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The Role of Type 17 Helper T Cells and Regulator T Cells in Human Immunodeficiency Virus (HIV) Infection: A Review

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ABSTRACT: The Human Immunodeficiency Virus (HIV) continues to be a major global health issue, affecting millions of individuals globally, in developing countries, specifically. HIV infection is indicated by the complex interactions between the virus and the host immune system. Among the various immune cell subsets involved, T regulatory cells (Tregs) and T helper 17 cells (Th17) play pivotal roles in preserving immunological homeostasis. This review provides a comprehensive overview of the current understanding of Treg and Th17 cell activities during HIV infection, exploring their complex interactions, how they affect immune dysregulation and disease progression, and possible therapeutic implications.

KEYWORDS: Human immunodeficiency virus (HIV); Immune system, Regulatory T cells; T helper 17; Virus

I. INTRODUCTION

The Human immunodeficiency virus (HIV) is a virus that attacks the human immune system and then causes AIDS. This virus can be passed from mother to child during childbirth and breastfeeding, as well as through sexual contact, blood transfusions, and sharing intravenous needles. HIV infection is characterized by a declining immune system, which can result in cancer, autoimmune disorders, and opportunistic infections.1 The virus attacks vital organs in the immune system, such as T4 CD4+ macrophages and dendritic cells, causing their depletion and malfunction.2-6 Progressive disruption and massive dysregulation of the immune system in humans, particularly the loss of CD4+ T helper cells, which ultimately leads to the development of acquired immunodeficiency syndrome (AIDS).5-6

Under normal conditions, the human immune system fights various kinds of incoming foreign objects, including pathogens. HIV infects human immune system cells and destroys or disrupts their function. This viral infection causes a continuous decline in the immune system, resulting in immune deficiency. The immune system is considered deficient when the system can no longer carry out its function of fighting infections and diseases. People who are immune deficient become more susceptible to various conditions, most of which rarely affect people who do not have an immune deficiency.

In HIV, several cells experience dysregulation, including regulatory T cells (Tregs)7 and helper T cells (Th17). Tregs are known for their immunosuppressive functions, and Th17, crucial for mucosal immunity. Therefore, Treg and Th17 cells are two distinct subsets of CD4+ T cells that can develop to promote or regulate tissue inflammation.8

This article will discuss the role of Tregs and Th17 cells in HIV pathogenesis, shedding light on their interactions and the consequences for the host immune response. Thus, it can increase understanding of the human immune system in abnormal conditions, especially viral infections.

II. DISCUSSION

Human Immunodeficiency Virus (HIV)

Human immunodeficiency virus (HIV) is a virus that attacks the human immune system and then causes AIDS. HIV is an RNA virus belonging to the Retroviridae family, Lentivirinae subfamily.[9] Retroviruses can use their RNA and host DNA to form DNA viruses and are recognized during long incubation periods. Once infected with a retrovirus, this infection will be permanent for life.

HIV consists of an envelope and a core. The HIV consists of 2 sub-types, namely HIV-1 and HIV-2. HIV-1 mutates faster because it replicates more quickly.[9] Structurally and morphologically, HIV forms consist of A cylinder surrounded by a circular fat covering. At the center of the circle is a strand of RNA. HIV has three genes, which are functional and structural components, namely gag (group antigen), pol (polymerase), and env (envelope) (See Fig.1).

HIV has a reverse transcriptase enzyme, which can change genetic information and then integrate it into the knowledge of the attacked lymphocyte cells. In this way, HIV can utilize the lymphocyte cell mechanism to copy itself into a

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new virus that has the characteristics of HIV.[10] HIV attacks the human immune system by attacking T helper lymphocytes with CD4 receptors on their surface. T helper lymphocytes, among other functions, produce chemicals that act as stimulants for the growth and formation of other cells in the immune system and the construction of antibodies so that not only T lymphocytes are disturbed but also B lymphocytes, monocytes, macrophages, and so on and damage the immune system.[11] Furthermore, it can facilitate opportunistic infections in the body. This condition is called AIDS.

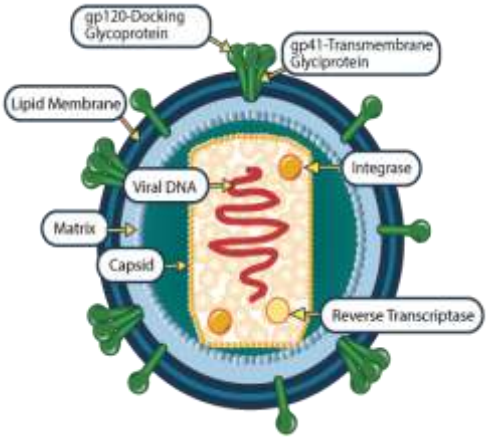

Figure 1. Structure of HIV[10]

In its original form, HIV is an inert particle, unable to grow or injure until it enters the target cell. Therefore, the target cells of this virus, especially lymphocyte cells, have a receptor for HIV called CD-4.[12] In lymphocyte cells, the virus can develop and, like other retroviruses, can remain alive for a long time in cells in an inactive state. However, the virus in the body of a person with HIV is always considered infectious, can be active at any time, and can be transmitted during the life of the sufferer. The genetics of the infected person play an important role. Some people are immune to some strains of HIV. An example is a person with the CCR5-Δ32 mutation (a 32 nucleotide deletion in the gene encoding the chemokine receptor CCR5 that affects T cell function).[13]

The primary basis of HIV pathogenesis is the lack of helper/inducer types of T lymphocytes that contain the CD4+ marker (T4 cells). T4 lymphocytes are the central cells that directly or indirectly induce immunological functions. The decrease or loss of the cellular immune system occurs because HIV selectively infects T4 lymphocyte cells.[14]

HIV infects CD4 receptor molecules and chemotactic cytokines through the virus's glycoprotein, gp120.[15] The mechanism of action of HIV infection is that GP 120 binds to the CD4 receptor and chemokine receptors (CXCR 4 and CCR5).[16-17] HIV only effectively binds to this receptor and thus proves that viral infection only occurs in specific cells, for example, T helper lymphocyte cells in the human body's immunization system. Once HIV binds to the CD4 molecule and co-receptor, the virus enters, and the envelope falls off.[12] By the reverse transcriptase enzyme, RNA will be changed in shape so that it can combine with the DNA of the target cell. Furthermore, the cells that multiply will contain the virus's genetic material. HIV infection thus becomes irreversible and lasts a lifetime.

The viral DNA, which is perceived by the body as stem cell DNA, will form RNA with the facility of the stem cell, while protease enzymes will convert the MRNA in the cytoplasm into HIV particles. The particle then takes the envelope of the stem cell material to be released as another HIV.[18] This mechanism in the immune system (immunosuppression) will cause a reduction and disruption of the number and function of T lymphocyte cells.

At the start of infection, HIV does not immediately cause the death of the infected cells but first undergoes replication (doubling) so that there is an opportunity to develop in the sufferer's body, which will gradually deplete or damage up to a certain number of T4 lymphocyte cells. After several months to several years, the sufferer will show clinical symptoms as a result of the HIV infection.

Regulatory T-cells (Tregs)

The immune system has regulatory mechanisms that prevent sustained inflammatory responses and attacks on healthy tissue. Regulatory T lymphocytes are a subset of CD4+ T cells that suppress immune responses and maintain self-tolerance.[19] Most of these CD4+ Treg lymphocytes express interleukin-2 (IL-2) receptor α chain (CD25) at high levels but not other markers of T cell activation.[20] A transcription factor called FoxP3 is essential for the development and function of most regulatory T cells. Mice with mutations in the Foxp3 gene and mice in which this gene has been knocked out develop a multisystem autoimmune disease associated with the absence of CD25+ regulatory T cells.[21]

Another primary function of Treg cells is to inhibit the function of antigen-presenting cells and T effector cells (Teff cells). Regulatory T cells

inhibit the ability of APCs to stimulate T cells. One of these mechanisms relies on CTLA-4, expressed by FoxP3+ regulatory cells, and appears to be required for their function.[22] CTLA-4 on regulatory cells may bind to B7 molecules on APCs and either block these molecules or eliminate them by internalizing them, thereby reducing the availability of B7 and being unable to provide adequate costimulation for the immune response.[23-24]

Regulatory T cells are produced through self-antigen recognition in the thymus (sometimes called natural regulatory cells) through self-antigen recognition in peripheral lymphoid organs, called inducible or adaptive regulatory cells. The development and survival of these regulatory T cells require IL-2 and the transcription factor FoxP3.[25-26.] Activated Tregs will suppress the reactivity of autoregressive cells.

Tregs will be activated if CTLA-4 on their surface binds to the CD80/CD86 molecules on the APC surface. CTLA-4:CD80/CD86 binding will increase the expression of IDO (Indoleamine 2, 3-dioxygenase) in APC. An increase in IDO will deplete the availability of tryptophan in the area around the APC. This situation results in the cessation of proliferation of effector T cells and other autoreactive cells. Several other facts show that a lack of tryptophan will cause effector cells to undergo apoptosis. Tregs that have been activated by an antigen not only suppress the cells carrying the antigen, but they will carry out non-specific work on all effector cells, so the use of Tregs in therapy must consider matters related to the importance of effector cell function.[23-24]

T-helper 17 (Th17) cells

CD4+ T cells are essential in initiating immune responses by assisting other cells and assuming various effector functions during immune reactions. Naive CD4+ T cells respond to antigenic stimulation by activating, proliferating, and differentiating into effector subsets known as T helpers (Th1), Th2, Th9, Th17, and Th22. These subsets are distinguished by their production of unique cytokines and effector functions.[27]

Th17 cells have been identified as one of the significant Th cell populations. Like Th1 and Th2 cells, Th17 cells require specific cytokine and transcription factors to differentiate. Th17 cells have an important role in driving the inflammatory process, a direct protective response of the body against foreign pathogens. Those cells can also produce tumor necrosis factor (TNF)-a, IL-6, IL-22, IL-21, and IL-26,[28] but as cytokines, these are also produced by other Th cell subsets. The chemokine and cytokine receptor expression patterns of human Th17 cells have been studied extensively, and it is now generally accepted that they express CCR4, CCR6, and IL-23R but not CXCR3.[29-31]

Many studies suggested that Th17 cells are crucial in maintaining mucosal barrier integrity and defending against pathogens. The lack of Th17 cells contributes to chronic immune activation and inflammation, hallmark features of progressive HIV infection. HIV preferentially targets mucosal CD4+ T cells, depleting Th17 cells and compromising mucosal immunity.[8]

Treg and Th17 Cells Activity in HIV Pathogenesis

Th17 cells are functionally distinct from Th1 and Th2 cells and are associated with chronic inflammatory diseases and autoimmune disorders. Th17 can enhance host defense against microbial agents and may be essential in maintaining the inflammatory state, especially in gastrointestinal (GI) enterocyte homeostasis in progressive HIV disease. Loss of Th17 cells in HIV infection may result in bacterial translocation from the intestine to the systemic circulation and may lead to immune activation, leading to HIV infection.

Meanwhile, Treg cells can interfere with protective immune responses and control T cell self-reactivity. The influence of Tregs on HIV infection is still unclear. Several research groups have reported that Tregs can explain HIV pathogenesis by altering the function of HIV-specific T cell responses, thereby accelerating viral replication. Other studies have shown that Tregs play a beneficial role by limiting or suppressing immune system activation, which is also one of the main mechanisms in T cell dysfunction and depletion.

Tregs secrete TGFβ and IL-10 and require the specific cytokine TGFβ and the transcription factor FoxP3 to differentiate. While Th17 cells promote autoimmunity[32], Tregs control Th17 cells. Thus, the Th17/Treg ratio is necessary to control immunity mediated by Th17 cells. Some studies found that the frequency of Th17 decreased continuously over time in the peripheral blood of HIV-infected individuals.[33] Changes in the frequency of Th17 cells and the number of CD4+ T cells had a strong positive correlation during the progression of HIV-1 infection. These data are consistent with many recent studies showing preferential depletion of Th17 cells from infection with the pathogen simian immunodeficiency virus (SIV) in the gut and HIV in the blood.

Contrary to the decrease in Th17 cells, the frequency of Treg cells was markedly higher in HIV-1-infected patients and increased post-HIV infection. In addition, the frequency of Treg cells was inversely related to the number of CD4+ T cells and positively correlated with viral load. The progressive loss of Th17 and increase in Treg cells in HIV-1-infected individuals, especially those with advanced disease, suggests that a functional Th17/Treg imbalance exists, and the Th17/Treg ratio gradually decreases throughout disease progression.[34] This conclusion is supported by recent studies showing that IDO 1 (indoleamine 2, 3-dioxygenase 1)-dependent tryptophan catabolism may be important in controlling the Th17/Treg balance.[35] Various studies emphasize that the Th17/Treg ratio plays quite an important role in the pathogenesis of chronic HIV infection.

This Th17/Treg functional imbalance provides a paradigm. It also gives a new target for our understanding of HIV pathogenesis and future considerations regarding the treatment of chronic HIV infection and the development of an HIV vaccine. It is also possible to manipulate Th17 and Treg function to cure immunodeficiency.

Therapeutic Implications

HIV infection affects the human immune system, causing immunodeficiency and immunosuppression, ultimately increasing vulnerability to opportunistic infections and illnesses. Some studies have shown that many immunotherapies can enhance and control the immune system of HIV-infected individuals. Restoring Immune Balance is a potential strategy to rebalance Th17 and Treg cells. Th17/Treg balance is strictly maintained in a healthy state and is essential to preserving the immunological homeostasis of human beings. Antiretroviral therapy (ART), for instance, significantly decreases the incidence and severity of opportunistic diseases and death.[36] Mucosal Immunity Restoration is also an alternative strategy to restore Th17 cells, enhance mucosal barrier integrity, and defend against pathogens. Improving mucosal immunity will minimize the impact of HIV on mucosal tissues.

III. CONCLUSION

Understanding the dynamic interplay between Tregs and Th17 cells during HIV infection is essential for unraveling the complexities of immune dysregulation. Therapeutic approaches that target immunological homeostasis and mucosal immunity have the potential to improve clinical outcomes in HIV-positive patients. More investigation is necessary to fully understand the mechanisms underlying Tregs-Th17 dynamics and convert these discoveries into helpful treatment strategies.

REFERENCES

[1]. Boasso A, Shearer GM, Chougnet C. Immune Dysregulation in Human Immunodeficiency Virus Infection: Know It, Fix It, Prevent It? J. Intern. Med. 2009, 265, 78–96. https://doi.org/10.1111/j.1365-2796.2008.02043.x

[2]. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T Cells and Human Disease. Annual Review of Immunology 2020;38(1):541–66. https://doi.org/10.1146/annurev-immunol-042718-041717

[3]. Jenabian MA, Ancuta P, Gilmore N, Routy JP. Regulatory T cells in HIV infection: can immunotherapy regulate the regulator? Clin Dev Immunol 2012;2012:908314. https://doi.org/10.1155/2012/908314

[4]. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. Annu Rev Immunol 2012;30:531–64. https://doi.org/10.1146/annurev.immunol.25.022106.141623

[5]. Okoye AA, Picker LJ. CD4+ T Cell Depletion in HIV Infection: Mechanisms of Immunological Failure. Immunol. Rev. 2013;254:54–64. https://doi.org/10.1111/imr.12066

[6]. Février M, Dorgham K, Rebollo A. CD4+ T Cell Depletion in Human Immunodeficiency Virus (HIV) Infection: Role of Apoptosis. Viruses 2011;3:586–612. https://doi.org/10.3390/v3050586

[7]. Yero A, Shi T, Farnos O, Routy JP, Tremblay C, Durand M, et al. Dynamics and epigenetic signature of regulatory T-cells following antiretroviral therapy initiation in acute HIV infection. EBioMedicine 2021;71(103570). https://doi.org/10.1016/j.ebiom.2021.103570

[8]. Renault C, Veyrenche N, Mennechet F, Bedin A, Routy J, Reynes J, & Tuaillon E. Th17 CD4+ T-Cell as a Preferential Target for HIV Reservoirs. Frontiers in Immunology 2022;13, 822576. https://doi.org/10.3389/fimmu.2022.822576

[9]. German Advisory Committee Blood. Human Immunodeficiency Virus (HIV). Transfus. Med. Hemotherapy 2016; 43: 203–222. https://doi.org/10.1159%2F000445852

[10]. Kuby, J. Immunology. New York: W.H. Freeman and Co; 2007.
[11]. Vidya Vijayan KK, Karthigeyan KP, Tripathi SP, Hanna LE. Pathophysiology of CD4+ T-Cell Depletion in HIV-1 and HIV-2 Infections. Front Immunol. 2017 May 23;8:580. https://doi.org/10.3389%2Ffimmu.2017.00580
[12]. Wilen CB, Tilton JC, Doms RW . Molecular mechanisms of HIV entry. Adv Exp Med Biol 2012; 726:223–242.
[13]. Pan, X., Baldauf, HM., Keppler, O. et al. Restrictions to HIV-1 replication in resting CD4+ T lymphocytes. Cell Res 23, 876–885 (2013). https://doi.org/10.1038/cr.2013.74
[14]. Nishimura Y, Brown CR, Mattapallil JJ, Igarashi T, Buckler-White A, Lafont BA, et al. Resting naive CD4+ T cells are massively infected and eliminated by X4-tropic simian-human immunodeficiency viruses in macaques. Proc Natl Acad Sci U S A (2005) 102(22):8000–5. https://doi.org/10.1073/pnas.0503233102
[15]. Woodham AW, Skeate JG, Sanna AM, Taylor JR, Da Silva DM, Cannon PM, Kast WM. Human Immunodeficiency Virus Immune Cell Receptors, Coreceptors, and Cofactors: Implications for Prevention and Treatment. AIDS Patient Care STDS. 2016 Jul;30(7):291-306. https://doi.org/10.1089%2Fapc.2016.0100
[16]. Bleul CC, Wu L, Hoxie JA, Springer TA, Mackay CR. The HIV coreceptors CXCR4 and CCR5 are differentially expressed and regulated on human T lymphocytes. Proc Natl Acad Sci U S A 1997;94:1925–1930. https://doi.org/10.1073/pnas.94.5.1925
[17]. Pérez-Nueno VI, Pettersson S, Ritchie DW, Borrell JI, Teixidó J. Discovery of novel HIV entry inhibitors for the CXCR4 receptor by prospective virtual screening. J Chem Inf Model. 2009 Apr;49(4):810-23. https://doi.org/10.1021/ci800468q
[18]. Szpara ML, Van Doorslaer K. Mechanisms of DNA Virus Evolution. Encyclopedia of Virology. 2021:71–8. doi: 10.1016/B978-0-12-809633-8.20993-X. Epub 2021 Mar 1. PMCID: PMC7173537. https://doi.org/10.1016%2FB978-0-12-809633-8.20993-X
[19]. Khan M, Siddiqi R, Shpall EJ, Olson A. Principles and Applications of Cellular Therapy in the Setting of Hematopoietic Cell Transplant. In: Bashir Q, Hamadani M, editors. Hematopoietic Cell Transplantation for Malignant Conditions. Philadelphia (USA): Elsevier; 2019. p.395-416. https://doi.org/10.1016/B978-0-323-56802-9.00028-6
[20]. Triplett TA, Curti BD, Bonafede PR, Miller WL, Walker EB, Weinberg AD. Defining a functionally distinct subset of human memory CD4+ T cells that are CD25POS and FOXP3NEG. Eur J Immunol. 2012 Jul;42(7):1893-905. https://doi.org/10.1002/eji.201242444
[21]. Rudensky AY. Regulatory T cells and Foxp3. Immunol Rev. 2011 May;241(1):260-8. https://doi.org/10.1111%2Fj.1600-065X.2011.01018.x
[22]. Schmidt A, Oberle N, Krammer PH. Molecular Mechanisms of Treg-Mediated T Cell Suppression. Frontiers in Immunology 2012; 3:21442. https://doi.org/10.3389/fimmu.2012.00051
[23]. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. American Journal of Clinical Oncology 2016; 39(1):98-106. https://doi.org/10.1097/COC.0000000000000239
[24]. Masteller EL, Chuang E, Mullen AC, Reiner SL, Thompson CB. Structural analysis of CTLA-4 function in vivo. J Immunol. 2000 May 15;164(10):5319-27. https://doi.org/10.4049/jimmunol.164.10.5319
[25]. Chinen T, Kannan AK, Levine AG, Fan X, Klein U, Zheng Y, Gasteiger G, Feng Y, Fontenot JD, Rudensky AY. An essential role for the IL-2 receptor in Treg cell function. Nat Immunol. 2016 Nov;17(11):1322-1333. https://doi.org/10.1038%2Fni.3540
[26]. Rudensky AY. Regulatory T cells and Foxp3. Immunol Rev. 2011 May;241(1):260-8. https://doi.org/10.1111%2Fj.1600-065X.2011.01018.x
[27]. Zambrano-Zaragoza JF, Romo-Martínez EJ., Durán-Avelar J, García-Magallanes N, Vibanco-Pérez N. Th17 Cells in Autoimmune and Infectious Diseases. Int J Inflam. 2014; 2014: 651503. https://doi.org/10.1155/2014/651503
[28]. Medara N, Lenzo JC, Walsh KA, Darby IB, O'Brien-Simpson NM, Reynolds EC. T helper 17 cell-related cytokines in serum and saliva during management of periodontitis.

Cytokine 2020;134:155186. https://doi.org/10.1016/j.cyto.2020.155186
[29]. Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, Sallusto F, Napolitani G. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. Nat Immunol. 2007 Jun;8(6):639-46. https://doi.org/10.1038/ni1467
[30]. Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, Parente E, Filì L, Ferri S, Frosali F, Giudici F, Romagnani P, Parronchi P, Tonelli F, Maggi E, Romagnani S. Phenotypic and functional features of human Th17 cells. J Exp Med. 2007 Aug 6;204(8):1849-61. https://doi.org/10.1084/jem.20070663
[31]. Annunziato F., Cosmi L, Liotta F, Maggi E, Romagnani S. Human Th17 cells: Are they different from murine Th17 cells? European Journal of Immunology 2009; 39(3): 637-640. https://doi.org/10.1002/eji.200839050
[32]. Noack M, Miossec P. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmunity Reviews. 2014;13(6):668–677. https://doi.org/10.1016/j.autrev.2013.12.004
[33]. Zayas JP, Mamede JI. HIV Infection and Spread between Th17 Cells. Viruses 2022; 14(2). https://doi.org/10.3390/v14020404
[34]. Li D, Chen J, Jia M, Hong K, Ruan Y, Liang H, et al. Loss of balance between T helper type 17 and regulatory T cells in chronic human immunodeficiency virus infection. Clinical and Experimental Immunology 2011; 165(3): 363-371. https://doi.org/10.1111/j.1365-2249.2011.04435.x
[35]. Favre D, Mold J, Hunt PW, Kanwar B, Loke P, Seu L, Barbour JD, Lowe MM, Jayawardene A, Aweeka F, Huang Y, Douek DC, Brenchley JM, Martin JN, Hecht FM, Deeks SG, McCune JM. Tryptophan catabolism by indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. Sci Transl Med. 2010 May 19;2(32):32ra36. https://doi.org/10.1126/scitranslmed.3000632
[36]. Wilson MP, Sereti I. Immune restoration after antiretroviral therapy: The pitfalls of hasty or incomplete repairs. Immunological Reviews 2013;254(1):343. https://doi.org/10.1111/imr.12064