



Mini Review

Human T-lymphotropic virus type 1 (HTLV-1) and innate immunity

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Human T-cell lymphotropic virus type 1 (HTLV-1) is a T lymphotropic human retrovirus that causes adult T-cell leukemia/lymphoma (ATL) and is associated with immunological disorders such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). A higher viral load in HTLV-1-infected individuals increases the risk of HAM/TSP and ATL; furthermore, it affects the disease severity of HAM/TSP. Therefore, the precise immune mechanisms controlling HTLV-1-infected cells must be further characterized. In this regard, the role of HTLV-1-specific CD8⁺ cytotoxic T lymphocytes (CTLs) has been studied intensively. However, there are few reports describing the role of innate immunity in controlling the proliferation of HTLV-1-infected cells.

Natural killer (NK) and invariant natural killer T (iNKT) cells are the cellular components of innate immunity that regulate the immune response to general viral infection and cancers. Dendritic cells (DCs) play important roles in the activation of these NK and iNKT cells as well as CTLs. In this review, we summarize the characteristics of DCs, NK cells, and iNKT cells in individuals infected with HTLV-1.

In the peripheral blood of HAM/TSP and ATL patients, the decreased number and impaired functionality of DCs, NK cells, and iNKT cells have been reported. Even in asymptomatic carriers, the functions of these cell populations are perturbed by HTLV-1 infection, while their frequencies are comparable to those of healthy individuals. These observations suggest that abnormalities of DCs, NK cells, and iNKT cells are implicated in the pathogenesis of HTLV-1-associated diseases via insufficient viral control.

Rec.3/30/2010,Acc.7/20/2010

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Key words: HTLV-1, HTLV-1-associated myelopathy, adult T cell leukemia, innate immunity, natural killer T cells



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), and another 0.25–3% develop a chronic progressive inflammatory neurologic disease known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)¹. One of the most important pathogenic factors in HAM/TSP is the increased HTLV-1 provirus load in the peripheral blood and cerebrospinal fluid^{2,3}, suggesting that the immune control of the virus is inadequate in affected persons. A higher HTLV-1 provirus load increases the risk of HAM/TSP and ATL^{2,4}; therefore, the precise immune mechanisms controlling HTLV-1-infected cells must be characterized in more detail. With regard to the host defense mechanisms involved in HTLV-1 infection, the role of HTLV-1-specific CD8⁺ cytotoxic T lymphocytes (CTLs) has been studied⁵. The HTLV-1-specific CTL response is critical for the maintenance of a low viral load⁵. Despite the high frequency of HTLV-1-specific CTLs, the number of HTLV-1-infected T cells is surprisingly high in HAM/TSP patients³. We and other researchers have reported that the maturation and function of HTLV-1-specific CTLs are impaired in HAM/TSP patients, although in vitro studies have shown that these CTLs exert cytolytic activity against HTLV-1-expressing target cells^{6,7}. Therefore, we hypothesize that there may be another non-CTL cell population that contributes to the control of HTLV-1-infected T cells.

Besides CTLs, there are several cell populations that have cytolytic activity against virus-infected cells in the human immune system (Fig. 1), e.g., 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. Because there is little evidence suggesting a role for $\gamma\delta$ T cells in the pathogenesis of HTLV-1-associated disorders, this review focuses on the role of DCs, NK cells, and NKT cells in HTLV-1-associated diseases by comparing with the role of these

cells in HIV-1 infection.

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 major histocompatibility complex (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. DCs consist of two main subsets: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). These cells play important roles in the regulation of innate and adaptive immunity (Fig. 1). mDCs can induce the activation of invariant NKT (iNKT) cells by the surface expression of the CD1d / glycolipid complex. pDCs secrete type 1 interferon (IFN) after antigen capture. Type 1 IFN 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 cells⁸. This study suggested the mechanism of HTLV-1 transmission and that the 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^{9,10}, and infected pDCs have an impaired ability to produce type I IFN¹⁰. In addition, we recently reported that the frequency of mDCs and pDCs is significantly decreased in patients with both HAM/TSP and ATL¹¹. These studies imply that the decreased number and impaired functionality of DCs are implicated in pathogenesis by interfering with innate immunity.

Natural killer cells and HTLV-1

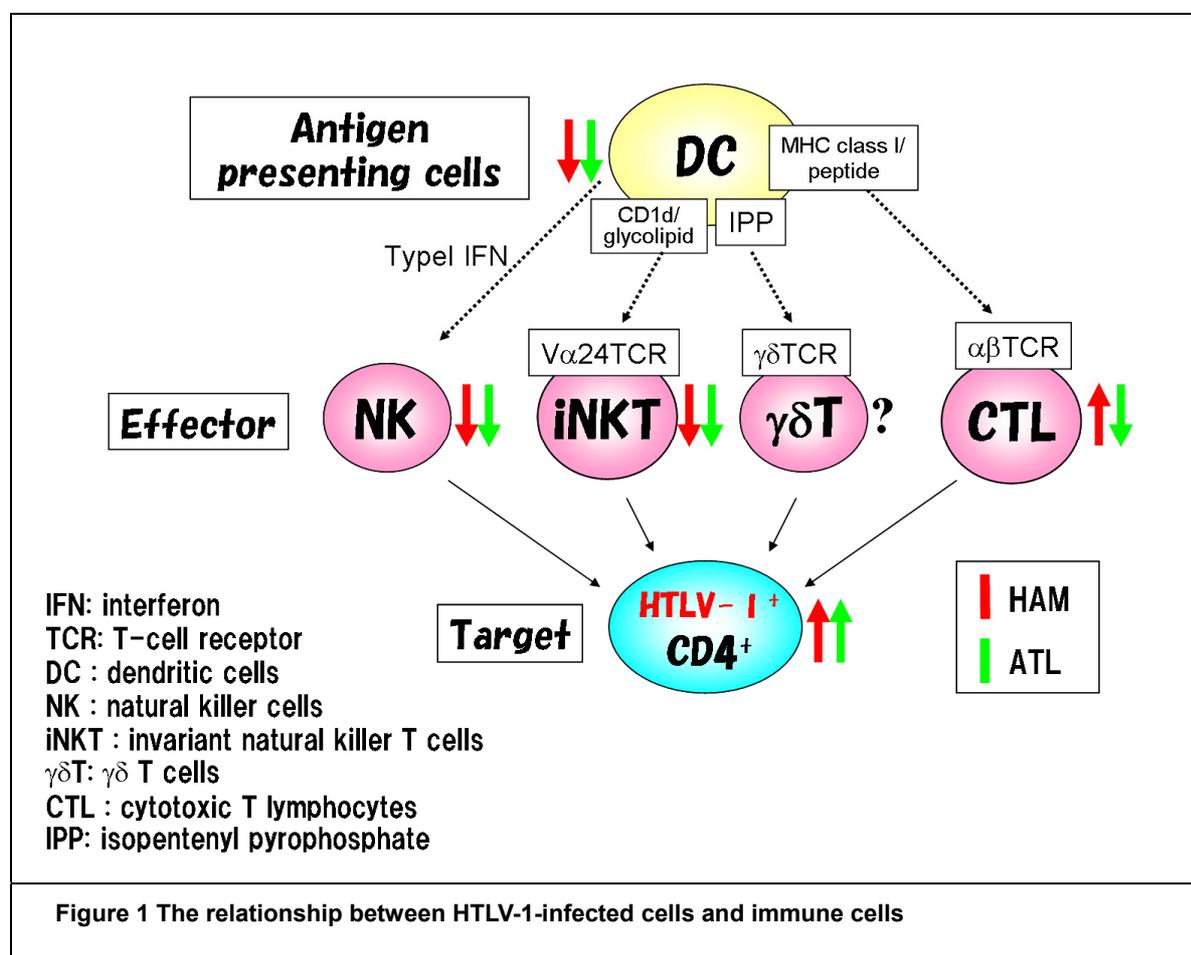
NK cells are major components of the innate immune system and comprise 10–15% of peripheral blood mononuclear cells (PBMCs) in normal individuals. They have direct and indirect cytolytic activity against tumor cells and virus-infected cells by producing perforins, granzymes, and IFN- γ . Human NK cells can be divided into two 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 absence or presence of HAM/TSP by modulating the activities of those cell populations^{12,13}.

In HIV-1-infected individuals, the number and function of the NK cell subsets are impaired¹⁴, as observed in HTLV-1-infected individuals. We and other investigators have

reported that the number of CD56⁺CD16⁺ NK cells in HAM/TSP and ATL patients are significantly reduced as compared to that in healthy controls^{11,15}. The activity of NK cells in HAM/TSP patients was significantly decreased as compared to that in healthy controls¹⁵. In addition, the HTLV-1 infection of primary CD4⁺ T cells leads to their escape from NK cell-mediated cytotoxicity; HTLV-1 p12^I downregulates the expression of intercellular adhesion molecule-1 (ICAM-1) and -2 on the cell surface of infected CD4⁺ T cells that result in the reduced adherence of NK cells to these HTLV-1-infected CD4⁺ T cells¹⁶.



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 T-cell receptor (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 24Ja18 TCR chain that preferentially as-



sociates with Vβ11. These T cells are referred to as invariant NKT (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 (Fig. 1). 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 cancer¹⁷.

	HTLV-1 infection	ATL		HAM		AC	
		Freq.	Function	Freq.	Function	Freq.	Function
mDCs	+ ⁹⁾	↓↓ ^{10,11)}	↓↓	↓ ¹¹⁾	↓	→ ^{10,11)}	↓
pDCs	+ ¹⁰⁾	↓ ^{10,11)}	↓↓	↓ ^{10,11)}	↓	→ ^{10,11)}	↓ ¹⁰⁾ : IFNα production
NK cells	- ²¹⁾	↓↓ ¹¹⁾	↓↓	↓ ^{11,15)}	↓ ¹⁵⁾ : cytolytic activity	→ ¹¹⁾	↓ ¹⁵⁾ : cytolytic activity
iNKT cells	+ ¹¹⁾	↓↓ ¹¹⁾	↓↓	↓↓ ^{11,22)}	↓ ¹¹⁾ : intra-cellular perforin	→ ¹¹⁾	↓ ¹¹⁾ : intra-cellular perforin

Table 1. The immunological conditions of DCs, NK cells, and NKT cells in HTLV-1-infected individuals

DCs, dendritic cells; mDCs, myeloid DCs; pDCs, plasmacytoid DCs; NK, natural killer cells; NKT, natural killer T-cells; iNKT, invariant NKT cells; IFN, interferon; Freq., frequency; ATL, adult T-cell leukemia; HAM, HTLV-1-associated myelopathy; ACs, asymptomatic carriers

HIV-1-infected subjects had a reduced number of iNKT cells in the peripheral blood as compared to healthy donors^{18,19}. The proliferative potential and INF-γ production of residual iNKT cells were impaired in HIV-1-infected individuals²⁰; likewise, patients with HTLV-1-associated disorders had a decreased frequency of iNKT cells in the peripheral blood¹¹. Interestingly, unlike HIV-1 infection, CD4⁻ iNKT cells were preferentially decreased by HTLV-1 infection¹¹. The production of perforin in iNKT cells was impaired in ACs and HAM/TSP patients¹¹. In addition, there was an inverse correlation between the frequency of iNKT cells and the HTLV-1 proviral load in the peripheral blood of HTLV-1-infected individuals¹¹. Notably, in vitro stimulation of peripheral blood cells with α-GalCer led 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 ACs¹¹. These results suggest that iNKT cells contribute to the immune defense against HTLV-1, and iNKT cell depletion plays an important role in the pathogenesis of HAM/TSP and ATL.

Conclusion

In Figure 1 and Table 1, we summarize the immunological conditions of DCs, NK cells, and iNKT cells in HTLV-1-infected individuals. In ACs, the functions of these cell populations are perturbed by HTLV-1 infection, whereas their frequencies are comparable to those of healthy individuals. These conditions may suggest the latent immunosuppressive state of HTLV-1 carriers. In patients with ATL and HAM/TSP, not only the functional impairment of DCs, NK cells, and iNKT cells but also the decreased number of these cell populations has been observed. These conditions may contribute to inadequate viral control and have an important role in the pathogenesis of HTLV-1-associated disorders.

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