

# Th17 Cells and Tregs in HTLV-1 Infection

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**Abstract:** HTLV-1 (human T-lymphotropic virus type 1) causes chronic infection of human T lymphocytes. HTLV-1 infection is known to be related to multiple diseases, including neoplastic growth of HTLV-1-infected T cells (ATL) and neoplastic inflammatory conditions, such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), Sjögren's syndrome with arthritis, polymyositis uveitis, and bronchoalveolitis. Regulatory T cells (Tregs) regulate inflammatory cells, such as Th17 cells. The purpose of this study was to evaluate Tregs and Th17 cells, as well as the expression of related transcription factors (ROR- $\gamma$ t and FOXP3) and cytokines (IL-10, TGF- $\beta$ , IL-6, and IL-17A) in HTLV-1 infection.

**Keywords:** Tregs; Th17 cells; HTLV-1, HAM/TSP

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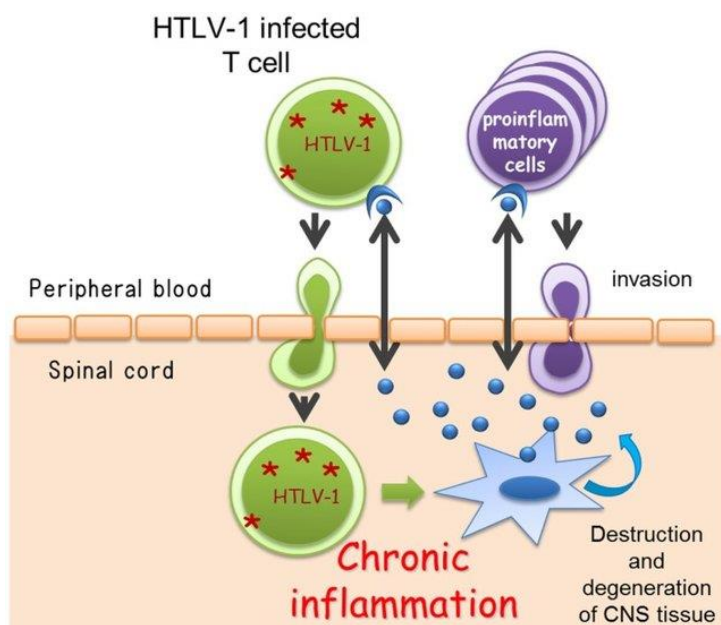
## 1. Introduction

Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus that causes chronic infection of human T lymphocytes. Its main highly endemic regions are Japan, Melanesia, Middle East, certain regions in South America, and Africa [1-3]. However, a considerable percentage of affected carriers are asymptomatic [4,5]. HTLV-1 infection is known to be related to multiple diseases, including neoplastic growth of HTLV-1-infected T cells (ATL) and neoplastic inflammatory conditions, such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), Sjögren's syndrome with arthritis, polymyositis uveitis, and bronchoalveolitis [2,5,6]. Inflammation plays a major role in the pathogenesis of HTLV-1 (**Figure 1**).

Heparin, glucose transporter 1, sulfate proteoglycans, and neuropilin-1 are all HTLV-1 receptors. Therefore, HTLV-1 may infect various hematopoietic cells in vitro [7,8].

Tregs (regulatory T cells; CD127<sup>-</sup> CD4<sup>+</sup> CD25<sup>+</sup> FOXP3<sup>+</sup>) and Th17 cells (T helper 17; CD4<sup>+</sup> IL-17A<sup>+</sup>) are the two subsets of CD4<sup>+</sup> T cells [9]. Tregs express several cell surface molecules, including CD25, CD45R, CD62L, CD127, CD103, cytotoxic T-lymphocyte antigen-4 (CTLA-4, or CD152), glucocorticoid-induced TNF receptor family-related gene (GITR), and programmed cell death 1 (PD-1), thus enabling them to be characterized and isolated [10]. FOXP3 is a Tregs-specific transcription factor that plays a significant role in the differentiation, development, and function of Tregs, as well as a specific marker for Tregs characterization [11]. Tregs can regulate the functions and proliferation of innate immune cells (macrophages and dendritic cells) as well as suppress the overactivity of lymphocytes (Th1, Th2, Th17, and B cells) via direct cell interaction and the indirect production of potent anti-inflammatory cytokines, such as TGF- $\beta$  and IL-10 [12]. This leads to the inhibition of excessive immune responses that may contribute

to the pathogenesis of viral infections, such as HTLV-1 infection<sup>[13,14]</sup>. TGF- $\beta$  is a multifunctional cytokine secreted by Tregs and other immune and non-immune cells, including macrophages, dendritic cells, fibroblasts, keratinocytes, and others. TGF- $\beta$  plays a regulatory role in maintaining peripheral tolerance<sup>[15,16]</sup>. IL-10, as a pleiotropic cytokine, is secreted by Tregs. It activates Th2 cells, B cells, monocytes, and macrophages, as well as plays a central role in limiting adverse inflammatory responses, which could contribute to tissue injury<sup>[15,16]</sup>. In addition, IL-10 is essential for immune homeostasis<sup>[15,16]</sup>.



**Figure 1.** Cellular mechanisms underlying the pathogenesis of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (CNS refers to central nervous system)

Th17 cells elicit inflammatory reactions by producing various pro-inflammatory cytokines, such as IL-22, IL-21, IL-17A, IL-17 F, and TNF $\alpha$ <sup>[17,20]</sup>. The overreaction of Th17 cells may result in uncontrolled inflammatory reactions that may lead to CNS inflammation and tissue damage in HTLV-1 infection<sup>[21]</sup>. As Tregs regulate the activity of Th17 cells, the imbalance of the Treg/Th17 axis is a key contributor to the pathogenesis of HTLV-1 infection.

ROR- $\gamma$ t plays a role in Th17 differentiation<sup>[22]</sup>. IL-17A is responsible for inducing cell types to produce other pro-inflammatory cytokines, chemokines, and metalloproteinases, resulting in the recruitment of neutrophils to tissues, and thereby contributing to the inflammatory process<sup>[23]</sup>. IL-6 is a pro-inflammatory cytokine, which is a marker of both acute and chronic inflammation<sup>[24]</sup>. IL-6 contributes to Th17 differentiation by suppressing the gene expressions of FOXP3 and TGF- $\beta$  in Tregs<sup>[24]</sup>.

MT-2 is a human HTLV-1-infected cell line derived from leukemic cells in adult T-cell leukemia patients<sup>[25]</sup>. It can be used to determine the molecular and cellular factors involved in the pathogenesis of HTLV-1 infection<sup>[26]</sup>. It has been discovered that the majority of MT-2 cells are regulatory T cells (CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup>), implying that HTLV-1 transforms infected CD4<sup>+</sup> T cells to Tregs and leads to clonal proliferation<sup>[25]</sup>. Similarly, Tregs have also been suggested to be the most HTLV-1-infected cells in patients with ATL and HAMP/TSP<sup>[4]</sup>. The proliferation of Tregs increases in response to HTLV-1 infection, and these cells have been shown to be functionally impaired *in vivo* and *in vitro*, which might be one of the mechanisms behind the triggering of inflammatory responses<sup>[4,27]</sup>. Th17-mediated pro-inflammatory responses can enhance viral replication. However, the contributions of Tregs and Th17 cells in HTLV-1-associated conditions vary depending on the infection stage and host immunological state<sup>[4,21, 28-30]</sup>.

As an HTLV-1-infected human T cell line, the MT-2 cell line can be useful in determining the molecular and cellular factors involved in HTLV-1-related diseases [26]. The majority of MT-2 cells are regulatory T cells [25]. Furthermore, Tregs have been suggested to be the most HTLV-1-infected cells in vivo [4]. On the other hand, HTLV-1-infected CD4<sup>+</sup> T cells from HAM/TSP patients spontaneously proliferate as a result of oncogene activity, and Tregs are known as the subpopulation of TCD4<sup>+</sup> cells [31]. Tregs, which express FOXP3 as the key transcription factor and secrete immunosuppressive cytokines, including IL-10 and TGF- $\beta$ , regulate immune cell functions [13]. Tregs have shown to be useful for cell-based immunotherapy in autoimmune and inflammatory disorders because they promote immune homeostasis and the regulation of adverse inflammatory responses [32,33]. Previous research has shown that increased FOXP3 expression in patients with ATL contributes to enhanced Tregs activity, leading to increased secretion of TGF- $\beta$  and IL-10, which then activates the immunosuppression phenotype seen in HAM/TSP patients [32]. Therefore, it can be concluded that the role of Tregs in the pathogenesis of HTLV-1 infection varies based on the stage of infection and the host immune status [4,21,28,29]. Th17 cells, which express ROR- $\gamma$ t as a transcription factor and secrete IL-17A, are one of the most prominent subsets of inflammatory cells [34,35]. ROR- $\gamma$ t expression has been shown to be elevated in ATL patients' skin and other tissues, which has been linked to inflammatory responses [21]. Th17 cells, on the other hand, have been linked to inhibiting viral transmission in some cases. As a result, similar to Tregs, Th17 cell functions vary depending on the stage of infection and the host immunological background during viral infection [4,21].

The impairment of Tregs was thought to have a role in Th17 cell overreaction, resulting in uncontrolled inflammatory responses that might worsen viral infection, since Th17 cell activities are regulated by Tregs [21].

In the pathogenesis of HTLV-1, an immunosuppressive microenvironment with regulatory T cell contribution may have two opposing roles. On the one hand, the regulatory functions of Tregs in suppressing immune responses may have enabled HTLV-1 to escape host immunity, thus resulting in the progression of its infection [7]. In this scenario, Tregs might exacerbate the pathogenic cascade of HAM/TSP [36]. HTLV-1, on the other hand, inhibits the functions of Tregs, thus increasing their proliferation and potentially impairing the suppressive activity of Tregs; ultimately, unregulated inflammation occurs in support of virus survival [37-40]. However, the effect of anti-inflammatory and pro-inflammatory responses on viral infection is assumed to be dependent on the stage of infection and the host immune status [4,7].

HTLV-1 infection disrupts immune homeostasis by altering Treg and Th17 activities, as well as some associated cytokines, such as IL-17A, IL-10, and TGF- $\beta$ , resulting in an imbalance of inflammatory and anti-inflammatory responses, in addition to a failure of tolerance and the exacerbation of inflammation [31, 41-45].

## 2. Conclusion

In HTLV-1 infection, Tregs are impaired, whereas Th17 cell differentiation and functions are enhanced, indicating that the inflammatory state in HTLV-1 infection may contribute to the pathogenesis of HTLV-1-associated diseases, such as ATL and HAM/TSP. Therefore, immunomodulator agents, such as VitD3 and curcumin, may be effective in preventing and treating HTLV-1 infection. In light of this potential, clinical trials in the field of using VitD3 as a complementary therapy in patients with HTLV-1 infection are recommended.

## Disclosure statement

The authors declare no conflict of interest.

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