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REVIEW ARTICLE

Inflammatory and anti-inflammatory responses in human T-lymphotropic virus Type 1 infection

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Abstract

Human T-lymphotropic virus Type 1 (HTLV-1) is a viral infectious agent that may cause chronic infection of T lymphocytes. HTLV-1 infection is related to multiple human diseases, including adult T-cell leukemia, which is a neoplastic growth of HTLV-1-infected T cells, and neoplastic inflammatory conditions such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), Sjögren's syndrome, polymyositis uveitis, and bronchoalveolitis. T regulatory cells (Tregs), also known as regulatory T cells, and T helper 17 (Th17) cells, a distinct subset of cluster differentiation T cells with interleukin-17 as their major cytokine, orchestrate the pathogenesis of anti-inflammatory and inflammatory responses in HTLV-1-mediated diseases. In this review, we aim to evaluate the immune responses of Tregs as anti-inflammatory cells and Th17 cells as inflammatory cells in HTLV-1 infection.

Keywords: Inflammatory responses; Anti-inflammatory responses; Human T-lymphotropic virus type 1; HTLV-1-associated myelopathy/tropical spastic paraparesis

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1. Introduction

Human T-lymphotropic virus Type 1 (HTLV-1) is anoncogenic virus that may cause chronic infection of human T cells. It is endemic in several countries, such as Southern Japan, the Caribbean region, areas in South America and tropical Africa, and some foci in the Middle East, Australia, and Melanesia[1-3]. The majority of patients who are infected with HTLV-1 are without certain symptoms, including fever, cough, shortness of breath, nausea, and diarrhea[4,5]. HTLV-1 infection is associated with several disorders, of which the main conditions are adult T-cell leukemia (ATL), which is a neoplastic growth of HTLV-1-infected T cells, and neoplastic inflammatory conditions, such as HTLV-1-associated myelopathy/tropical spastic paraparesis(HAM/TSP), Sjögren's syndrome, polymyositis uveitis, and bronchoalveolitis[2,5,6]. Inflammation may have a major role in the pathogenesis of HTLV-1, as shown in Figure 1.

Neuropilin-1, glucose transporter 1 (GLUT1), and heparin sulfate proteoglycans (HSPGs) are all HTLV-1 receptors[7,8]. Since both GLUT1 and neuropilin-1 are found on various cell surfaces, it is possible that HTLV-1 infects various hematopoietic cells and hematopoietic stem cells (HSCs),such as T cells[7,8]. These receptors facilitate the binding of HTLV-1 with hematopoietic cells. The entry of retroviruses into target cells involves

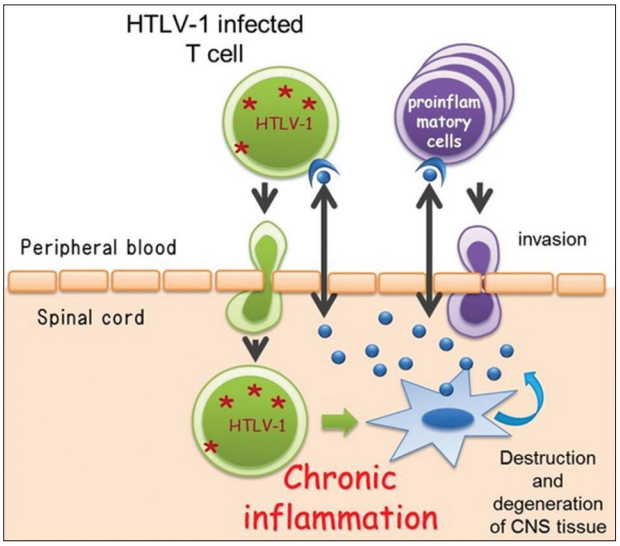

Figure 1. Cellular mechanisms underlying the pathogenesis of human T-lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-1-specific immune responses and secondary inflammations inflated in the CNS may lead to subsequent CNS damage. CNS, central nervous system; HTLV-1, human T-lymphotropic virus Type 1; *HTLV-1.

interactions between viral envelope (Env) glycoproteins, a surface glycoprotein (SU) and a transmembrane glycoprotein (TM), with specific cell surface molecules, referred to as receptors. SU is involved in receptor recognition, while TM triggers the fusion of viral and cellular membranes, allowing viral particles to enter target cells[9,10]. GLUT1 has been shown to specifically bind to a truncated soluble form of HTLV-1 and HTLV-2 SU proteins, and the level of GLUT1 in target cells has been found to be correlated with the titer of HTLV-2 Env-pseudotyped virus[10,11]. HSPGs might play a role in HTLV-1 entry. T-helper 17 (Th17) cells and regulatory T cells (Tregs) are two subsets of $CD4^+$ T cells[12].

2. Regulatory T cells

Tregs are a subpopulation of $CD4^+$T cells[13]. Tregs have multiple markers, including CD25, glucocorticoid-induced tumor necrosis factor receptor family-related protein(GITR), CD45R, CD62L, CD127, CD103, cytotoxic Tlymphocyte antigen-4 (CTLA-4), and programmed cell death 1 (PD-1) [14]. Forkhead box P3 (FOXP3) is a master transcription factor of Tregs that plays a key role in Tregs activity[15].

Tregs have shown to be useful for immunotherapy in autoimmune and inflammatory conditions as they contribute to establishing and maintaining immune homeostasis[12,16]. Tregs can regulate innate immune cells and adaptive immune cells as well as suppress adverse inflammatory responses of both T and B cells in adaptive immunity. The functions of Tregs include cell contact and production of potent tolerogenic cytokines, such as interleukin (IL)-10, IL-35, and transforming growth factor beta (TGF-β)[17]. Therefore, Tregs can modulate the adverse immune responses that may be involved in the pathogenesis of HTLV-1 infection[18,19]. TGF-β plays a regulatory role in establishing and maintaining peripheral and tissue tolerance[20,21]. IL-10, as a multifunctional cytokine, can effectively limit adverse inflammatory response[20,21]. In addition, IL-10 is also essential for immune homeostasis[20,21]. IL-35 is an inhibitory cytokine composed of Epstein-Barr virus-induced gene 3 and p35 subunits released by Tregs[22]. IL-35 appears to play a critical role in infectious tolerance not only by suppressing the proliferation of effector T cells, but also by inducing the production of IL-35 by non-FOXP3 conventional T cells (Tconvs), which areknown as iTr35 cells[23]. IL-35 has also been associated with the suppression of various autoimmune diseases and atherosclerosis[23,24].

3. T-helper 17 cells

Th17 cells are the subpopulation of $CD4^+$ T cells, with a pro-inflammatory cytokine profile, including IL-21, IL-22, IL-17A, IL-17 F, and tumor necrosis factor alpha (TNFα)[25-28]. Retinoicacidreceptor-related orphan nuclear receptor gammat (ROR-γt) is the most important transcription factor involved in Th17 cell differentiation and function[29]. The N terminus of RORγt has a transcription modulation domain (TMD) comprising deoxyribonucleic acid(DNA)-binding amino acid residues and isotype-specific sequences that may play key roles in the functional specificity of RORγt[30]. RORγt, induced at the early stage of Th17 cell differentiation following IL-6 and TGF-β stimulation, has a pivotal role inTh17 cell lineage commitment[31]. RORγt specifically binds to and regulates Th17-associated genes, such as*IL17A*, *IL17F*, and*IL23R*, by activating their transcription in coordination with other transcription factors[32]. Therefore, targeting RORγt by small molecules either genetically or pharmacologically is effective in ameliorating Th17-related inflammatory disorders, including experimental autoimmune encephalomyelitis (EAE), psoriasis, arthritis, colitis, and glomerulonephritis, especially in preventative disease models[33].

IL-17A is responsible for inducing cell types to produce other pro-inflammatory cytokines, chemokines, and metalloproteinases, thereby recruiting neutrophils to the tissue and contributing to the inflammation process[34]. IL-22 is a key cytokine produced by Th17 cells, and it plays an important role in maintaining homeostasis and remodeling epithelial tissues. The importance of IL-22 has been highlighted in the pathogenesis of psoriasis[35,36]. In a study, *IL-22* mRNA expression was found to be

upregulated in psoriatic skin as compared to normal skin, whereas the expression of *IL-22* mRNA in peripheral blood mononuclear cells of both psoriatic patients and normal controls were similar[36]. IL-17F, which is very similar to IL-17, is considered an inflammatory cytokine since it induces many pro-inflammatory cytokines and chemokines[37]. *IL-17F* mRNA has also been reported to be associated with activated monocytes, basophils, and mast cells[37].

IL-6 is a pro-inflammatory cytokine that is a marker of both acute and chronic inflammation[38]. IL-6 is involved in immune responses, inflammation, hematopoiesis, bone metabolism, and embryonic development. IL-6 plays various roles in chronic inflammation (closely related to chronic inflammatory diseases, autoimmune diseases, and cancer) and even in the cytokine storm of the coronavirus disease (COVID-19)[39].

4. Role of Treg/Th17 axis in human T-lymphotropic virus Type 1infection

The adverse inflammatory reactions resulting in the central nervous system (CNS) inflammation and tissue damage followingHTLV-1 infection may be caused by the inappropriate function of Th17 cells[40]. The imbalance of the Treg/Th17 axis is a probable factor in the pathogenesis of HTLV-1 infection because Tregs regulate the function of Th17 cells. IL-6 contributes toTh17 cell differentiation by suppressing *FOXP3* and *TGF-β*gene expressions in Tregs[38]. Through direct cell interaction and the release of anti-inflammatory cytokines, both natural and induced (i) Tregs regulate the proliferation and activities of innate immune cells (dendritic cells and macrophages) and suppress self-reactive lymphocytes, such as Th17cells[41].

MT-2 is a human HTLV-1-infected cell line obtained from the leukemic cells of ATL patients[42]. This cell line can be used to determine the molecular and cellular factors that are involved in the pathogenesis of HTLV-1 infection[43]. The majority of MT-2 are regulatory T cells ($CD4^+CD25^+FOXP^+$), which imply that HTLV-1 transforms infected $CD4^+$ T cells into Tregs and causes clonal proliferation[42]. Similarly, Tregs have been suggested to be the cells most infected with HTLV-1 in patients with ATL and HAM/TSP[4]. The proliferation of Tregs increases in response to HTLV-1 infection, but these cells have been shown to be functionally impaired *in vivo* and *in vitro*, which might be one of the mechanisms behind the triggering inflammatory responses[4,44]. Th17-mediated pro-inflammatory responses can enhance viral replication. However, the contributions of Tregs and Th17 cells in HTLV-1-associated illnesses[4] vary depending on the stage of infection and the host's immunological state[4,40,45-47]. The previous research has shown that increased FOXP3 expression in patients with ATL contributes to enhanced Tregs activity, which subsequently leads to increased TGF-β and IL-10secretion, thus activating the immunosuppression phenotype observed in HAM/TSP patients[13]. As mentioned, Th17 cells, as pro-inflammatory cells, express ROR-γt, as a transcription factor, and secrete IL-17A[48,49]. ROR-γt expression has been shown to be elevated in ATL patients' skin and other tissues, which can be attributed to inflammatory reactions[40]. Since Th17 cell actions are regulated by Tregs, it has been hypothesized that Tregs impairment may contribute toTh17 cell overreaction, leading to uncontrolled inflammation and consequently the exacerbation of inflammation in viral infection[40]. However, it has been indicated that Th17 cells may be important for viral transmission suppression in some cases. A study has shown significantly lower levels of Th17 cells in HAM/TSP patients compared to uninfected subjects and a trend toward reduced number of IL-17-secreting cells compared to HTLV-1 asymptomatic carriers. Th17 cell functions vary depending on the stage of infection and the host immune status in viral infection, similar to Tregs[4,40]. Therefore, we conclude that the role of Tregs in the pathogenesis of HTLV-1 infection varies depending on the stage of infection and the host immune status[4,40,45,46].

In the pathogenesis of HTLV-1, the immunosuppressive microenvironment mediated by Tregs may have two opposing roles. On the one hand, the regulatory function of Tregs in suppressing immune responses may have enabled HTLV-1 to escape host immunity, resulting in viral infection progression[50]. In this scenario, Tregs could worsen the HAM/TSP pathogenic process[51]. On the other hand, HTLV-1 functionally inhibits Tregs by increasing its proliferation, which leads to potential impairment of

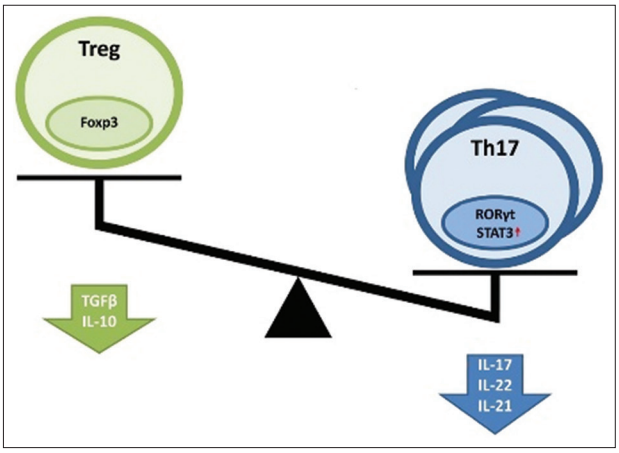

Figure 2. Treg/Th17 imbalance in human T-lymphotropic virus Type 1 infection.

Table 1. Characteristics and results of selected studies

Author	Year of publication	Study design	Number of participants	Neurological disease (HAM/TSP)	Hematologic disease (ATL)	Results
Champs *et al.*[47]	1986	Experimental (*in vitro*)	–	–	Yes	Production of 1,25(OH_2) D by lymphoma cells may contribute to the pathogenesis of hypercalcemia in ATL.
Satou *et al.*[53]	1986	Case series	5	–	Yes	Five patients with ATL had 1,25(OH_2) D levels within or below the normal range, and it was not associated with the usual cause of hypercalcemia in such patients.
Nakao *et al.*[62]	1987	Experimental (*in vitro*)	–	–	Yes	1,25(OH_2) D inhibited the proliferation and *de novo* DNA synthesis of certain HTLV-positive T cell lines.
Nakao *et al.*[62]	1987	Case series	18	–	Yes	Two ATL patients with hypercalcemia had low 1,25(OH_2) D levels. Hypercalcemia in ATL patients may be a result of the production of factor (s) that stimulate osteoclastic bone resorption by tumor cells.
Reichel *et al.*[63]	1987	Experimental (*in vitro*)	–	–	Yes	HTLV-1-transformed lymphocytes can produce 1,25(OH_2) D but the excess production of 1,25(OH_2) D was unlikely to be associated with the pathogenesis of ATL-associated hypercalcemia.
Koizumi *et al.*[64]	1989	Experimental (*in vitro*)	–	–	Yes	1,25(OH_2) D and glucocorticoid-inhibited cellular proliferation and *c-myc* mRNA expression in HTLV-1-infected T-cell line, KH-2.
Inoue *et al.*[65]	1993	Experimental (*in vitro*)	–	–	Yes	22-oxa-1,25(OH_2)D_3 (non-calcemic analog) and 1,25(OH) $_2$D suppressed cell proliferation and *PTHrP* gene expression by binding to overexpressed Vitamin D receptor in HTLV-1-infected T cells.
Elstner *et al.*[66]	1994	Experimental (*in vitro*)	-	–	Yes	1,25(OH_2)-20-epi-D_3, the potent 1,25(OH_2) D analog, was identified with anti-proliferative and differentiating effects on leukemic cells.
Peter *et al.*[67]	1995	Case report	2	–	Yes	Hypercalcemia with normal Vitamin D levels. PTHrP seemed to be the supposed factor for hypercalcemia associated with ATL.
Masutani *et al.*[68]	2005	Review	–	–	Yes	The expression of TBP-2/VDUP1, a growth suppressor, was suppressed in HTLV-1-transformed cells.

1,25(OH_2) D: 1,25-dihydroxyvitamin D; HAM/TSP: HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1: Human T-lymphotropic virus type 1; TBP-2: Thioredoxin-binding protein-2; VDUP1: Vitamin D_3 upregulated protein 1

the suppressive activity of Tregs and the up regulation of inflammation in support of virus survival[52-55]. However, the effects of anti-inflammatory and pro-inflammatory responses on viral infection are assumed to be dependent on the stage of infection phase and host immune status[4,7].

Taken together, HTLV-1 infection disrupts immune homeostasis, by altering Treg/Th17 balance (Figure 2), and their associated cytokines, such as IL-17A, IL-10, and TGF-β, which may result in an imbalance of inflammatory and anti-inflammatory responses, tolerance failure, and an exacerbation of inflammation[13,56-60].

Tregs can regulate Th17 cells through direct cell interaction and indirectly by producing potent anti-inflammatory cytokines, such as TGF-β and IL-10. This leads to the inhibition of excessive immune responses that may contribute to the pathogenesis of viral infections, such as HTLV-1 infection. Treg/Th17 axis imbalance is the key contributor to the pathogenesis of HTLV-1 infection.

5. Conclusion

A growing number of evidence has indicated that both Tregs impairment and Th17 cell differentiation are

enhanced in HTLV-1 infection, and the inflammatory state in HTL-V1 infection may contribute to the pathogenesis of HTLV-1-related diseases, such as ATL and HAM/TSP. Therefore, immunomodulator agents such as Vitamin D3 (VitD3) may be effective in the prevention and treatment of HTLV-1 infection[61].

Recently, it has been suggested that1,25-dihydroxyvitamin D3 (1,25-VitD3) may act as both an immunoregulatory agent (improving Tregs functions) and an immunosuppressive agent (attenuatingTh17 cell functions), delineating the role of VitD3 as an immunomodulator in HTLV-1 infection. This highlights the importance of sufficient Vitamin D levels and also taking VitD3 supplementation in HTLV-1 infection[61] (Table 1). With regard to its potential, clinical trials in the field investigating the benefits of using VitD3 as a complementary therapy in patients with HTLV-1 infection are recommended. According to the Table 1, the use of VitD3 as a complementary therapy in patients with HTLV-1 infection is recommended.

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Conflict of interest

No conflicts of interest.

Author contributions

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Ethics approval and consent to participate

Not applicable

Consent for publication

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