HIV and AIDS Research Journal

Review Article

A SciTechnol Journal

FOXP3 Gene and T Regulatory Cells Behavior in AIDS Patients

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Abstract

Regulatory T cells (CD4+, CD25+) recruited by FOXP3 gene, are necessary for the initiation and conservation of self-tolerance and avoidance of autoimmunity by decreasing the auto reactive T cells. According to one research, it was being planned to examine the aspect of Tregs in immune system of HIV+ patients and noticed that number of Tregs are above the normal but function is extremely decreased with noticeable HIV-1 RNA in plasma in contrast to healthy control. In agreement with other analysis, the effect of HIV infection on regulatory T cells (CD4+, CD25 high) was figured out via flow cytometry and FOXP3 quantitative reverse transcriptase PCR. FOXP3 mRNA was taken and calibrated in purified CD4+ lymphocytes or peripheral blood mononuclear cells from HIV+ lymphopenic patients. Hence, three HIV positive patients named as A, B and C were distributed clinically and antiretroviral therapy was administered to them. Consequently, it was evaluated through flow cytometry that frequency of Tregs are decreased in HIV+ positive patients while in group of uninfected, no reduction of tregs was observed. This clarifies that FOXP3 mRNA expression is reduced in HIV+ positive patients as compared to controls.

Keywords

HIV; AIDS; FOXP3; Tregs; CD4; Infection

Introduction

Human immunodeficiency virus (HIV) becomes one of the most severe endemic virus that advances around the world in deadly manner. Present day, Acquired Immunodeficiency Syndrome (AIDS) considers as fourth dominant root of deaths all over the world. In early 1980, it was firstly discovered; billions of AIDS patients have been arising and among them, mostly are dying per year. Currently, no well-known remedial therapy available that knock out virus from HIV patients, anyhow, the accessible antiretroviral drugs act vital aspect in lessening rate of fatality and also restraining the infection's development [1]. Development of HIV infection differs extensively among individuals. The average time from infection to progression of AIDS is about 8 to 10 years, though less number (not exceed than 5% to 10%) of patients are termed as nonprogressors. Nonprogressors are those who have normal count of CD4 cells and donot develop symptoms of infection without antiretroviral therapy and viral quantity is less or insignificant, although HIV infection extended continuously [2].

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Received: January 26, 2018 **Accepted:** July 10, 2018 **Published:** July 17, 2018

Epidemiology and Prevalence of HIV

Among HIV, HIV-1 develops constant infections in individuals resulting in syndrome, called Acquired Immunodeficiency Syndrome (AIDS) [3]. In various regions of the world, AIDS has already appeared as fatal virulent disease in US, as recent deaths of AIDS cases were reported. HIV/AIDS epidemic has also left marked as detrimental in developing countries. More than 40% preponderance rates in huge risk populations have been found in Sub-Saharan Africa. In Pakistan, HIV was first revealed in 1987 and from then, its case number has raised as recorded by Pakistan National AIDS Control Program (NACP) [4]. In 2003, Larkana, Pakistan, HIV/AIDS was first reported as dominant epidemic infection among individuals [5]. In Pakistan, beyond 90% of persons are persisting with HIV resulting the allocation of Pakistan among 12 countries which bear HIV infection and in excess of 90% advanced HIV infections are detected in Asia region. National AIDS Control Program has evaluated that Pakistan retains relatively 102,000 HIV/AIDS patients and only 16,300 patients are taking medication from different centers all over the country. In 2015, 1.1 million individual's deaths occurred by cause of HIV/AIDS and 36.7 million of HIV patients are living at the end of 2015, as reported by UNAIDS [6]. Human Sciences Research Council (HSRC) manipulated the course of HIV endemic over the past decade in other countries like South Africa. HIV prevalence in South Africa remained comparatively balanced between 2002 and 2008, having range between 10.6% and 11.4%. HIV preponderance increment occurred from 10.6% in 2008 to 12.2% in 2012 [7].

In another survey, South Africa had approximately 35.3 million people with HIV infection in 2012, indicating the largest global load of HIV nearly 70.8% in (Figure 1). HIV preponderance has expanded from 31.0 million in 2002 to 35.3million in 2012 on account of people surviving longer due to taking antiretroviral therapy. While global incidence has decreased from 3.3 million in 2002 to 2.3 million in 2012 [8]. HIV prevalence has increased very swiftly globally like in Eastern Europe and Central Asia with recent spreading HIV cases depicted in (Figure 2) [9]. The particular feature of HIV is its notably number of replication cycles during infection of single individual's life. This results in epidemic and drives its pathogenic life through mutated genome of individual [10].

HIV Genome

Among family of Retroviridae, Human immunodeficiency virus belongs to genus Lentivirus. HIV is filed into two categories (HIV-1 and HIV-2) on the ground of genome aspects and diversity in viral antigens. HIV genome contains two identical single stranded RNA molecules, confined in body of virus particle. HIV becomes provirus having proviral DNA, when RNA is reverse transcribed into DNA, resulting in downgrading of RNA and integration into human genome. RNA genome flanks by long terminal repeat sequences (5'LTR and 3'LTR). From 5' to 3' direction, three major genes exist i.e., *gag, pol* and *env* on reading frame (Figure 3). *Gag* gene encodes the capsid protein (CA, p24), a smaller nucleic acid-stabilising protein and the nucleocapsid (NC, p7) the proteins of the outer core membrane (MA, p17). Adjacent to gag, *Pol* gene encodes integrase (IN, p32), reverse transcriptase (RT, p51), the enzymes protease (PR, p12), and RNase H (p15). *Pol* reading frame is followed by *env*

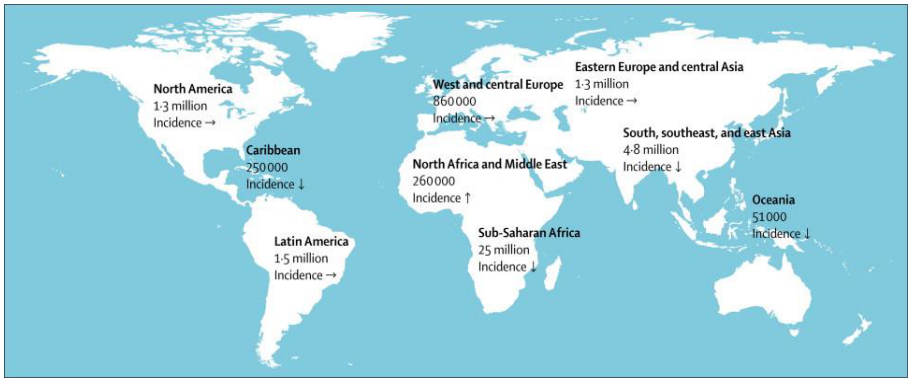

Figure 1: Estimated number of people living with HIV in 2012 and trends in the incidence of new infections from 2001 to 2012 by global region.

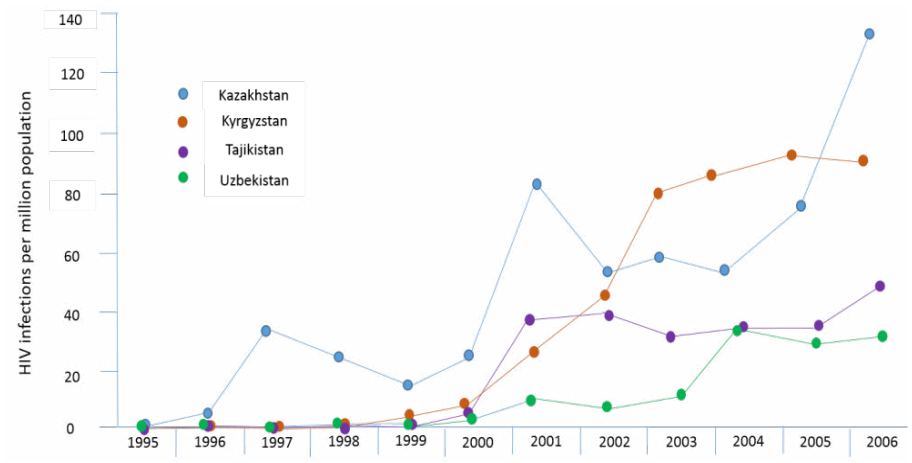

Figure 2: New HIV infections by country and year of report.

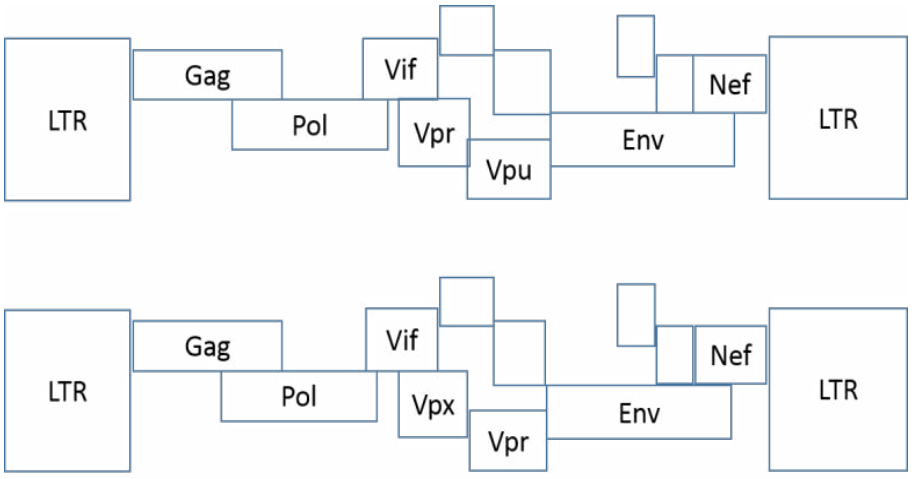

Figure 3: Diagrammatic representation of genome of HIV-1 (A) and HIV-2 (B). Major three genes *gag, pol* and *env*. Difference between two structures lies having Vpr in HIV-2 instead of Vpu in HIV-1.

coding for gp41 (transmembrane protein, TM) and gp120 (surface protein, SU). There are some regulatory proteins associating in HIV replication like Rev (RNA spilicing-regulator) and Tat (transactivator protein). Additional regulatory proteins are Vif (viral infectivity factor), Nef (negative regulating factor), Vpu (virus protein unique) and Vpr (virus protein r) have an essential role in pathogenesis, viral budding and virus replication. HIV-2 has low pathogenicity due to Vpx (virus protein x) rather Vpu [11].

HIV Transmission

HIV infection starts mostly through sexually transmitted virus handling with contaminated syringes, mother to fetus during pregnancy and transplantation of HIV infected organs to other humans [12]. Long lasting sexual relationship and huge infectiousness both in primary HIV infection has been implied as a basic operator of immense expansion of HIV in common individuals [13]. Initial data were of peculiar significant to researchers included in HIV-1 vaccine research and to those implicated in HIV-1 natural history, biology and pathogenesis because they lifted the probability that selective pressure can enhance the transmission of virus. This concept was further supported by the following discovery of corecptors (CCR5 and CXCR4) for the transmission of HIV-1 into cells [14].

Firstly, mature HIV transmitted to host cell by binding of surface glycoproteins gp120 present on HIV to CD4 receptors on host cell surface. Astrocytes, dendritic cells, macrophages and T helper cells have CD4 receptors, vulnerable to HIV attachment. Structural changings occur in CD4 receptors after binding of CD4 to C4-domain of gp120. In result, providing access to additional receptors, called co-receptors i.e., chemokine receptor 4 (CXCR4) or chemokine receptor on cell surface. Supplementary changings occur in gp120 and later in gp41 due to attachment of gp120 to CD4. Viral membrane confers N-terminus of gp4, that makes medium and by cause of hydrophobicity, implants into target cell's plasma membrane and finally viral envelope is ended [15]. After entrance into the cell, reverse transcription process starts, for the formation of provirus DNA. Some complex processes occur during transcription process in an infected cell for integration of provirus DNA into host DNA [16].

When HIV provirus will assimilate into host cellular DNA, both viral components and cellular DNA become mandatory to trigger the viral expression genes. Indigenously, cell forms the cellular components or different types of signals like cytokines, heat, mitogens, UV, mitogens, heterologous gene products are responsible for cellular factors production. When cellular factors will stimulate HIV provirus, first viral gene will start to express, encoding nonstructural proteins with regulatory functions. Tat protein encoding by tat gene is vital among all proteins that is strong transactivator of gene expression and is necessary for HIV production. Tat is regarded to throw its outcome in two possible means: by triggering RNA transcription of HIV provirus or by formation of full-length RNA transcripts. Spliced proliferation of full-length RNA transcripts occur and transferred to cytoplasm where expression of HIV regulatory proteins are manifested. Rev as another mandatory regulatory protein becomes prevalent in viral life cycle. Major objective of this gene expression is to respond the transport of spliced and unspliced mRNA from nucleus to cytoplasm. HIV enzymatic and structural proteins both are encoded by both mRNA that is necessary for infectious and mature virion assemblage on host cell's surface [17].

Cell to cell HIV transmission occurs through various kinds of bridges such as nanotubes formation, connecting the CD4+ T cells and helping in facilitation of HIV transmission (Sundquist and Kräusslich). Simultaneously, replicas of HIV start to assemble in targeted cells and major immune system becomes infected [18]. According to HIV research, main target of HIV are T helper cells (CD4+ T cells) and most well-known and examined immune cells. HIV infection is the indication of reduction of vital immune cells and confers the symptomatic expression that designates AIDS [19]. The earliest records of AIDS were perceptive in knowing that subtle reduction of circulating CD4+ T cells was key to immune insufficiency that interpreted the disorder [20].

CD+ T cells are controlled by the regulatory T cells with inhibiting characteristics involved in regulation of self-immune tolerance. Treg activity is also regulated by the cell to cell communication and also through the generation of bioactive molecules like TGF and IL-10 [21]. During primary infection of HIV disease, CD4 and CD8 t cells behave as central to control the viral point and manage the early viremia. For maintenance of early viremia, high levels of expression of nuclear transcription factor forkhead box p3 (FOXP3) and CD25 (chain of IL-2 receptor) was done by CD4 natural regulatory T cells (nTregs) [22]. During the chronic state of HIV infection, *FOXP3* gene transcription occurs excessively for the immense production of Treg cells, their main target is to regulate immune activation resulting in limit the target cells for HIV infection and also minimize the pathology linked with immune arousal during HIV infection [23].

FOXP3 Gene

Wild type *FOXP3* gene (Forkhead box, P3) transcription involves the production and synthesis of natural regulatory T cells (Treg cells). For proper and regular immune homeostasis, Tregs cells play an important role by regulation of T cells stimulation. Any disturbance in regulation of *FOXP3* gene stimulates in irregular production or lacking of Treg cells resulting in overexpression of CD4+T cells and cytokines, that confers disorders called autoimmune diseases. In contrary, Polymorphisms in promoters, exons and introns regions of *FOXP3* gene have been reported that results in overexpression of Tregs cells. This cause induced different types of cancers in patients, examined from the peripheral blood, tumor and lymph nodes specimens [24].

FOXP3 gene and Tregs behavior during HIV infection

In the course of HIV infection, Tregs display split personality by reducing the immune activation or by suppressing the anti-HIV immune responses leaning on the phase of disease i.e., Acute infection (viral replication resulting AIDS) *vs.* Chronic infection (immune activation resulting in slow disease progression) (Figure 4) [25]. As HIV infection maintains its replication in conventional T cells, subsequently Tregs cells become active to control T cells activation resulting in inhibition of HIV replication during early infection, whereas effector immune cells have not being activated. This defensive act of Tregs could have subtle effect on infection outcome [26].

Overexpression of *FOXP3* gene enables to inhibit the HIV replication in CD4+ T cells during primary infection, preventing the infection of both FOXP3+ and FOXP3- cells. Additionally, it has been examined that HIV-1 LTR transcriptional repression occurs through *FOXP3* gene. *FOXP3* gene expression decreases the binding of NFAT2 to the HIV-1 LTR which is necessary for the transcription of HIV-1. This evidence clarifies that Regulatory T cells, produced by *FOXP3* gene, show somewhat resistance towards the HIV-1 infection by LTR transcriptional inhibition [27]. Although Tregs are relatively resistant to HIV-1 and also has effective impact of HIV in primary infection by inhibiting HIV specific responses *in vitro* studies. Contrary to this, Tregs become dysfunctional or decreased later in AIDS patients [28]. In another review, FOXP3 modified T cells came to be more prone to HIV infection. Surprisingly, less count of CD4+ and greater amount of mobilized T cells have less number of FOXP3+CD4+CD25 hi T cells found in HIV positive patients, implying dysregulation of

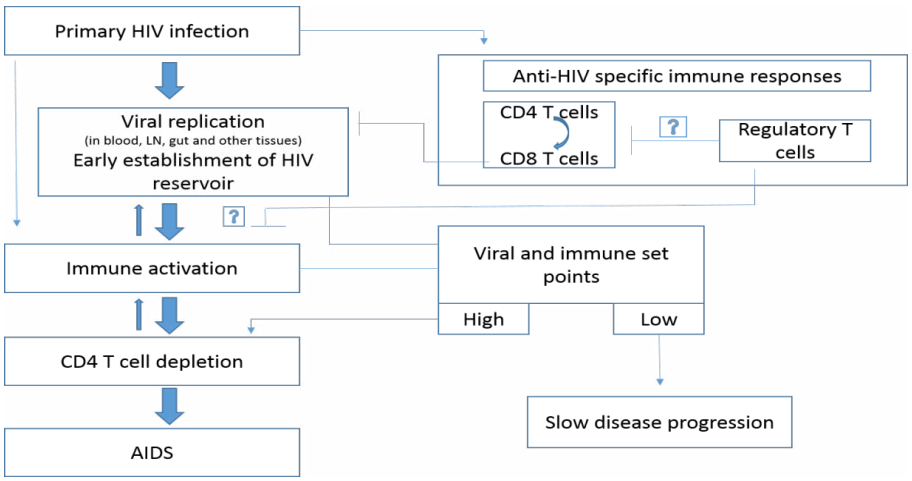

Figure 4: Split personality of Tregs by inhibiting anti-HIV immune responses or by decreasing immune activation depending on primary and chronic HIV infection.

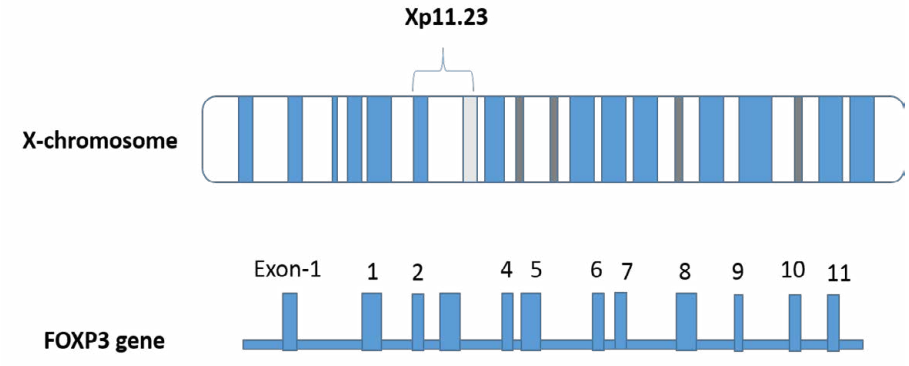

Figure 5: Gene mapping of *FOXP3* gene on, Xp11.23 is shown by arrow sign.

Tregs in the course of HIV infection. This results in contribution of over production of conventional T cells, tendency of HIV disease advancement [29].

Depiction of the act of Tregs cells during HIV infection has been questionable, most markedly for inadequacy of persistent investigation of a Treg structure along with scientific methods for investigating Tregs numbers in HIV patients and loss of perception of the tendency of Tregs in peripheral blood during the course of infection. Hence, diverse groups have depicted that Tregs count are either deteriorated in or elevated in during HIV-1 infection [30-34]. In scientific literature, repressing activity of Treg in HIV positive patients is analytical because of their significance on inhibiting the immune overexpression, while it could have adverse outcome by inactivating HIV-specific immune responses. Recent studies have exposed that HIV-1 can adversely affect Tregs by altering their phenotype and inhibition capacity through diverse processes. These activities encompass FOXP3 and CD25 dysregulation and deterioration of inhibition capacity [35].

One more investigation emphasize that receptors on CD4+ cells (Chemokine 4, CD4+ and chemokine 5) are prone to infect by HIV strains (R5 and X4). Diverse effects are being observed in conventional CD4+ T cells as a result of HIV infection. Still slight information is available about possible effects of HIV infection on Tregs function and phenotype that is necessary to interpret the real role of Treg in HIV+ patients [36] On the onset of AIDS pandemic, it has been recorded that chronic immune activation is solid indication of AIDS advancement. It has been suggested that Treg cells may be defected or reduced by HIV-1, resulting in HIV disease advancement, inducing immune hyperactivation. There are paradoxical descriptions about whether Tregs quantity in HIV patients expands or declines by HIV-1 infection. Many previous data emphasized that HIV infection depletes Treg function or count in the peripheral blood.

Future Outlooks

So above mentioned information about AIDS emphasize that further investigations require at genetic level that may result in downregulation of *FOXP3* gene expression resulting in suppressing the production of regulatory T cells in HIV patients. The gene mapping of *FOXP3* gene is showed in (Figure 5).

Acknowledgement

I acknowledge Higher Education Commission (HEC) of Pakistan for providing access to world's top journals.

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