Gamma-Delta T Cells

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Recent advances in γδ T cell biology have focused on the unique attributes of these cells and their role in regulating innate and adaptive immunity, promoting tissue homeostasis, and providing resistance to various disorders. Numerous bacterial and viral pathogens, including human immunodeficiency virus-1 (HIV), greatly alter the composition of γδ T cells *in vivo*. Despite the effectiveness of antiretroviral therapy (ART) in controlling HIV and restoring health in those affected, γδ T cells are dramatically impacted during HIV infection and fail to reconstitute to normal levels in HIV-infected individuals during ART for reasons that are not clearly understood. Importantly, their role in controlling HIV infection, and the implications of their failure to rebound during ART are also largely unknown and understudied.

Gamma-Delta T Cells,γδ T cells,Human Immunodeficiency Virus

1. Introduction

Although conventional alpha-beta (αβ) T cells have been studied intensively as a current “known” in the field of immunology, with the basis of their recognition of processed peptides in the context of MHC molecules being well-understood, far less attention has been paid to gamma delta (γδ) T cells. This is in part due to their relatively limited numbers in the blood and spleen, and because they reside primarily in tissues less readily accessible for study. They have important early innate immune functions, recognizing relatively conserved pathogen-associated molecules, simple metabolites, and stress ligands expressed on infected and transformed cells. They can mount rapid and direct cytolytic responses while producing cytokines and chemokines to promote the function and mobilization of other immune effector cells [1]. They are widely distributed throughout the body [2], particularly within epithelial sites, and have the capability to recognize a variety of self-, as well as non-self-antigens without regard to MHC constraint. Their prospective utilization or strategic targeting in novel immunotherapeutic approaches to treat a variety of chronic diseases is quite attractive. This is especially true in instances where classical αβ T cell immune escape may be of particular concern. However, because their frequency and function can be severely altered in the setting of diseases such as HIV, and because there are still so many “unknowns” regarding the basic biology of γδ T cells in health and disease, there are hurdles to be addressed before their therapeutic potential can be fully appreciated.

2. γδ T Cells in HIV-1 Infection

While γδ T cells have been described to provide protective immunity against tumors of epithelial [3][4] and hematological origin [5][6], they have also been explored in the setting of various chronic viral [7][8][9][10][11] and

bacterial diseases [12][13], as well as malaria [14][15]. Furthermore, γδ T cells contribute to the pathogenesis and regulation of autoimmune diseases, including rheumatoid arthritis and psoriasis [16][17]. For the remainder of this paper, we have chosen to focus our attention on the function of these cells in the setting of chronic HIV-1 infection, and to shed some light on the immunotherapeutic potential of γδ T cells for the treatment of HIV/AIDS.

2.1. Impact of HIV on γδ T Cells

In healthy individuals, Vγ9Vδ2 T cells contribute to 90–95% of the total γδ population in the peripheral blood, and the remaining 5–10% are $Vδ2^{neg}$, such as Vδ1 and Vδ3s [18]. In HIV-infected individuals, Vγ9Vδ2 T cells are drastically depleted, and the Vδ2:Vδ1 ratio is inverted in peripheral blood [18]. Interestingly, Vγ9Vδ2 cell depletion occurs very early during the infection and correlates with viral load and CD4+ T cell depletion [19]. HIV preferentially depletes phosphoantigen responsive Vγ9Vδ2 cells with Vγ9-Jγ1.2 TCR rearrangement [20]. Although the precise mechanism of depletion of Vδ2 cells in HIV-infected individuals is not understood, some studies indicate that α4β7 and CCR5 receptors form a complex on Vγ9Vδ2 cells, which facilitates the binding of the bV3 loop of HIV gp120 to CCR5 in the absence of expression of the CD4 co-receptor. This interaction leads to p38 kinase activation and induces apoptosis in these cells [21]. Additionally, HIV infection leads to loss of Th17 CD4+ T cells, important for maintaining epithelial barrier integrity in the gut [22]. Depletion results in dysregulation of mucosal immunity and allows microbial translocation into the circulation, resulting in systemic immune activation [23] and expansion of Vδ1 cell numbers in viremic patients [24]. Moreover, the Vγ9Vδ2 subset from HIV-infected individuals fails to proliferate or produce cytokines in response to mycobacterial infection in vitro, suggesting that Vγ9Vδ2 cells are functionally inactive [25]. This functional anergy in residual Vγ9Vδ2 cells is also characterized by their decrease in responsiveness to phosphoantigens and lytic activity toward the Daudi lymphoma cell line [26].

Vδ1 cells are enriched in the gut mucosa, where they help in maintaining tissue homeostasis. HIV infection further increases the frequency of Vδ1 cells in the mucosa, similar to the increased levels observed in peripheral blood of HIV-infected individuals [27]. Despite immunologic control of viral replication, elite controllers (EC) also display elevated levels of Vδ1 cells in the gut mucosa [28]. Few studies demonstrated that HIV-mediated disruption of gut epithelial barrier leads to translocation of gut microbiota, which activates Vδ1 T cells to produce pro-inflammatory cytokines and exacerbate the chronic inflammation [24][29]. The increase in Vδ1 T cell numbers seen in EC strongly correlated with the gut viral load, implying that viral replication in the mucosa and disruption in the gut epithelial barrier integrity and microbial translocation may contribute to enhanced Vδ1 T cell proliferation, also along with other immune activation events and disease progression. However, further studies are needed to better understand the causation and mechanism of Vδ1 T cell expansion in the gut during HIV infection and the net impact of this on disease progression.

2.2. Impact of γδ T Cell Perturbations on Immune Control of HIV

As previously alluded to, much of the impact of γδ T cells on immune function in health and disease is mediated through their bi-directional cross-talk with other immune cells [30]. In healthy individuals, activated γδ T cells induce the maturation and differentiation of DCs and B cells into functional APCs, but in HIV-infected individuals, this

immunomodulatory capacity of γδ T cells is compromised [31]. Typically, upon activation, Vγ9Vδ2 T cells can drive the upregulation of CD80, CD86, HLA-DR, and CD40 surface expression on APCs, enhancing their capacity to induce primary αβ T cell responses [32]. HIV infection alters the ability of APCs to process and present antigens, inhibiting the ability of Vγ9Vδ2 T cells to effectively interact with and positively impact the phenotype and function of APCs [31].

HIV infection may also impair the APC function of γδ T cells and their ability to induce αβ T cell responses [33]. Activated γδ T cells produce large quantities of chemokines, including the macrophage inflammatory protein (MIP)-1α/CCL3, MIP-1β/CCL4, and CCL5/RANTES, which binds to, and can compete with the HIV coreceptor CCR5 to block HIV infection of the target cells. Again, alteration of γδ T cells in HIV infection may lead to reduced protection against new infection of target cells. Vδ2 T cells cultured in the presence of HMBPP and IL-21 express B cell-attracting chemokine CXCL13, and the CXCL13 receptor CXCR5. This promotes B cell somatic mutation, productive rearrangement, and maturation in the germinal center, thereby promoting antibody production by B cells [34][35][36]. Due to the loss of γδ T cells in HIV infected individuals, it is likely that these crucial helper functions will also be compromised.

Numerous studies have demonstrated the protective role of γδ T cells in inducing cytotoxicity in HIV-infected cells and controlling HIV replication [37][38][39]. However, γδ T cells can also contribute to negative outcomes in HIV infection. γδ T cells from HIV-infected individuals express high levels of the inhibitory receptor TIGIT, and they are the primary inflammatory driver in ART-suppressed HIV infection, and they contribute to age-associated morbidity and mortality [40]. This negative outcome is particularly highlighted in respiratory conditions, where alveolar immune cell homeostasis is disrupted in HIV-infected adults, characterized by the increased infiltration of γδ T cells and other immune cells in broncho-alveolar lavage fluid, resulting in an enhanced susceptibility of these individuals to lower respiratory tract infections [41].

2.3. γδ T Cell Contribution to HIV Reservoirs

Even though current ART effectively suppresses HIV replication, the integrated viral genome remains transcriptionally silent in host chromatin, representing a major challenge towards efforts to eradicate infection [42]. Resting memory CD4+ T lymphocytes have long been considered the major reservoir site for HIV [43]. However, recent studies demonstrate that other cell types can also contribute to the latent HIV reservoir, including γδ T cells [28].

In one study, replication-competent HIV could be obtained from highly purified Vδ2 T cells from HIV-infected people during ART, thus identifying a previously unrecognized latent HIV reservoir within Vδ2 T cells at an unexpectedly high frequency [44]. Although the precise mechanism is not known, γδ T cells can be infected by the CXCR4-tropic laboratory clone, HIV_{LAI} [26]. Possible mechanisms of infection include the binding of HIV envelope glycoproteins to the highly expressed CCR5/α4β7 receptor on Vγ9Vδ2 T cells, leading to infection through a CD4-independent pathway [21]. Alternatively, HIV infection has been shown to induce immune activation and subsequent upregulation of CD4 receptors on some γδ T cells, potentially making them more susceptible to HIV infection [44]. Preliminary

findings from our group, utilizing a humanized mouse model, suggest that activated Vγ9Vδ2 cells can indeed serve as early targets for HIV infection and play a critical role in the early stages of viral dissemination [45]. Depletion of these cells during early infection would likely negatively impact immune defenses, particularly due to the important roles they serve by producing chemokines that can act as competitive inhibitors to block HIV entry and to recruit other immune effector cells to promote HIV clearance [8]. However, the increased presence and survival of activated γδ T cells, which can also serve as targets for HIV infection, could contribute to enhancement in viral production and rebound. This raises more questions about the role of γδ T cells in the initial sequelae of HIV infection and their potential contribution to the HIV reservoir.

2.4. Impact of Anti-Retroviral Therapy on γδ T Cells in HIV-Infection

Although ART is very effective in restoring CD4+ T cell counts and suppressing the virus below detectable levels, it fails to fully restore standard frequencies of Vγ9Vδ2 T cells in HIV-infected individuals [18]. Long-term ART partially restored the Jγ1.2 repertoire of the Vδ2 subset [20]. These Vγ9Vδ2 cells are highly activated [46] but are functionally compromised, with diminished cytokine production, cytotoxicity, and proliferation [47]. At the same time, expanded Vδ1 levels remain stable during ART in peripheral blood and mucosal sites, and they produce pro-inflammatory cytokines and express the inhibitory molecule CD279 (PD-1) [48]. Whether long-term ART impacts the number of Vδ1 T cells and/or their activation status is not clearly understood. Studies suggest that the loss of Vγ9Vδ2 cells in viral controllers is significantly lower than untreated or ART-treated individuals and that γδ17 cells are highly preserved. This preserved γδ population may be responsible for preventing microbial translocation and controlling chronic systemic immune activation [49][50].

2.5. γδ T Cells in HIV Immunotherapy

γδ T cells are the first line of defense against many pathogens, but their number and functions are severely altered in many infectious diseases, including HIV. Despite the long-term ART, γδ T cells are not reconstituted to the original frequency in HIV-infected individuals. However, in elite controllers, the Vγ9Vδ2 T cell numbers are maintained at normal levels, implying that immunotherapy using Vγ9Vδ2 T cells might recapitulate the immune status seen with those capable of naturally controlling HIV infection [49]. Several efforts were made to develop suitable methods for activating and expanding γδ T cells *in vitro* and *in vivo*. *In vitro* methods involve stimulating PBMCs with bisphosphonates, such as IPP, HMBPP, and zoledronate [51]. Zoledronate blocks the metabolic conversion of IPP, allowing this phosphoantigen to accumulate until stimulatory levels are reached, resulting in the selective activation and expansion of Vγ9Vδ2 T cells [51]. Bisphosphonate-mediated expansion of γδ T cells is a rapid means to generate large quantities of these cells for adoptive cell therapy. On the other hand, the delta one T (DOT) cell subtype of γδ T cells can be expanded using OKT-3 monoclonal antibody and a cytokine cocktail consisting of rIL-4, rIFN-γ, rIL-21, and rIL-1β [52]. A high yield of DOT cells could be obtained by treating PBMCs with Con-A and rIL-2 and rIL-4 [53]. Alternative strategies for expanding γδ T cells that do not respond to pAgs or N-BP involve the use of agonistic monoclonal antibodies (mAb). Using γδ TCR-specific antibodies, low levels of expansion of Vδ1, and Vδ2 T cells has been achieved, but it has not been very successful to date. However, 20.1, an agonistic Ab specific for CD277 (a member of BTN3 subfamily), mimics pAg-induced Vγ9Vδ2 cell activation.

This antibody may simulate a conformational change in the CD277 molecule to activate and expand Vγ9Vδ2 T cells [54].

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