Human γδ T Cells and Immune Regulation

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Abstract: Human γδ T cells appear to belong to non-classical T cells with both innate and adaptive immune features. Vγ2Vδ2 (also termed Vγ9Vδ2) T cell subset exists only in primates, and in humans that represents a major γδ T cell subpopulation in the blood. Vγ2Vδ2 T cells remain to be the only γδ T cell subpopulation that can recognize a well-defined foreign microbial phosphoantigen. This article reviews the recent progress in our understanding immune regulation of Vγ2Vδ2 T cells.

Keywords: Immune regulation, $CD4^+CD25^+Foxp3^+$ regulatory T cells, γδ T cells, phosphoantigen, HMBPP, HIV/AIDS, tuberculosis.

INTRODUCTION

γδ T cells are a minor cell population in the T cell pool. Unlike adaptive αβ T cells, γδ T cells have been long considered innate immune cells due to the historical absence of antigen-mediated major clonal expansion and recall immune responses in infection or re-infections. However, accumulating experience suggests that human γδ T cells function as non-classical T cells and contribute to both innate and adaptive immune responses in infections [1, 2]. Vγ2Vδ2 (also termed Vγ9Vδ2) T cells exist only in primates, and in humans represent a major circulating γδ T-cell subset that normally constitutes up to 65-90% of total peripheral blood γδ T cells. Since macaque Vγ2Vδ2 T cells resemble their human counterparts, in-depth studies in nonhuman primates have been undertaken to understand biology and function of human Vγ2Vδ2 T cells. While much progress has been made to understand immune recognition of nonpeptide ligands by human γδ T cells, studies demonstrate that Vγ2Vδ2 T cells can undergo major clonal expansion in infections, and mount rapid recall-like expansion after mycobacterial re-infection [1]. Here, I review the recent progress in human and nonhuman primate studies for our understanding immune regulation of human γδ T cells. I will focus on the following areas: (i) immune regulation dictating molecular interaction of Vγ2Vδ2 T cells with naturally-occurring microbial phosphoantigen; (ii) innate and adaptive features of Vγ2Vδ2 T cells in infections; (iii) unique ability of Vγ2Vδ2 T cells to traffic to and accumulate in lungs, and their effector function; (iv) Vγ2Vδ2 T effector cells and their immune regulation antagonizing CD4+CD25+Foxp3+ T regulatory cells (Treg) and Treg-driven suppression of antigen-specific αβ T-cell immune responses.

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IMMUNE REGULATION DICTATING Vγ2Vδ2 T CELL RECEPTOR INTERACTION WITH NATURALLY-OCCURRING PHOSPHOANTIGEN HMBPP

Human γδ T cells appear to belong to non-classical T cells with both innate and adaptive immune features [3-6]. It is important to note that primate Vγ2Vδ2 T cells remain the only γδ T-cell subset that can recognize a foreign microbial phosphoantigen. If Vγ2Vδ2 T cells contribute to adaptive immune responses and thus are not simply innate cells, one would imagine that Vγ2Vδ2 T cell receptor (TCR) binding to microbial antigen complex would be immunologically regulated by an elegant mechanism. This notion is supported by a line of evidence provided by a number of laboratories. It has been well known that Vγ2Vδ2 T cells can be activated by certain low m.w. foreign- and self-nonpeptidic phosphorylated metabolites of isoprenoid biosynthesis [e.g. (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP), isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP)] [7-11] commonly referred to as phosphoantigens. HMBPP is produced in the 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway of isoprenoid biosynthesis of most eubacteria, apicomplexan protozoa, plant chloroplasts and algae [1]. While the chemistry of phosphoantigens and their ability to activate Vγ2Vδ2 T cells have been well described, little is known about molecular mechanisms by which HMBPP interacts with γδ T cells [12, 13]. Most studies done to date have been focused on prenyl pyrophosphates particularly IPP, but rarely the naturally-occurring microbial phosphoantigen HMBPP [12, 14]. Earlier experiments using Vγ2Vδ2 T-cell activation as readouts demonstrated that IPP does not need to undergo cell-entry or processing and that phosphoantigen activation of Vγ2Vδ2 T cells requires cell-cell contact [12, 15]. A putative molecule, but not MHC class I, class II, CD1, appears to be required to present IPP for immune activation of Vγ2Vδ2 T cells [12]. Despite decade-long studies, however, there has been no direct evidence indicating that human or macaque Vγ2Vδ2 TCR (instead of human-

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INNATE AND ADAPTIVE FEATURES OF Vγ2Vδ2 T CELLS IN INFECTIONS

Accumulating evidence suggests that Vγ2Vδ2 T cells possess both innate and adaptive immune features [21-24]. The finding that "unprimed" Vγ2Vδ2 T cells can recognize and react to wide ranges of nonpeptide phospholigands with the capability of "naïve" production of cytokines has been interpreted as a pattern-recognition-like feature of innate immune cells. On the other hand, the capacity of Vγ2Vδ2 T cells to undergo major clonal expansion in primary infection and to mount rapid recall-like expansion upon re-infection has been proposed as adaptive (memory-type) immune response of these γδ T cells [24]. Consistent with these memory-type responses is the demonstration of memory phenotypes of Vγ2Vδ2 T cells in the blood of humans [25], long-term expansion of memory-like Vδ2 T cells and *in vitro* recall expansion of blood γδ T cells in vaccinated or infected humans [26-29]. Interestingly, while AIDS virus infection suppresses primary and recall-like expansion of Vγ2Vδ2 T cells, anti-retroviral therapy can indeed restore the capacity of Vγ2Vδ2 T cells to undergo recall-like expansion during active mycobacterial re-infection [30, 31].

With synthetic phospholigands available for *in vivo* treatment, innate versus adaptive features of Vγ2Vδ2 T cells have been re-visited. While *in vivo* phospholigand or HMBPP treatment in combination with IL-2 has been shown to induce remarkable expansion of Vγ2Vδ2 T cells in nonhuman primates [32-34], repeated treatments with phosphostim plus IL-2 can induce re-expansion of Vγ2Vδ2 T cells each time, but not necessarily stimulate greater magnitudes of recall expansion each time after the treatment [33]. While this finding cannot rule out the possibility that Vγ2Vδ2 T cells can contribute to adaptive immune responses in infections, it certainly suggests that Vγ2Vδ2 T cells do not exactly resemble their αβ T cell counterpart mounting the typical recall or memory responses in response to the simple treatment comprised only of very small phospholigand molecule and IL-2. One of the explanations is that the initial phospholigand and IL-2 treatment has already reached the maximum activation/expansion potential of Vγ2Vδ2 T cells, and subsequent treatments will not be able to go beyond the saturated points.

Expansion and recall-like expansion of Vγ2Vδ2 T cells *in vivo* and *in vitro* after primary and secondary microbial infection may be driven by some other host and microbial factors, but not simply only by phosphoantigen and IL-2. Interaction or cross-talk between APC, particularly DC, and Vγ2Vδ2 T cells may confer upon these γδ T cells some capability to undergo major expansion or recall-like expansion during infection and re-infection [35]. Moreover, some cytokines may contribute to the development of adaptive immune responses of Vγ2Vδ2 T cells in infections. This scenario is supported by the studies from us [36] and others [37]. We found that *M. tuberculosis* and BCG infections of macaques induced major expansion of Vγ2Vδ2 T cells and coincident expression of variant IL-4 (VIL-4) mRNA encoding a protein comprised of N-terminal 97 amino acids (a.a.) identical to IL-4, and unique C-terminal 96 a.a. including a signaling-related proline-rich motif. We then expressed and purified VIL-4 to test the possibility that this variant cytokine can contribute to major expansion of Vγ2Vδ2 T cells. The purified VIL-4 induces apparent expansion of phosphoantigen HMBPP-specific Vγ2Vδ2 T cells at dose- and time-dependent manners [36]. The unique C-terminal 96 a.a. bearing the proline-rich motif (PPPCPP) of VIL-4 appear to confer the ability to expand Vγ2Vδ2 T cells, since simultaneously produced IL-4 has only subtle effect on these γδ T cells. Moreover, VIL-4 seems to utilize IL-4 receptor α for signaling and activation, as the VIL-4-induced expansion of Vγ2Vδ2 T cells can be blocked by anti-IL-4R α mAb but not anti-IL-4 mAb [36]. Surprisingly, VIL-4-expanded Vγ2Vδ2 T cells after HMBPP stimulation appear to be heterologous effector cells capable of producing IL-4, IFN-γ and TNF-α [36]. Thus, mycobacterial infections of macaques induced variant mRNA encoding VIL-4 that functions as growth factor promoting expansion of HMBPP-specific Vγ2Vδ2 T effector cells [36]. We presume that other cytokines may also exert similar effects facilitating major expansion of Vγ2Vδ2 T cells during mycobacterial infections. In fact, it has been reported that IL-21 can also stimulate marked expansion of HMBPP-specific Vγ2Vδ2 T cells [37].

UNIQUE ABILITY OF Vγ2Vδ2 T CELLS TO TRAFFIC AND ACCUMULATE IN LUNGS, AND THEIR EFFECTOR FUNCTION

Most pathogens invade through mucosae resulting from airborne, oral or sexual-associated transmission. Recruiting immune cells to mucosal interface or infected tissues is therefore an important defense mechanism for immune control of infection. While chemoattraction of leukocytes during inflammation has been well studied, tissue trafficking and localization of antigen-specific γδ T cells in immune responses to infecting microbes remain understudied. Our serial *in vivo* studies have allowed us to address these issues. Our earlier studies demonstrated that rapid recall-like increases in numbers of Vγ2Vδ2 T cells can be seen in bronchoalveolar lavage fluid following *M. tuberculosis* aerosol challenge of BCG-vaccinated monkeys [1, 30]. These increases are associated with an inflammatory cell response characterized by increased numbers of neutrophils and macrophages in BAL fluid. The accumulation of Vγ2Vδ2 T cells in the lung is likely due to recruitment of these cells from the peripheral blood or lymphoid tissues, not due to local clonal expansion, after *M. tuberculosis* challenge. Interestingly, increases in numbers of Vγ2Vδ2 T cells are also apparent in pulmonary and intestinal mucosae in pulmonary and intestinal mucosae when an expansion of these cells is seen in the blood of monkeys inoculated intravenously with BCG [1, 30]. This increased number of Vγ2Vδ2 T cells is particularly marked in the lung despite the fact that BCG loads in the lung are undetectable or extremely low. In addition, no apparent inflammation can be seen in the pulmonary compartment following intravenous BCG inoculation. Surprisingly, greater increases in numbers of Vγ2Vδ2 T cells than αβ T cells are evident in the lung of the monkeys intravenously inoculated with BCG [1, 30]. These results suggest that there may be a preferential migration of activated Vγ2Vδ2 T cells to the lung from the circulation or lymphoid tissues after mycobacterial infection.

More recently, we have undertaken in-depth studies to assess phosphoantigen-specific Vγ2Vδ2 T cells regarding their tissue distribution, anatomical localization, and correlation

responses and monocyte differentiation to DC, and facilitate development CD4 T helper cells in the presence of additional microbial stimulants [35]. We presume that HMBPP activation of Vγ2Vδ2 T cells may also have direct impact on other T cell populations *in vivo* during infections or vaccination. Virtually, we have recently initiated *in vivo* studies to investigate the interplay between CD4+CD25+ Foxp3+ T regulatory cells (Treg) and HMBPP-activated Vγ2Vδ2 T effector cells during mycobacterial infection.

Foxp3+ Treg control immune responses to self- and foreign-antigens and play a major role in maintaining the balance between immunity and tolerance [46-49]. Treg have been shown to broadly suppress activation, proliferation and/or effector functions of various immune cell populations such as conventional $CD4^+$ and $CD8^+$ T cells [50], NK T cells [51], B cells [52], dendritic cells [53], monocytes/ macrophages [54], neutrophils [55], and mast cells [56]. Depletion of CD4+CD25+ T cells induces effective anti-tumour immunity, enhances immune responses to invading microbes, triggers allergic responses to innocuous environmental substances [46]. However, T cell subsets capable of antagonizing Treg and their function have not been demonstrated. Development of a useful model system may help to identify potential mutual regulatory effects of Treg and other immune cells or elements. Interestingly, recent studies have shown that human recombinant IL-2 administration can lead to an increase in the frequency of circulating CD4+CD25+ regulatory T cells in cancer patients [57-60]. We and others have also shown that IL-2 plus phospholigand treatment can induce remarkable expansion of Vγ2Vδ2 T cells in nonhuman primates [32-34]. We therefore took advantage of the IL-2-based *in vivo* model systems to assess potential interplay or mutual regulations between Vγ2Vδ2 T cells and Treg during early mycobacterial infection in nonhuman primates.

A short-term IL-2 treatment regimen induced marked expansion of $CD4^+CD25^+Foxp3^+$ T cells and subsequent suppression of mycobacterium-driven increases in Vγ2Vδ2 T cells in acutely BCG-infected macaques. Surprisingly, activation of Vγ2Vδ2 T cells by adding phosphoantigen Picostim (similar to HMBPP) to the IL-2 treatment regimen apparently down-regulates IL-2-induced expansion of

Fig. (3). A five-day IL-2 administration regimen induced an apparent expansion of $CD4^+CD25^+Foxp3^+$ T cells (Treg) in PBMC; adding Picostim to the IL-2 treatment regimen induced Vγ2Vδ2 T cell expansion and down-regulated IL-2-induced increases in numbers of Treg in BCG-infected macaques. (**a**) Changes in percentage and absolute numbers of $CD4^+CD25^+Foxp3^+$ T regulatory cells in PBMC of three groups of monkeys (BCG; BCG + IL-2; BCG + IL-2+Picostim) over time after treatment/infection. Shown are the mean values with SEM from 6 monkeys for each group. ** $P < 0.01$; * $P < 0.05$ for differences between BCG +IL-2 and BCG groups and between BCG +IL-2 and BCG +IL-2. (**b**) Changes in percentage and absolute numbers of Vγ2Vδ2 T cells in PBMC of three groups of monkeys (BCG; BCG + IL-2; BCG + IL-2+Picostim) over time after treatment/infection. ** $P < 0.01$; * $P < 0.05$ for differences between BCG+IL-2 and BCG groups, and between BCG+IL-2+Picostim and BCG groups or BCG+IL-2+Picostim and BCG +IL-2 groups. Note that IL-2-induced expansion of T reg (**a**) led to subsequent suppression of BCG-induced expansion of Vγ2Vδ2 T cells at days 21-42 (* $P < 0.05$ for differences between BCG +IL-2 and BCG groups as well as BCG+IL-2 and BCG+IL-2+Picostim groups at days 21 and 28).

$CD4^+CD25^+Foxp3^+$ T cells (Fig. **3a**, **b**, [41]). The down-regulation of IL-2-induced expansion of Treg leads to the sustained increases in numbers of Vγ2Vδ2 T cells through 42 days after the Picostim/IL-2 treatment and superimposed BCG infection. Consistently, *in vitro* activation of Vγ2Vδ2 T cells in PBMC by phosphoantigen+IL-2 can down-regulate IL-2-induced expansion of $CD4^+CD25^+Foxp3^+$ T cells, but HMBPP-mediated antagonizing effect appears to require APC (monocytes) or other lymphocytes [41]. Since activated Vγ2Vδ2 T cells alone had no inhibiting effect on $CD4^+CD25^+Foxp3^+$ T cells in the culture without APC and other cells in PBMC, we sought to determine whether some cytokines produced by phosphoantigen-activated Vγ2Vδ2 T cells contributed to the down-regulation of the IL-2-induced proliferation of T reg. We set up cytokine-neutralizing experiments in the proliferation assays using anti-IFN-γ, anti-IL-4, or anti-TGF-β neutralizing antibodies because HMBPP phosphoantigen stimulation could up-regulate many genes including those encoding these cytokines (Wang *et al*, data not shown). Surprisingly, while anti-TGF-β or anti-IL-4 neutralizing antibodies did not affect the HMBPP-mediated down-regulation of Treg, anti-IFN-γ neutralizing antibody significantly reduced the ability of HMBPP-activated Vγ2Vδ2 T cells to antagonize Treg expansion [41]. This suggests that IFN-γ and its network contributed to Vγ2Vδ2 T cells' antagonizing effects. Furthermore, activation of Vγ2Vδ2 T cells by Picostim+IL-2 treatment appears to reverse Treg-driven suppression of immune responses of phosphoantigen-specific IFNγ+ or perforin+ Vγ2Vδ2 T cells and PPD-specific IFNγ+ αβ T cells [41]. Thus, phosphoantigen-activation of Vγ2Vδ2 T cells antagonizes IL-2-induced expansion of Treg and subsequent suppression of and anti-microbial T-cell responses in mycobacterial infections. The findings from phosphoantigen/IL-2 treatment of macaques in the context of mycobacterial infection provide the first evidence suggesting that certain T-cell subsets in the immune system can antagonize Foxp3+ Treg and their suppression of microbe-specific T-cell immune responses in infections.

In conclusion, much progress has been made for understanding immune regulation of phosphoantigen-specific human γδ T cells. Since polyfunctional human γδ T cells can be readily expanded by phosphoantigen/IL-2 treatment regimens, future γδ T-cell research will elucidate mutual regulation or cross-talks between human γδ T cells and other immune cells in the context of infection and immunity. The field is also in the position to test hypothetical broad functions of Vγ2Vδ2 T cells in infections and cancers.

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ABBREVIATIONS

Foxp3 = Forkhead/winged-helix box p3

IL = Interleukin

HMBPP = (E)-4-hydroxy-3-methyl-but-2-enyl diphosphate

Picostim (HDMAPP) = HydroxyDimethylAllylPyro Phosphonate

BCG = *Mycobacterium bovis* bacille Calmette-Guerin

TCR = T cell receptor

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