

Immune Activation in HIV Infection: Friend or Foe

Preeti Bharaj^{1*} and Harendra Singh Chahar²

¹Department of Biomedical Sciences, Center of Excellence for Infectious Diseases, Texas Tech University Health Science Center, USA

²Department of Pediatrics, Division of Clinical and Experimental Immunology and Infectious Diseases, University of Texas Medical Branch, Galveston, USA

Nearly 35 million people all over the world are infected with Human Immunodeficiency Virus (HIV) and around 2 million people get infected with the virus each year and the pandemic continues to devastate despite three decades of our understanding of the pathogenesis [1]. Several immunological features play a crucial role in causing progression to AIDS of which chronic immune activation is the most prominent reason [2,3]. It is characterized by increased pro-inflammatory cytokines; increased expression of T cell activation or exhaustion markers like CD38 and HLA-DR, Programmed Death-1 (PD-1), Tim-3, CTLA-4 and newly described immune regulator PD-1 Homologue (PD-1H) that may interfere with on-going HIV specific cell responses [4-7]. It is now believed that levels of chronic immune activation predict the progression to AIDS independently from viral loads or CD4⁺ T lymphocyte counts. Both HIV and Simian Immunodeficiency Virus (SIV) infections of natural hosts are associated with loss of integrity of the mucosal barrier in the intestine leading to translocation of microbial products like Lipopolysaccharide (LPS) and flagellins into the circulation [8].

Immune activation is a natural response by a body during an infection that eventually gets resolved itself to prevent immune-mediated pathology and exhaustion. However, in case of HIV infection, the virus persists indefinitely and in response the body maintains its state of immune activation. Once the viral loads are brought under control, immune activation decreases dramatically but residual virus provides a constant trigger to the immune system and low-level activation persists. A potential mechanism contributing to chronic immune activation is the mucosal immune dysfunction demonstrated by severe and rapid depletion of CD4⁺ T cells from the gut associated with loss of intestinal epithelial cells, disruption of tight junctions, and compromised integrity of the mucosal intestinal barrier that results in a significant increase in bacterial components, including LPS, flagellin, peptidoglycan, and bacterial CpG-rich DNA domains that are recognized by Toll Like Receptor (TLR) 2, 5, and 9 respectively and 16s DNA in the blood [8,9]. Through the stimulation of TLRs, these bacterial products may also induce pro-inflammatory cytokine production such as TNF- α , IL-6, IL-8, IL-1 β and type I interferons [10]. In addition, HIV virus particles themselves are the prime cause of immune activation that activate TLRs and lead to release of pro-inflammatory cytokines like IFN- α , IL-6, IL-8, macrophage inflammatory protein (MIP)-1a, adhesion molecules like ICAM and VCAM. As CD4⁺ T cells are the prime targets for HIV/SIV infection, perturbations in their subsets like Th17 and Tregs [11,12], memory cells [13] and T-follicular (Tfh) helper cells [14] should be pursued as targets to control immune activation.

In addition to immune activation, another feature of chronic HIV-1 infection is 'immune exhaustion' which is characterized by the loss of T cell effector functions, up regulation of regulatory markers like PD-1, Tim-3, CD160, CTLA-4 on both CD4 and CD8⁺ T cells [4-6]. Blocking of negative regulatory molecules like PD-1 has received considerable attention due to partial restoration of immune functions upon modulation of these receptors [6]. Recently a new member of PD-1 family called PD-1 Homologue (PD-1H) was implicated to play an important role in pro inflammatory cytokine secretion and enhancing immune responses to HIV antigens [7].

Targeting chronic immune activation is of prime importance in optimizing HIV infection in humans. Although ART has achieved reduction in immune activation to significantly lower levels with successful control of viremia, the immune activation never returns to the baseline like uninfected controls. Alternative drug therapies like co administration of cyclosporine A with combination ART may inhibit T cell activation, proliferation and effector functions by inhibiting gene expression of pro-inflammatory cytokines like IL-2, IL-4, TNF- α and upregulation of TGF- β an immune suppressive cytokine [15]. Among other classes of tested agents include chloroquine that showed significant promise in reducing HIV viral loads in ART naïve patients without the patients developing drug resistance [16]. Administering exogenous cytokines like IL-7 has been shown to restore naïve and memory CD4⁺ T cell function [17]. Certain other compounds like rapamycin and mycophenolic acid may help as additive therapy in conjunction with ART in HIV infected patients by reducing T cell proliferation and activation, thus reducing available targets for HIV replication and viral loads as well [18,19].

In conclusion, HIV causes progressive impairment of the immune system in humans and 30 years after its discovery, its role to the exhaustion of immune system is still incompletely understood. Generalized immune activation associated with HIV infection has become the major driving force behind perturbations of the immune system and predictor of progression to AIDS. Both viral and host factors contribute to this phenomenon and the lack of understanding of patho-physiological mechanisms causing this is negatively impacting our ability to improve patient lifestyle. This editorial highlights the benefits associated with targeting immune activation to reduce disease progression and non-AIDS related pathological side effects on HIV induced chronic immune activation.

References

1. Ebrary Inc (2009) AIDS epidemic update December 2009. Geneva, Switzerland: UNAIDS.
2. Chakrabarti LA, Lewin SR, Zhang L, Gettie A, Luckay A, et al. (2000) Normal T-cell turnover in sooty mangabeys harboring active simian immunodeficiency virus infection. *J Virol* 74: 1209-1223.
3. Silvestri G, Sodora DL, Koup RA, Paiardini M, O'Neil SP, et al. (2003) Nonpathogenic SIV infection of sooty mangabeys is characterized by limited bystander immunopathology despite chronic high-level viremia. *Immunity* 18: 441-452.

*Corresponding author: Preeti Bharaj, Department of Biomedical Sciences, Center of Excellence for Infectious Diseases, Texas Tech University Health Science Center, 5001 El Paso Dr, El Paso, Texas, USA, Tel: 915-215-4249; E-mail: preetibh@gmail.com

Received January 12, 2015; Accepted January 15, 2015; Published January 22, 2015

Citation: Bharaj P, Chahar HS (2015) Immune Activation in HIV Infection: Friend or Foe. *J Antivir Antiretrovir* 7: XLVI-XLVII. doi:10.4172/jaa.1000e123

Copyright: © 2015 Bharaj P, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

4. Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, et al. (2006) PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature* 443: 350-354.
5. Trautmann L, Janbazian L, Chomont N, Said EA, Gimmig S, et al. (2006) Upregulation of PD-1 expression on HIV-specific CD8⁺ T cells leads to reversible immune dysfunction. *Nat Med* 12: 1198-1202.
6. Kaufmann DE, Kavanagh DG, Pereyra F, Zaunders JJ, Mackey EW, et al. (2007) Upregulation of CTLA-4 by HIV-specific CD4⁺ T cells correlates with disease progression and defines a reversible immune dysfunction. *Nat Immunol* 8: 1246-1254.
7. Bharaj P, Chahar HS, Alozie OK, Rodarte L, Bansal A, et al. (2014) Characterization of programmed death-1 homologue-1 (PD-1H) expression and function in normal and HIV infected individuals. *PLoS One* 9: e109103.
8. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, et al. (2006) Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 12: 1365-1371.
9. Miedema F, Hazenberg MD, Tesselaar K, van Baarle D, de Boer RJ, et al. (2013) Immune activation and collateral damage in AIDS pathogenesis. *Front Immunol* 4: 298.
10. Birx DL, Redfield RR, Tencer K, Fowler A, Burke DS, et al. (1990) Induction of interleukin-6 during human immunodeficiency virus infection. *Blood* 76: 2303-2310.
11. Beignon AS, McKenna K, Skoberne M, Manches O, DaSilva I, et al. (2005) Endocytosis of HIV-1 activates plasmacytoid dendritic cells via toll-like receptor-viral RNA interactions. *J Clin Invest* 115: 3265-3275.
12. Cecchinato V, Trindade CJ, Laurence A, Heraud JM, Brenchley JM, et al. (2008) Altered balance between Th17 and Th1 cells at mucosal sites predicts AIDS progression in simian immunodeficiency virus-infected macaques. *Mucosal Immunol* 1: 279-288.
13. Chase AJ, Yang HC, Zhang H, Blankson JN, Siliciano RF (2008) Preservation of FoxP3⁺ regulatory T cells in the peripheral blood of human immunodeficiency virus type 1-infected elite suppressors correlates with low CD4⁺ T-cell activation. *J Virol* 82: 8307-8315.
14. Perreau M, Savoye AL, De Crignis E, Corpataux JM, Cubas R, et al. (2013) Follicular helper T cells serve as the major CD4 T cell compartment for HIV-1 infection, replication, and production. *J Exp Med* 210: 143-156.
15. Emmel EA, Verweij CL, Durand DB, Higgins KM, Lacy E, et al. (1989) Cyclosporin A specifically inhibits function of nuclear proteins involved in T cell activation. *Science* 246: 1617-1620.
16. Sperber K, Louie M, Kraus T, Proner J, Sapira E, et al. (1995) Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1. *Clin Ther* 17: 622-636.
17. Paiardini M (2011) Hijacking the IL-7/IL-7R system in HIV infection. *J Leukoc Biol* 89: 491-493.
18. Chapuis AG, Paolo Rizzardi G, D'Agostino C, Attinger A, Knabenhans C, et al. (2000) Effects of mycophenolic acid on human immunodeficiency virus infection in vitro and in vivo. *Nat Med* 6: 762-768.
19. Di Benedetto F, Di Sandro S, De Ruvo N, Montalti R, Ballarin R, et al. (2010) First report on a series of HIV patients undergoing rapamycin monotherapy after liver transplantation. *Transplantation* 89: 733-738.