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Host Immune System Abnormalities Among Patients with Human T-Lymphotropic Virus Type 1 (HTLV-1)-Associated Disorders

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1. Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a human retrovirus that causes persistent infection in the host. While most infected persons remain asymptomatic carriers (ACs), 3–5% develop a T-cell malignancy termed adult T-cell leukemia (ATL) (Uchiyama et al., 1977), and another 0.25–3% develop a chronic progressive inflammatory neurologic disease known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Gessain et al., 1985; Osame et al. 1986). Although HTLV-1-associated disorders have been extensively studied, the exact mechanism by which they are induced by HTLV-1 is not completely understood. The proviral load of HTLV-1 could contribute to the development of these disorders, since the circulating number of HTLV-1-infected T cells in the peripheral blood is associated with the risk of developing HAM/TSP and ATL (Iwanaga et al., 2010; Nagai et al. 1998). However, more detail on the precise immune mechanisms controlling HTLV-1-infected cells is still needed.

HTLV-1 preferentially infects CD4⁺ T cells, the central regulators of the acquired immune system (Richardson et al., 1990). This is known to induce a variety of abnormalities, such as proliferation, cellular activation, and proinflammatory changes (Boxus et al., 2009; Satou et al., 2010; Yamano et al. 2009). These abnormalities, in turn, may deregulate the balance of the host immune system.

HTLV-1 also causes abnormalities among uninfected immune cells. Patients with HTLV-1-associated disorders demonstrate abnormalities in both the amount and function of CD8⁺ cytotoxic T lymphocytes (CTL), an important component of host immune response against HTLV-1 (Bangham 2009; Kannagi et al., 2011; Matsuura et al., 2010). Patients with ATL and HAM/TSP may also experience reductions in the amount and efficacy of cellular components of innate immunity, which is vital in regulating the immune response against general viral infections and cancers (Azakami et al., 2009; Matsuura et al., 2010). In this chapter, we have summarized the host immune system abnormalities that are associated with HTLV-1 infection.

2. Abnormality of HTLV-1-infected CD4⁺ T cells

2.1 CD4⁺CD25⁺CCR4⁺ T Cells are a major reservoir of HTLV-1-infected T cells, which increase in HAM/TSP and ATL patients

HTLV-1 mainly infects CD4⁺ T helper (Th) cells, which play a central role in adaptive immune responses (Richardson et al., 1990). CD4⁺ Th cells recruit and activate other immune cells, including B cells, CD8 T cells, macrophages, mast cells, neutrophils, eosinophils, and basophils (Zhu et al., 2010). Based on their function, their pattern of cytokine secretion, and their expression of specific transcription factors and chemokine receptors, CD4⁺ Th cells, differentiated from naïve CD4⁺ T cells, are classified into 4 major lineages: Th1, Th2, Th17, and T regulatory (Treg) cells. To understand the effects of HTLV-1 infection on the function of CD4 Th cells, it is necessary to know which Th population HTLV-1 infects.

It was recently shown that the chemokine receptor CCR4 is expressed on HTLV-1-infected leukemia cells in ATL patients (Yoshie et al., 2002). CCR4 is selectively expressed on suppressive T cell subsets, such as Treg and Th2 cells, in HTLV-1-seronegative healthy individuals (Yoshie et al., 2001). Using molecular and immunological techniques, we also demonstrated that CD4⁺CD25⁺CCR4⁺ T cells were the predominant viral reservoir in both ACs and HAM/TSP patients, and that this T cell subset was increased in HAM/TSP patients (Yamano et al., 2009). Thus, CD4⁺CD25⁺CCR4⁺ T cells are a major population of HTLV-1-infected T cells, which increase in number in both HAM/TSP and ATL patients.

The molecular mechanism of HTLV-1 tropism to CCR4 expressing CD4⁺ T cells was recently uncovered (Hieshima et al., 2008). HTLV-1 Tax, a transcriptional regulator encoded by the HTLV-1 genome, does not induce expression of CCR4, but it does induce expression of CCL22, the ligand for CCR4. Because HTLV-1-infected T cells selectively interact with CCR4⁺CD4⁺ T cells, this results in preferential transmission of HTLV-1 to CCR4⁺CD4⁺ T cells.

2.2 Differences in the fates of CD4⁺CD25⁺CCR4⁺ T cells in HAM/TSP and ATL patients

Among CD4⁺ Th cells, the major reservoir of HTLV-1 is CD4⁺CD25⁺CCR4⁺ T cells, including suppressive T cell subsets such as Treg and Th2 under healthy conditions. The exact mechanism by which HTLV-1 induces the deregulation of the host immune system is not completely understood. However, the recent discovery of Treg cells has provided new opportunities and generated increased interest in this issue. In healthy individuals, Treg cells suppress the proliferation of, and cytokine production by, pathogenic T cells, and thereby plays a key role in the maintenance of immune system homeostasis (Sakaguchi et al., 1995). Treg cells can be identified *ex vivo* by the intracellular expression of the transcriptional regulator Foxp3 (Hori et al., 2003), which is critical for the development and function of Treg cells in both mice and humans.

Significant reductions in Foxp3 expression and/or Treg cell function have been observed in several human autoimmune diseases (Sakaguchi et al., 2008), suggesting that defects in Foxp3 expression and/or Treg function may precipitate the loss of immunologic tolerance. Recently, significant reductions in Foxp3 expression and Treg cell function have also been observed in CD4⁺CD25⁺ T cells and/or CD4⁺CD25⁺CCR4⁺ T cells from patients with HAM/TSP (Hayashi et al., 2008; Michaelsson et al., 2008; Oh et al., 2006; Ramirez et al., 2010; Yamano et al., 2005). Furthermore, decreased expression levels of the Treg-associated immune suppressive molecules CTLA-4 and GITR were also observed on CD4⁺CD25⁺ T cells in HAM/TSP patients (Ramirez et al., 2010; Yamano et al., 2005). Notably, overexpression of HTLV-1 *tax* can reduce

Foxp3 expression and inhibit the suppressive function of Treg cells (Yamano et al., 2005). Furthermore, because of a Tax-induced defect in TGF- β signaling, HAM/TSP patients experience reductions in Foxp3 expression and impairment of Treg function (Grant et al., 2008). Moreover, a significant reduction in CD4⁺CD25⁺Foxp3⁺ Treg cells was demonstrated in HTLV-1-*tax*-expressing transgenic mice, which develop an inflammatory arthropathy (Ohsugi et al., 2011). Thus, HAM/TSP patients display a decreased ratio of Foxp3⁺ Treg cells within HTLV-1-infected CD4⁺CD25⁺CCR4⁺ T cells.

Importantly, a more detailed flow cytometric analysis of Foxp3 expression in CD4⁺CD25⁺CCR4⁺ T cells demonstrated that the frequency of "Foxp3⁻ population" was extraordinary high in HAM/TSP patients (Yamano et al., 2009). Moreover, an analysis of proinflammatory cytokine expression in this Foxp3⁻CD4⁺CD25⁺CCR4⁺ T cell subset demonstrated that these cells were unique because, in healthy individuals, they produced multiple proinflammatory cytokines such as IL-2, IL-17, and few interferon (IFN)- γ , while Foxp3⁺CD4⁺CD25⁺CCR4⁺ T cells (Treg cells) did not. Furthermore, HAM/TSP patients were found to exhibit only a few Foxp3⁺CD4⁺CD25⁺CCR4⁺ T cells that did not produce such cytokines. Rather, these patients had an increased number of Foxp3⁻CD4⁺CD25⁺CCR4⁺ T cells, which were found to overproduce IFN- γ . Further, given the increase of clinical diseases and severity of HAM/TSP observed in these patients, it appears likely that the frequency of these IFN- γ -producing Foxp3⁻CD4⁺CD25⁺CCR4⁺ T cells may have a functional consequence (Yamano et al., 2009). Thus, while the CD4⁺CD25⁺CCR4⁺ T cell population in healthy patients mainly comprises suppressive T cell subsets such as Treg and Th2, HAM/TSP patients possess an increased proportion of IFN- γ -producing Foxp3⁻CD4⁺CD25⁺CCR4⁺ T cells, which are rarely encountered in healthy individuals and lead to an overproduction of IFN- γ (Figure 1).

Although Foxp3 expression is decreased by CD4⁺CD25⁺ (CCR4⁺) T cells in HAM/TSP patients (Hayashi et al., 2008; Michaelsson et al., 2008; Oh et al., 2006; Ramirez et al., 2010; Yamano et al., 2005), it is increased by CD4⁺CD25⁺(CCR4⁺) ATL cells in most ATL patients (Karube et al., 2004; Roncador et al., 2005) (Figure 1). Therefore, it has been hypothesized that ATL cells may be derived from Treg cells (Kohno et al., 2005). Interestingly, some ATL cells exhibit immunosuppressive functions similar to those of Treg cells, which may contribute to the cellular immunodeficiency that has been clinically observed in ATL patients (Chen et al., 2006; Kohno et al., 2005; Matsubar et al., 2006); however, some ATL cells lose this regulatory function (Shimauchi et al., 2008).

2.3 HTLV-1 may induce plasticity of Foxp3⁺ cells into exFoxp3⁺ cell

In HTLV-1-seronegative healthy individuals, CD4⁺CD25⁺CCR4⁺ T cells mainly include suppressive T cell subsets such as Treg and Th2 (Yoshie et al., 2001). In ATL patients, most of this subset develops leukemogenesis by maintaining the Foxp3⁺ Treg phenotype (Figure 1). However, as mentioned above, T cells of this subset become Th1-like cells that overproduce IFN- γ in HAM/TSP patients (Figure 1). Since HTLV-1 may preferentially transmit to CCR4⁺CD4⁺ T cells, these findings suggest that HTLV-1 may intracellularly induce T-cell plasticity of Treg cells into IFN- γ ⁺ T cells. Indeed, one recent report indicated that loss of Foxp3 in Treg cells and acquisition of IFN- γ may result in the conversion of suppressor T cells into highly autoaggressive lymphocytes (exFoxp3⁺ cells), which can favor the development of autoimmune conditions (Tsuiji et al., 2009; Zhou et al., 2009). Importantly, Toulza et al. (2008) demonstrated that the rate of CTL-mediated lysis was

negatively correlated with the number of HTLV-1-Tax⁻ CD4⁺Foxp3⁺ cells, but not with the number of Tax⁺ CD4⁺Foxp3⁺ cells, suggesting that HTLV-1-infected Treg cells lose their regulatory function, while HTLV-1-uninfected Treg cells contribute substantially to immune control of HTLV-1 infection. Additionally, functional impairment of CD4⁺Foxp3⁺ Treg cells was observed in mice that were transgenic mice for the *HTLV-1 bZIP factor (HBZ)* gene, which encodes the minus strand of HTLV-1 (Satou et al., 2011). These findings support the hypothesis that HTLV-1 may be one of the exogenous retrovirus genes responsible for immune dysregulation through interference of CD4⁺CD25⁺ Treg cell function. This hypothesis is currently under investigation to elucidate the precise molecular mechanisms by which HTLV-1 influences the fate and function of CD4⁺CD25⁺CCR4⁺ T cells, especially Foxp3⁺ Treg cells.

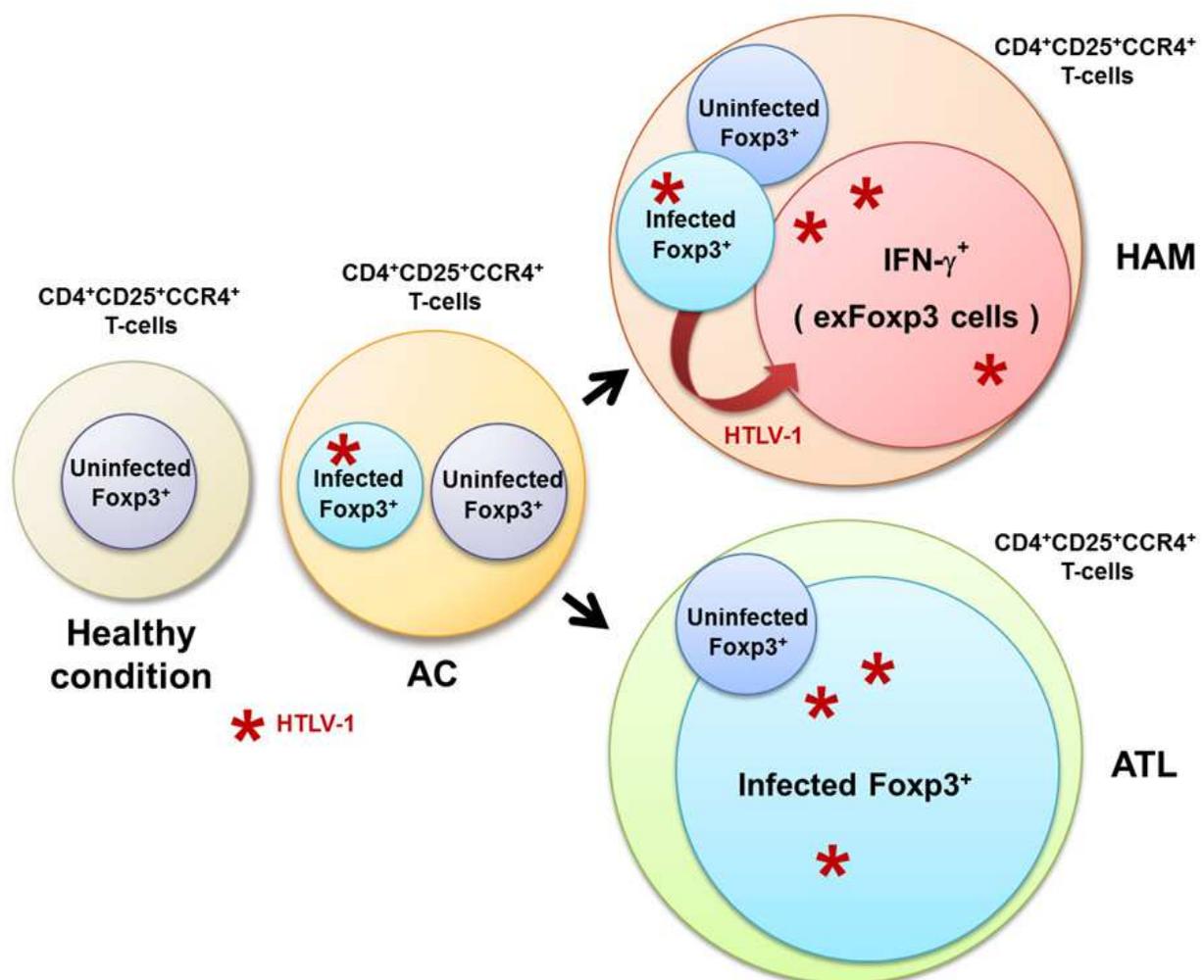


Fig. 1. Cellular components of CD4⁺CD25⁺CCR4⁺ T cells in healthy individuals, asymptomatic carriers, ATL, and HAM/TSP patients.

3. Abnormality of cytotoxic T lymphocyte (CTL) response

CD8⁺ Cytotoxic T lymphocyte (CTL) responses are an effective host defense system against all virus infections and malignancies. CTLs act by killing autologous cells that express viral

or cancer antigen in association with major histocompatibility complex (MHC) class I molecules and by suppressing viral replication and tumor development via IFN- γ secretion. Elucidating the role of HTLV-1-specific CD8⁺ CTLs has been considered a priority issue in studies of host defense mechanisms involved in HTLV-1 infection (Bangham, 2008; Jacobson, 2002; Kannagi, 2007).

3.1 HTLV-1-specific cytotoxic T lymphocytes

T-cell receptors (TCR) on CTLs recognize peptide fragments derived from viral and tumor antigens that are presented on MHC class I molecules by antigen-presenting cells or virus-infected cells. After TCR binds to the peptide-MHC complex, CTLs are activated and fulfill an effector function. There are 3 main effector mechanisms by which the CD8⁺ CTL kills virus-infected or tumor cells. One is to release perforin and granzymes. Perforin forms pores in the plasma membrane of the target cells, allowing entry of granzymes; caspases are then activated, leading to apoptosis. Apoptosis may also be induced via a Fas-FasL interaction between CTLs and target cells. Finally, CD8⁺ cells can produce IFN- γ , which has indirect cytolytic effects by promoting NK cell activity and macrophage activation.

The Tax protein is an immunodominant antigen in HTLV-1 infections. Therefore, CTL activity is predominantly restricted to products of the HTLV-1 Tax gene, although HTLV-1 Env, Pol, Rof, Tof, and HBZ (Elovaara et al., 1993; Hilburn et al., 2011; Macnamara et al., 2010; Pique et al., 2000) could also be target proteins of HTLV-1-specific CTL. In a study that utilized properties of the CTL antigen recognition system, human MHC class I HLA-A2(*0201) tetramers loaded with HTLV-1 Tax peptide were used to detect HTLV-1 Tax specific HLA-A2-restricted CD8⁺ cells (Bieganowska et al., 1999, Greten et al., 1998). This technique facilitates quantification of the frequency of antigen-specific T cells, as well as direct characterization of these cells. HLA genotype determines which part of the viral protein is presented as an antigen peptide. For HLA-A*0201 and HLA-A*2402, for example, the major epitopes are the Tax 11-19 and Tax 301-309 amino acids, respectively.

3.2 Abnormal CTL response in patients with ATL

An increasing number of studies in patients with HTLV-1-associated disorders have documented an association between the disorders and abnormalities in both the frequency of CTLs and their response to HTLV-1. When peripheral blood mononuclear cells (PBMCs) from HTLV-1 carriers are stimulated with autologous HTLV-1-infected cells *in vitro*, proliferation of HTLV-1-specific CD8⁺ CTLs is often observed in the presence of IL-2. An increased level of HTLV-1-specific CTL responses occurs in all HAM/TSP patients and in some asymptomatic HTLV-1 carriers; however, HTLV-1-specific CTL responses are rarely induced in PBMC cultures from ATL patients (Jacobson et al., 1990; Kannagi et al., 1984, Parker et al., 1992). HTLV-1-specific CTLs are also present in ATL patients but do not expand sufficiently (Arnulf et al., 2004). Impairment of the HTLV-1 specific CTL response was observed in some individuals during the earlier stages of HTLV-1 infection (AC and smoldering ATL), as well as in advanced ATL patients (Shimizu et al., 2009). This observation suggests that the T-cell insufficiency in ATL patients is present prior to disease onset. In addition, a recent report indicated that, in comparison to ACs, ATL patients have a smaller and less diverse population of HTLV-1 specific CD8⁺ T cells, as well as lower anti-HTLV-1 CD8⁺ T cell expression of perforin and granzyme B (Kozako et al., 2006). Thus, the decreased number and functional impairment of CTLs might contribute to the onset and progression of ATL.

Furthermore, Tax-specific CTL responses were strongly activated in some ATL patients who achieved complete remission after hematopoietic stem cell transplantation (HSCT), but were not observed in the same patients before transplantation (Harashima et al., 2004). This suggests that HTLV-1-specific CTLs, including Tax-specific CTLs, play an important role in surveillance against HTLV-1 leukemogenesis.

3.3 Abnormal CTL response in patients with HAM/TSP

One of the most striking features of the adaptive immune system in HAM/TSP patients is the larger number of HTLV-1-specific CD8⁺ CTLs (Elovaara et al., 1993; Greten et al., 1998; Jacobson et al., 1990; Kubota et al., 2002; Nagai et al., 2001a; Parker et al., 1992). While HTLV-1 specific CTLs are also detectable in the PBMC of ACs (Parker et al., 1992), the magnitude and frequency of these responses are clearly higher in patients with HAM/TSP, particularly in the CSF (Elovaara et al., 1993; Nagai et al., 2001a). In addition, the HTLV-1 proviral load of HAM/TSP patients may be 5- to 16-fold higher than that of ACs (Hashimoto et al., 1998; Kubota et al., 1993; Nagai et al., 1998). While some studies have found a positive correlation between the frequency of HTLV-1-specific CD8⁺ T cells and HTLV-1 proviral load has been detected in PBMCs from HAM/TSP patients (Kubota et al., 2000; Nagai et al., 2001b; Yamano et al., 2002), this result is not ubiquitous (Wodarz et al., 2001). Thus, the cytolytic activity of CTLs, rather than their frequency, might be impaired in HAM/TSP patients.

There are some methods to measure CTL cytolytic activity. One is the sensitive CD107a mobilization assay, which quantifies the amount of lysosomal membrane protein LAMP-1 (CD107a) present on the CTL surface (CD107a) (Betts et al., 2003). Among studies that have used this method to evaluate CTL function, results are conflicting; while one reported that HTLV-1-specific CTLs of HAM/TSP patients had significantly lower CD107a staining than those of ACs (Sabouri et al., 2008), another study reported the opposite (Abdelbary et al., 2011). Furthermore, higher expression of CD107a/IFN- γ was induced by tax peptide stimulation in the CD8⁺ T cells of HAM/TSP patients than in those of ACs (Enose-Akahata et al., 2008). Thus, it is not yet clear whether the cytolytic activity of HTLV-1-specific CTL in HAM/TSP patients is insufficient. However, these findings suggest that quantity of HTLV-1-infected cells is not determined by HTLV-1-specific CTL alone; additional factors, such as innate immunity and the proliferative ability of infected cells, must be relevant.

3.4 Pathogenic Role of CTL in HAM/TSP

In HAM/TSP patients, HTLV-1-specific CD8⁺ CTL levels are extraordinarily high in peripheral blood, and even higher in cerebrospinal fluid (CSF) (Elovaara et al., 1993; Greten et al., 1998; Jacobson et al., 1990; Kubota et al., 2002; Parker et al., 1994; Nagai et al., 2001; Yamano et al., 2002). Immunohistochemical analysis of affected spinal cord lesions in early-stage HAM/TSP patients revealed the presence of infiltrating CD4⁺ and CD8⁺ lymphocytes, among which CD8⁺ cells become increasingly dominant over the duration of the illness (Umehara et al., 1993). The expression of HLA class I antigens (Moore et al., 1989) and the existence of HTLV-1 specific CD8⁺ CTLs have also been found in such lesions (Levin et al., 1997). In addition, the infiltration of CD8⁺ CTLs in the affected spinal cord was characterized as positive for TIA-1 that is a marker of CTL (Umehara et al., 1994; Anderson et al., 1990). The number of TIA-1⁺ cells was clearly related to the amount of the proviral DNA *in situ*, and the number of infiltrating CD8⁺ cells appears to correlate with the presence of apoptotic cells.

Tax-specific CD8⁺ CTL clones secrete various inflammatory cytokines, chemokines, and matrix metalloproteinases (MMP), such as IFN- γ , TNF- α , monocyte inflammatory protein (MIP)-1 α , MIP-1 β , interleukin(IL)-16, and MMP-9 (Biddison et al., 1997). TNF- α induces cytotoxic damage to endothelial cells, thus decreasing the integrity of the blood-brain barrier. It can also directly injure oligodendrocytes. MIP-1 α and 1 β can enhance transendothelial migration of lymphocytes into the central nervous system. IL-16 is a chemoattractant for CD4⁺ cells, which are the major source of IL-2 required by IL-2 non-producer CD8⁺ cells for proliferation. Therefore, HTLV-1-specific CD8⁺ CTLs are an important source of proinflammatory soluble mediators that may contribute significantly to the pathogenesis of HAM/TSP. These observations continue to support the hypothesis that HTLV-1-specific CD8⁺ CTLs are a major contributing factor in the immunopathogenesis of HAM/TSP.

4. Abnormality of innate immunity

Besides CTLs, there are several cell populations in the human immune system that have cytolytic activity against virus-infected cells, including natural killer (NK) cells, natural killer T (NKT) cells, and $\gamma\delta$ T cells, which are cellular components of innate immunity. Dendritic cells (DCs) play an important role in the activation of these cell populations and CTLs. There is little evidence suggesting a role for $\gamma\delta$ T cells in the pathogenesis of HTLV-1-associated disorders. Thus, this section focuses solely on the roles of DCs, NK cells, and NKT cells in HTLV-1-associated diseases, by comparing with the role of these cells in HIV-1 infection.

4.1 Dendritic cells and HTLV-1

Immature DCs are located in peripheral tissues and can effectively capture antigens, leading to their maturation via the expression of MHC class I/II and co-stimulatory molecules such as CD80, CD86, and CD40. Mature DCs are professional antigen-presenting cells that are uniquely able to prime naïve T cells. There are 2 main subsets of DCs: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). These cells play important roles in the regulation of innate and adaptive immunity. mDCs can induce the activation of invariant NKT (iNKT) cells via surface expression of the CD1d/glycolipid complex. After antigen capture, pDCs secrete type 1 IFN, which induces the activation of NK cells and promotes the activation of iNKT cells by mDCs.

An *in vitro* study indicated that cell-free HTLV-1 effectively infects DCs, leading to the transmission and transformation of CD4⁺ T cells (Jones et al. 2008). In addition to suggesting a mechanism for HTLV-1 transmission, this study also indicated that HTLV-1 infection of DCs plays a role in the pathogenesis of HTLV-1-associated disorders. In fact, HTLV-1-infected DCs are observed in the peripheral blood of HTLV-1-infected individuals (Hishizawa et al., 2004; Macatonia et al., 1992), and infected pDCs have an impaired ability to produce type I IFN (Azakami et al., 2009; Hishizawa et al., 2004). In addition, we recently reported that the frequency of mDCs and pDCs is significantly lower in patients with both HAM/TSP and ATL (Azakami et al., 2009). Cumulatively, these studies imply that decreases in the number and functionality of DCs interfere with innate immunity, thus leading to pathogenesis.

4.2 Natural killer cells and HTLV-1

NK cells are major components of the innate immune system and account for 10–15% of PBMCs in normal individuals. They have direct and indirect cytolytic activity against tumor

cells and virus-infected cells by producing perforins, granzymes, and IFN- γ . Human NK cells can be divided into 2 subsets on the basis of their cell-surface markers: CD56⁺CD16⁺ and CD56^{bright}CD16⁻ NK cells. CD56⁺CD16⁺ NK cells are the major population of NK cells and have natural cytotoxic activity. CD56^{bright}CD16⁻ NK cells are not cytotoxic but have the capacity to produce large amounts of IFN- γ upon activation. The activity of NK cells is regulated by a balance between positive and negative signals from different activating and inhibitory NK receptors. CD94/NKG2 receptor family is expressed on CD8⁺ T cells and $\gamma\delta$ T cells as well as NK cells, and is involved in the pathogenesis of HAM/TSP by modulating the activities of those cell populations (Saito et al. 2003, Mosley et al. 2005).

In both HIV-1- and HTLV-1-infected individuals, the number and function of NK cell subsets are impaired (Fortis et al., 2005). Multiple investigators have reported that the numbers of CD56⁺CD16⁺ NK cells in HAM/TSP and ATL patients are significantly lower than those observed in healthy controls (Azakami et al., 2009; Yu et al., 1991). Furthermore, NK cell activity was also lower in HAM/TSP patients than in healthy controls (Yu et al., 1991). When primary CD4⁺ T cells are infected by HTLV-1, they can escape from NK cell-mediated cytotoxicity; HTLV-1 p12ⁱ downregulates the expression of intercellular adhesion molecule-1 (ICAM-1) and -2 on the surface of infected CD4⁺ T cells, resulting in a reduced adherence of NK cells to HTLV-1-infected CD4⁺ T cells (Banerjee et al., 2007).

4.3 Natural killer T cells and HTLV-1

Natural killer T (NKT) cells, a unique T cell subpopulation, constitute a subset of lymphocytes that share the features of innate and adaptive immune cells. Unlike conventional T cells, NKT cells express a TCR that recognizes glycolipids instead of protein antigens. Moreover, these cells share properties and receptors with NK cells. They rapidly produce granzymes and perforins upon stimulation. Among the CD3⁺ T cells in human blood, 10–25% express NK cell surface molecules such as CD161, and these cells are classified as NKT cells. A small population of T cells within this NKT cell subset expresses a highly conserved V α 24J α 18 TCR chain that preferentially associates with V β 11; these T cells are referred to as iNKT cells. Activation of human iNKT cells requires the presentation of glycolipids such as α -galactosylceramide (α -GalCer) on the MHC class I-like molecule CD1d. α -GalCer induces the rapid production of cytokines and potent antitumor and antipathogen responses by iNKT cells. CD4⁻ iNKT cells preferentially induce the Th1 response and are more important than CD4⁺ iNKT cells in controlling viral infection and cancer (Kim et al., 2002).

HIV-1-infected subjects have fewer iNKT cells in their peripheral blood than healthy donors (Sandberg et al., 2002; van der Vliet et al., 2002). The proliferative potential and INF- γ production of residual iNKT cells are impaired in HIV-1-infected individuals (Moll et al., 2009); likewise, patients with HTLV-1-associated disorders have a decreased frequency of iNKT cells in their peripheral blood (Azakami et al., 2009). Interestingly, in contrast to patterns observed in HIV-1 infections, HTLV-1 infection leads to preferential decreases of CD4⁻ iNKT cells (Azakami et al., 2009). The production of perforin in iNKT cells is impaired in both ACs and HAM/TSP patients (Azakami et al., 2009). In addition, there is an inverse correlation between the frequency of iNKT cells and the HTLV-1 proviral load in the peripheral blood of HTLV-1-infected individuals (Azakami et al., 2009). Notably, *in vitro* stimulation of peripheral blood cells with α -GalCer leads to an increase in the number of iNKT cells and a subsequent decrease in the number of HTLV-1-infected T cells in samples

from ACs (Azakami et al., 2009). These results suggest that iNKT cells contribute to the immune defense against HTLV-1, and that iNKT cell depletion plays an important role in the pathogenesis of HAM/TSP and ATL.

5. Conclusion

Advances in our understanding of the immune system enhance studies of virus-host relationships. Although HTLV-1 causes 2 different diseases (ATL and HTM/TSP), CD4⁺CD25⁺CCR4⁺ T cells are the common viral reservoir in both disorders. According to recent studies, however, characteristics of CD4⁺CD25⁺CCR4⁺ T cells are completely different in the 2 diseases: Foxp3⁺ leukemic cells are found in ATL patients, while Foxp3⁻ IFN- γ -producing cells are found in HAM/TSP patients. The host immune system plays a crucial role in controlling these HTLV-1-infected cells. HTLV-1-specific CTL is activated in patients with HAM/TSP, but not in those with ATL, indicating that impairment of acquired immunity is not universal. However, both ATL and HAM/TSP patients are known to experience decreases in innate immunity via the functional impairment of DCs, NK cells, and iNKT cells, as well as lower overall population numbers of these cell types. These conditions may contribute to inadequate viral control and play an important role in the pathogenesis of HTLV-1-associated disorders.

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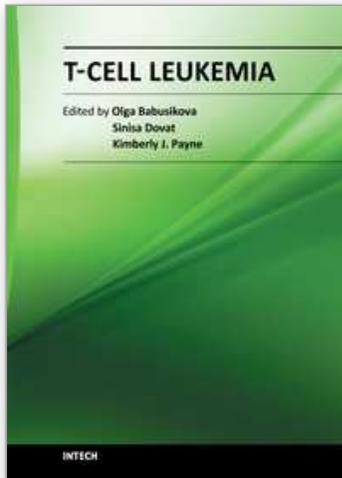
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The purpose of this book is to provide a comprehensive review of the scientific advances in T-cell malignancies and to highlight the most relevant findings that will help the reader understand both basic mechanisms of the disease and future directions that are likely to lead to novel therapies. In order to assure a thorough approach to these problems, contributors include basic scientists, translational researchers and clinicians who are experts in this field. Thus, the target audience for this book includes both basic scientists who will use this book as a review of the advances in our fundamental knowledge of the molecular mechanisms of T-cell malignancies, as well as clinicians who will use this book as a tool to understand rationales for the development of novel treatments for these diseases.

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