.[9–11]

Adenosine and its derivatives modulate many physiological processes, including innate and adaptive immunity. Extracellular adenosine levels are low in healthy individuals,[12] but increase 100- to 1000-fold during tissue injury and inflammation.[13] Adenosine reduces inflammation and tissue injury[14–17] by acting on four different types of adenosine receptor (AR): A1R, A2AR, A2BR, and A3R.[13,14] Adenosine is profoundly anti-inflammatory,[14–19] whereas both ATP and ADP are highly proinflammatory.[20–25] Intracellular concentrations of ATP are typically 10^4-fold higher than extracellular concentrations.[26] Under physiological conditions, extracellular ATP (eATP) concentration is kept in the nanomolar range (1–100 nM). During tissue damage, such as ischemia, eATP levels can be elevated by thousands-fold.[27,28] Studies have shown that elevated amounts of eATP trigger immune responses and function as a danger signal that activates the immune system.[22–25] Therefore, eATP is considered proinflammatory— not only by stimulating innate immune responses, but also by favoring effector T-cell activation. Our results have demonstrated that regulation of γδ T-cells in adaptive autoimmunity is associated with adenosine. Hence, a better understanding of the cellular and molecular mechanisms of the interactions between innate and adaptive immunity should allow us to manipulate the specific adaptive immune response more effectively; a rational therapeutic approach needs to take into account the balance between the two types of immune response.

II. REGULATORY EFFECT OF γδ T-CELLS IN AUTOIMMUNE DISEASES

The regulatory effect of γδ T-cells on immune responses has long been acknowledged. Studies have shown that γδ T-cells can either upregulate[29–32] or downregulate [33–35] an immune response. This functional diversity was once attributed to different γδ T-cell subsets expressing distinct T-cell receptors (TCRs).[36–40] Studies also demonstrated that the regulatory activity of γδ T-cells could be shaped by exposure to Toll ligands[41] or mycobacteria.[42] Clinical approaches have been developed to use γδ T-cells as a potential therapeutic modality for cancers[43] and infections[3,4]; however, limited knowledge of their regulatory mechanisms hampers an effective therapeutic application. Our studies using an established EAU model have repeatedly shown that the regulatory ability of γδ T-cells is determined by their activation status and is more effective toward Th17-type than Th1-type immune responses.[10,11,44–10,45] Hence, modulation of γδ T-cell activation status significantly affects immune responses.

III. TH1 AND TH17 PATHOGENIC RESPONSES IN THE PATHOGENESIS OF EAU

Over the past three decades, circumstantial evidence has supported the notion that a major subset of pathogenic T-cells in autoimmune diseases produces IFN-γ and IL-2 and belongs

to the Th1 CD4 T-cell family.[46–53] Recent studies have shown, however, that Th17 cells, which characteristically produce interleukin (IL-) –17A, IL-17F, IL-21, and IL-22, are another major subset of pathogenic T-cells. The finding that Th17 autoreactive T-cells are an important pathogenic T-cell subset in autoimmune diseases[54–56] raised the question of whether they differ from the previously characterized Th1 autoreactive T-cells in pathogenesis[57–61] and regulation.[62,63] On the other hand, studies from transgenic animals have demonstrated that animals can keep autoaggression in check, even in the face of huge numbers of self-reactive cells,[64,65] suggesting that the damaging effect of autoreactive T-cells must be balanced by a counter-reactive regulatory mechanism. Indeed, an aberrant immune response is frequently associated with regulatory cell dysfunction or an imbalance between regulatory and effector T-cells.[66,67] Therefore, extensive studies have investigated how a healthy regulatory cell function is produced and maintained, what causes the imbalance between regulatory and effector T-cells during disease, and what treatment can restore normal functioning. T-cells expressing Foxp3 have been well characterized as major regulatory cells for Th1 responses, but their effectiveness in Th17 autoimmune responses has been questioned.[62,63] Recent findings by our lab[9,10,68,69] and others[1,41,70,71] demonstrated that γδ T-cells have a strong regulatory effect on various, including autoimmune, diseases. Some questions arise: (1) Does γδ T-cell regulation of a given immune response differ from that of its regulation by αβ T-cells? (2) What are the key factors that determine the regulatory effect of γδ T-cells? And (3) What is the cellular and molecular basis of regulation by γδ T-cells in Th1 and Th17 autoreactive responses?

IV. ACTIVATION STATUS DETERMINES THE ENHANCING ACTIVITY OF γδ T-CELLS

One effective way to determine the regulatory effect of γδ T-cells is to compare immune responses between wild-type (WT) C57BL/6 (B6) and genetically compatible TCR-$\delta^{-/-}$ mice, which heritably lack the ability to develop γδ T-cells. Comparison of Th1 and Th17 autoimmune responses in immunized mice, including TCR-$\delta^{-/-}$ mice injected with an effective dose of γδ T-cells, allowed us to define the role of γδ T-cells in the regulation of immune responses. About a week after immunization, approximately 60% of the γδ T-cells found in the periphery of EAU-prone B6 mice expressed CD69 and CD44, whereas γδ T-cells of nonimmunized B6 mice rarely did so. Highly enriched γδ T-cells exert widely different effects on autoreactive αβ T-cells in EAU, depending on their activation status. Whereas nonactivated γδ T-cells (isolated from naïve B6 mice) had little effect on the activation of IRBP-specific αβ T-cells *in vitro* and *in vivo*, activated γδ T-cells (isolated from immunized or naïve B6 mice that had been stimulated with antiCD3 antibodies for two days) promoted generation of uveitogenic T-cells and exacerbated EAU development.[10,11,72] Similarly, TCR-$\delta^{-/-}$ mice injected with activated γδ T-cells generated an approximately fourfold higher percentage of IL-17^{+} IRBP-specific αβ T-cells by comparison with mice that received no injection or those injected with resting γδ T-cells. Notably, when adoptively transferred to naïve recipients, IRBP-specific T-cells from mice injected with activated γδ T-cells, but not from those injected with resting γδ T-cells, induced more severe EAU.

V. MOLECULAR MECHANISM BY WHICH γδ T-CELLS REGULATE TH17 CELLS

To determine whether the enhancing functions of γδ T-cells are associated with the expression of specific surface molecules, and to determine the underlying mechanism by which γδ cells switch their regulatory function, we examined a series of molecules that are differentially expressed on activated versus nonactivated γδ T-cells. We were able to show that, in addition to expressing increased amounts of T-cell activation markers such as CD69, CD44, and CD25, activated γδ T-cells express greatly increased levels of the adenosine A2A receptor (A2AR), which confers on them a greatly increased ability to bind adenosine when compared to other immune cell types such as αβ T-cells and dendritic cells (DCs).[45,73] Interestingly, ligation of A2AR-enhanced γδ T-cell activation, whereas it inhibited activation of αβ T-cells.[73,74] Thus, expression of increased amounts of A2AR enables activated γδ T-cells to bind adenosine more effectively and thereby attenuate adenosine's suppressive effect on αβ T-cells. Moreover, compared to resting cells, activated γδ T-cells express significantly lower levels of CD73,[45,73] an enzyme involved in the generation of extracellular adenosine.[18,75–78] Decreased expression of CD73 results in reduced generation of adenosine at the inflammatory site. Since both A2AR and CD73 molecules are crucially involved in metabolism, function, and the regulatory effect of extracellular ATP and adenosine,[12,13,18] we wondered whether the altered expression of adenosine-related functional molecules accounts for the altered regulatory function of activated γδ T-cells.[45,73,74,79]

VI. ROLE OF ADENOSINE IN γδ ACTIVATION AND REGULATION

ATP is dephosphorylated to ADP, AMP, and, ultimately, adenosine.[12,80] CD39 and CD73 are two well-characterized ectoenzymes involved in the conversion of ATP to adenosine.[75,76] The ecto-5-nucleotide enzyme CD73 is pivotal in the conversion of immunostimulatory ATP into immunosuppressive adenosine by conversion of eATP to adenosine.[75,76] Studies have shown that T-cells expressing higher levels of CD39 and CD73 suppress inflammatory responses through the production of adenosine.[16,17] Note that various immune cells are rich sources of extracellular adenosine, including B-cells,[81] neutrophils,[82] mast-cells,[15] endothelial cells,[82,83] and T-cells.[13] Adenosine affects the functions of many cell types, including T-cells,[77,84] macrophages/DCs,[16,84,85] NK cells,[86] neutrophils,[87] platelets,[88] and regulatory T-cells (Tregs).[16,17,89] Since adenosine affects Treg functions,[17,89–91] we wished to determine whether it also affects the regulatory function of γδ T-cells. Moreover, even though γδ T-cells are a major cell element in inflamed organs and tissues,[92–94] the connection between adenosine and γδ T-cells has remained largely unknown.

γδ T-cells can be activated via multiple pathways, such as cytokines and TLR ligands,[95–98] even in the absence of γδ TCR ligation. We were able to show that purified γδ T-cells can be activated by a number of proinflammatory cytokines, and that a mixture of IL-1, IL-7, and IL-23 has a strong stimulatory effect.[11] Although adenosine does not directly stimulate γδ T-cell activation, it significantly enhances activation induced by the cytokine mixture, an effect that can be blocked by the A2AR antagonist.[73] This activation of γδ T-cells leads to

augmented Th17 responses,[10,11,45] and the net effect of adenosine in Th17 responses is enhancing whereas its effect on Th1 response is mainly suppressive.[16,45,99–103] The fact that adenosine inhibits Th1 autoreactive T-cell response but enhances γδ T-cell and Th17 autoreactive T-cell response reveals that this molecule plays an important role in switching and balancing between Th1 and the Th17 responses in autoimmune pathogenesis.[73,74,79]

VII. γδ T-CELLS ACTIVELY PARTICIPATE IN THE CONVERSION OF EXTRACELLULAR ATP TO ADENOSINE

Our studies demonstrated that adenosine-mediated immunoregulation and γδ T-cell–mediated immunoregulation are intimately linked in EAU pathogenesis. In addition to the fact that adenosine affects the activation of αβ and γδ T-cells, γδ T-cells strongly influence extracellular ATP metabolism and adenosine generation[73,79] as well as adenosine function.[45,73,74,79] As we reported previously,[104] $CD73^+$ γδ T-cells are much more potent in converting AMP to adenosine compared to other $CD73^+$ immune cells, including $Foxp3^+$ αβ T-cells when tested in the pathogenesis of mouse EAU.[45,73]

Moreover, γδ T-cells express different amounts of CD73 during the different stages of EAU.[45] Changes in the expressed level of CD73 are correlated with the “switch” of pro- to anti-inflammatory activities of γδ T-cells in the regulation of Th17 autoimmune responses,[45] and low CD73 expression on γδ T-cells favors their enhancing effect on Th17 autoimmune responses.[45] These results suggest the possibility of modulating Th17 autoimmune responses by manipulating CD73 expression on γδ T-cells.

VIII. ROLE OF CD73 IN γδ T-CELLS’ REGULATORY FUNCTION

CD39 and CD73 in combination degrade ATP, ADP, and AMP to adenosine and have been viewed as “immunological switches” that shift ATP-driven proinflammatory immune cell activity toward an anti-inflammatory state mediated by adenosine.[76] Reduced CD73 expression decreases the conversion of AMP to adenosine, thus contributing to immune activation,[105] whereas cells that express higher levels of CD39 and CD73 may act to suppress inflammatory responses through the production of adenosine.[16,17]

Alteration of the CD39/CD73 machinery can disrupt the complex mechanisms underlying immune tolerance to self-antigens, driven mainly by Tregs, thus contributing to the development of several autoimmune diseases.[106] It has been reported that CD39 is expressed on human and murine Tregs but that CD73 is found on the surface of murine Tregs only.[90,107] Increased ATP-metabolizing activity appears to be critical for Treg immunosuppressive activity.[108]

IX. ROLE OF EXTRACELLULAR ATP/ADENOSINE METABOLISM AND ADENOSINE-MEDIATED IMMUNOREGULATION IN γδ REGULATION

We previously reported that $CD73^+$ αβ T-cells possess limited ability to convert AMP to adenosine as compared to $CD73^+$ γδ T-cells,[73] suggesting that the latter are the preeminent adenosine-converting cells among $CD73^+$ immune cells.[45,73] Moreover, γδ T-cells express

different amounts of CD73 during the different stages of EAU, and the enhancing activity of γδ T-cells correlate with decreased expression of CD73. γδ T-cells express different amounts of CD73 when activated by different pathways, enabling them to either enhance or inhibit an adaptive immune response.[45,73] Thus, activation of γδ T-cells alters not only adenosine-mediated immunoregulation but also adenosine metabolism. Our studies on isolated γδ T-cells from $CD73^{+/+}$ (WT-B6) and $CD73^{-/-}$ mice showed that failure to express CD73 greatly reduces both the enhancing and suppressive activities of γδ T-cells[45,73]; low CD73 expression on γδ T-cells correlates with enhanced Th17 response–promoting activity; and CD73 expressed on γδ T-cells is more functionally active than that expressed on αβ T-cells. Thus, ATP/adenosine metabolism plays a significant role in the interconversion of the enhancing and suppressive effects of γδ T-cells, and CD73 expressed by γδ T-cells is important in this process. These results demonstrate that the mechanisms involved in the proinflammatory effect of activated γδ T-cells in Th17-mediated autoimmune responses include both binding of adenosine by activated γδ T-cells and decreased CD73 expression on activated γδ T-cells. Further studies on the role of adenosine in inflammation and immune responses should result in improved immunotherapies based on adenosine and γδ T-cells.

X. ACTIVATED γδ T-CELLS ENHANCE IMMUNE RESPONSES BY EXPRESSION OF HIGH LEVELS OF A2AR

Extracellular adenosine, acting via A2AR, is an important negative regulator of T-cell development and function.[14,16,17,77] The importance of A2AR in mediating immunoregulation has been demonstrated in A2AR-deficient ($A2AR^{-/-}$) mice, whose inability to control inflammation leads to fatal tissue destruction.[14,109] Adenosine generated in injured tissue is destroyed by enzymes, mainly adenosine deaminase (ADA). Serum adenosine levels are significantly increased in $ADA^{-/-}$ mice, whereas levels of downstream products of ADA-mediated adenosine conversion, such as hypoxanthine, are significantly reduced.[110] Mice genetically deficient in ADA display altered inflammation.[14,109] Immune dysfunction, including autoimmune and allergic diseases, has been frequently observed in humans and rodents with ADA dysfunction.[111,112]

Many immune cell types have been studied in an effort to determine which is most affected by adenosine; these include T-cells,[77,84,113–115] macrophages/DCs,[16,116,117] NK cells,[86] neutrophils,[87,118] platelets,[88] and Tregs.[16,17,89] To determine whether A2AR is instrumental in the regulatory function of γδ T-cells, we isolated γδ T-cells from $A2AR^{-/-}$ ($A2AR^{-/-}$ γδ) and B6 mice ($A2AR^{+/+}$ γδ), and compared their enhancing and inhibiting function. We were able to show that $A2AR^{-/-}$ γδ T-cells lose their Th17-enhancing activity; likewise, $A2AR^{+/+}$ γδ T-cells lose their Th17-enhancing activity after treatment with an A2AR antagonist, suggesting that expression of increased amounts of A2AR allows γδ T-cells to bind adenosine and thereby attenuate its suppressive effect.

Comparisons between activated and nonactivated γδ T-cells showed that activated γδ T-cells expressed greatly increased levels of A2AR in addition to increased amounts of T-cell activation markers such as CD69, CD44, and CD25.[73] Importantly, using a binding assay,

we were able to show that activated γδ T-cells bind far more adenosine than other immune cells.[73] Increased expression of adenosine A2AR allows γδ T-cells to competitively bind adenosine in inflamed tissue, thus preventing its suppressive effect on αβ T-cells. A strong binding of adenosine by activated γδ T-cells represents more than a "sink"; for example, it enhances γδ activation and the expression of A2AR increases γδ activation,[73] rendering them more competitive in adenosine binding. Since activated γδ T-cells have a strong ability to enhance Th17 response, their binding of adenosine may also weaken the suppressive effect of adenosine on αβ T-cells, leading to enhanced immune response.[45,73] Our finding, that the effect of A2AR agonist on γδ T-cells is stimulatory rather than inhibitory, seems opposite to others' findings concerning A2AR agonists on other immune cells,[3,6,9–11] which is attributed to the high levels of A2AR in γδ T-cells. Expression of increased amounts of A2AR likely allows γδ T-cells to bind adenosine and thereby attenuate its suppressive effect.

XI. CONCLUDING REMARKS

The orchestration and modulation of inflammatory response in injured tissues by a number of regulatory mechanisms is quite sophisticated. Our studies showed that γδ T-cells have a strong regulatory effect on autoimmune responses, particularly Th17 types. Whereas the regulatory effect of γδ T-cells and that of extracellular ATP/adenosine metabolism in immune responses are well known, their intimate connection has yet to be completely elucidated and the cellular and molecular basis of this type of regulation has remained mostly unclear. We have made progress by demonstrating that γδ-mediated and adenosine-mediated immunoregulation are intimately linked. The outcome of studies such as ours should improve current available therapies, including those based on adenosine and γδ T-cell.

The studies summarized here are mostly derived from observations in a EAU mouse model, in which a dominant $V\gamma4^+$ γδ T-cell response is noted,[44,68] whereas in this experimental model $V\gamma1^+$ γδ T-cells remain mostly nonactivated.[44] Given that $V\gamma1^+$ γδ T-cells are dominantly activated in many infectious disease models,[119–124] and the dominant responses of γδ T-cell subsets expressing distinct TCR segments remain unclarified, further studies should determine whether all γδ T-cell subsets work essentially in the same way.

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ABBREVIATIONS:

ADA	adenosine deaminase
A2AR	adenosine A2A receptor
AR	adenosine receptor
EAU	experimental autoimmune uveitis

eATP	extracellular ATP
IRBP	interphotoreceptor retinoid-binding protein

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