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Review Article

STRATEGIES OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 TO COMBAT INNATE IMMUNITY

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ABSTRACT

During initial stages of Human immunodeficiency virus type 1 (HIV-1) infection, innate immunity of host appears a big hurdle in the way of successful pathogenesis. Innate immune cells produce wide variety of effector molecules like cytokines, chemokines, interferons and antiviral host restriction factors. These factors play crucial role in antiviral response by modulating downstream signaling that leads to maturation of DCs, activation of NK cells and macrophages, B-cells and T-cells. In spite of sturdy innate immunity, HIV-1 utilizes various unique strategies to override innate immune response. This review discusses the various strategies utilized by HIV-1 to overcome innate immunity.

Keywords: *Innate immunity, HIV-1, TLR, Macrophage, NK cells, DCs*

INTRODUCTION

During early phase of pathogen invasion, host mounts innate immunity to destroy the pathogen in antigen independent manner. Innate immune response is the first line of defense mechanism which can protect host against wide variety of pathogen. Innate immune system has ability to distinguish between self and non-self proteins and response accordingly. This immunity triggers after the identification of structural patterns present on the surface of pathogens. The major players of innate immunity are macrophages (MΦs), dendritic cells (DCs), natural killer cells (NK cells), neutrophils, eosinophils, mast cells and basophills. Majority of innate immune effector cells produces inflammatory cytokines and chemokines that act as chemical messengers. These chemokines and cytokines act as chemoattractants and regulate the trafficking of leukocytes. Innate immunity operates in systematic steps starting from pathogen recognition, signal transduction, gene expression and finally production of effector molecules (Chieux *et al.*, 1999; Guha & Ayyavoo, 2013). When any pathogen evades the physical barriers of host, it is recognized by pathogen recognition receptors (PRRs) present in either cytoplasm or on the surface of host cells. These PRRs recognizes the structural repeats of proteins or nucleic acids of the pathogen, known as pathogen associated molecular patterns (PAMPs) (Hajishengallis *et al.*, 2004). Toll like receptor proteins (TLRs) are the extensively studied PRRs. TLR3/7, TLR9, TLR8 recognizes viral nucleic acid and TLR2 and TLR4 identifies viral glycoproteins. In addition to TLRs, viral PAMPs are also detected by other PRRs like RIG-I, RIG-like receptors, MDA5, C-type lectin receptor (CLR) and DC-SIGN (Guha & Ayyavoo, 2013).

Retroviruses (enveloped RNA viruses), evades innate immune response and establishes long term infection in host. HIV-1 (member of retrovirus family), utilizes unique strategies to combat innate immunity as compared to other viruses (de Vries *et al.*, 2008; Lever & Lever, 2011). PAMPs of HIV-1 are not easily recognized by the PRRs of the host due to several modifications and mutations which helps the virus to evade pro-inflammatory and antiviral response (Malim & Emerman, 2008). Error prone reverse transcriptase enzyme of HIV leads to incorporation of high mutations in HIV proteins and nucleic acids. By escaping immune recognition, HIV successfully evades host innate and adaptive immune

response (Serra-Moreno *et al.,* 2011). This review emphasizes on the various strategies utilized by HIV-1 to overcome innate immunity.

HIV-1 Evasion through Mucosal Surfaces during Early Infections

HIV-1 enters into host mainly through mucosal surfaces of rectal and genital tissues during sexual transmission. Mucosa is the first line of defense against any invading pathogens.HIV-1 evades this first line of defense successfully and enters into host cell to establish infection. One such proposed mechanism by which virus crosses mucosal surfaces is by transcytosis or by capturing dendritic cells (DCs). HIV-1 also migrates through intercellular space of mucosal epithelium and contact with $CD4^+$ T cells and underlying mucosal langerhans cells (Guha & Ayyavoo, 2013; McMichael *et al.,* 2010). HIV-1 gp120 disrupts tight junction proteins present between the monolayer of mucosal surfaces by upregulating the production of inflammatory cytokines that leads toincrease in permeability for HIV-1. After crossing mucosal barrier, HIV-1 targets underlying $CD4^+$ Tcells and establishes acute infection. These infected cells disseminates with the help of pro-inflammatory cytokines viz. IL-1, IL-6, IL-8 and GM-CSF throughout the lymphoid tissues of the body including gut associated lymphoid tissues (GALT) where abundant $CD4^+$T cells are present. HIV-1 establishes successful infection in $CD4^+$T cells available in GALT and replicates at very high rates (Keele *et al.,* 2008). This results into peak viremia followed by induction of $CD8^+$T cells and severe loss of $CD4^+$T cells (Guha & Ayyavoo, 2013). Finally, viral load attains steady state that maintains throughout chronic phase of HIV-1 infection. Evasion through mucosal surface and attaining steady state of infection in $CD4^+$T cells is the first stage of success of HIV-1.

HIV-1 Evasion of Complement System

After evading mucosal barrier, complement system pose another barrier as host defense mechanism that contribute in restriction of viral replication by triggering the recruitment inflammatory cells. Complement system inhibits HIV-1 by lysing IgG and IgM bound viruses and infected cells. However, HIV-1 combats with complement system by activating classical pathway of complement system by binding C1q through its envelop glycoprotein gp41 (Marschang *et al.,* 1994). HIV-1 downregulates the expression of host complement receptor on monocytic cells that impairs its chemotactic response to inflammatory stimuli. At the same time, C3 and C5a deposited on surface of HIV-1 facilitate interaction of virus with macrophages (MΦ) and DCs resulting in onset of infection in these cells. HIV-1 also binds with CR1 present on the surface of erythrocytes and CR2 present on the surface of B-cells to exploit these cells as HIV-1 reservoir and to spread the infection in other organs of the body (Guha & Ayyavoo, 2013; Stoiber *et al.,* 1997). HIV gp41 and other viral proteins induces the expression of C3 in neurons and astrocytes that contributes towards HIV-1 induced neuropathogenesis. gp41 and gp120 also recruits Factor H, which prevents lysis of self-cells by complement system at multiple binding sites; that resulted in decreased complement mediated lysis of virus and infected cells *in vitro*.HIV-1 bound CD59 (Complement regulatory factor) also inhibits the lysis of antibody bound viral particles (Guha & Ayyavoo, 2013). Observations from above studies indicated that HIV-1 overrides complement system mediated antiviral defense mechanism for establishing successful infection.

Hiv-1 Evasion through Chemokine and Cytokines

HIV-1 exploits the network of cytokines and chemokines for successful pathogenesis throughout its life cycle. HIV-1 infection results in activation and altered functioning of macrophages, DCs, NK cells and B cells. This altered activation leads to increased production of pro-inflammatory and anti-inflammatory cytokines and chemokines including interferons (IFNs), interleukin (IL)-1, IL-2, IL-4, IL-6, IL-10, IL-15, interferon gama induced protein (IP)-10, tumor necrosis factor (TNF)-α and monocyte chemotactic protein-1 (MCP-1) (Guha & Ayyavoo, 2013; Stacey *et al.,* 2009). All these cytokines/chemokines either inhibit or enhance viral replication. Disease progression leads to shift from stimulatory Th1 response (IL-2 & IFN) to Th2 response (IL-1, IL-4, IL-6, IL-8, IL-10 and TNF). Attachment of gp120 to CD4 leads to production of CC chemokines viz. CCL2, CCL-3, CCL-4 and CCL-5 that attracts DCs, MΦs and lymphocytes at attachment site. Likewise, HIV-1 trans-activator of transcription (Tat) protein mimics β-chemokines and attracts monocytes and MΦs that leads to enhanced infection (Albini *et al.,* 1998). HIV-1

negative regulatory factor (Nef) protein enhances the production of pro-inflammatory cytokines (IL-1β, IL-12, IL-15 and TNF-α) and chemokines viz. IL-8, macrophage inflammatory protein (MIP)-1α and MIP- 1βwhen interacts with immature DCs. HIV-1 viral protein R (Vpr) also alters levels of pro-inflammatory cytokines (Guha & Ayyavoo, 2013). Overall, HIV-1 either mimics/regulates cytokine and chemokine network for effective pathogenesis and survival.

HIV-1 Evasion through Host Restriction Factors

Multiple host proteins inhibit HIV-1 by multiple ways and pose a big hurdle in successful HIV-1 pathogenesis. Apolipoprotein B editing catalytic polypeptide (APOBEC3) (cytidine deaminase protein) incorporates into HIV-1 by interacting with Gag protein. APOBEC3G converts cytidine into uridine by deamination in negative sense single stranded DNA which results into guanosine to adenosine mutation in positive sense C-DNA, thus making it prone for degradation by cellular nucleases (Douaisi *et al.,* 2004; Harris *et al.,* 2003; Mangeat *et al.,* 2003; Zennou *et al.,* 2004). However HIV-1 viral infectivity factor (vif) protein mediates ubiquitination of APOBEC3G through E3 ubiquitin ligase complex that lead to its proteosomal degradation (Guha & Ayyavoo, 2013).

Type I interferon enhanced the expression and production of tetherin or BST-2 (type II transmembrane protein and restriction factor) that prevents the budding of progeny viral particles from infected cells. BST-2 prvents the spread of HIV-1 from cell to cell by chelating progeny viral particle in infected cells. HIV-1 viral protein U (Vpu) interacts with BST-2 and causes its miss-localization and ubiquitination that leads to proteosomal degradation of restriction factor (Guha & Ayyavoo, 2013; Neil *et al.,* 2006).

SERINC3 and SERINC5 are the recently identified host restriction factor which incorporates into budding HIV-1 particle and significantly reduces its infectivity (Trautz *et al.,* 2016; Usami *et al.,* 2015). The detailed mechanism of SERINC3 and SERINC5 mediated decrease in HIV-1 infectivity is not known till date. However, Nef prevents the incorporation of these proteins into the budding virions for successful infectivity and pathogenesis.

HIV-1 Evasion of NK cells

NK cells are important arm of innate immunity and like other immune cells; it also has the ability to migrate at infection sites in response to pro-inflammatory cytokines and mediates the lysis of infected cells. NK cells has killer-cell immunologlobulin-like receptor (KIR) on its surface that recognize major histocompatibility complex-class-I (MHC-I) as inhibitory signal (Collins & Baltimore, 1999). HIV-1 downregulates NK cell ligands (MICA, ULBP-1 and ULBP-2) on infected cells and upregulates inhibitory signal receptors including KIR on NK cells to escape from cytotoxic effects of NK cells (Andre *et al.,* 1999; Cerboni *et al.,* 2007). HIV-1 infected cells express gp41 and gp120 on their cell surface that are the targets of NK cells via antibody dependent cell mediated cytotoxicity (ADCC) response. However, HIV-1 keeps on mutating its gp41 and gp120 to evade from ADCC response. HIV-1 Tat also inhibits Ca^{2+} influx that leads to inhibition of NK cell cytotoxic activity (Guha & Ayyavoo, 2013).

HIV-1 Evasion through Plasmcytoid Dendritic Cells (pDCs)

The first antiviral response after HIV-1 entry is primarily posed by pDCs through interferon. Toll like receptor (TLR) 7 and TLR9 present on the surface of pDCs, binds to ssRNA unmethylated CpG DNA respectively of HIV-1 that activates IRF7 for production of IFNs. HIV-1 reduces the total count of pDCs in blood to reduce IFN response (Guha & Ayyavoo, 2013). Furthermore, gp120 of HIV-1 suppresses the activation and production of proinflammatory cytokines by pDCs mediated through TLR9 (Martinelli *et al.,* 2007). Other evidences suggest that HIV-1 inhibits pDCs through the suppression TLR7 and TLR8.

CONCLUSION

The HIV-1 and host interaction is very complex network. Host cells utilize its available machinery to defend and eliminate infection, whereas HIV-1 uses its own tools to combat successfully with host restriction and utilizes host machinery for its own propagation. Since the time of entry into host cells to successful infection establishment, HIV-1 utilizes unique strategies like modification of PAMPs, rapid mutation in its genetic material, increase secretion of inflammatory factors, downregulation of

complement receptors, downregulation of NK cell function to evade innate immunity. Currently researches are trying to understand these strategies to evade innate immunity at multiple levels. Understanding the ability of HIV-1 to effectively evade innate immunity at multiple levels may help us in development of appropriate therapeutic antiviral drugs.

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CONFLICT OF INTEREST
The author declares that he has no conflict of interest.

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