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Review Article

HIV-1 strategies to overcome the immune system by evading and invading innate immune system

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ABSTRACT

HIV-1 infection is a major public health problem and an important cause of death among adults. In light of innate immune system being the first, rapid and nonspecific response, this highlights the importance of exploiting the active arms of innate immunity to eradicate the invader and triggering a more specific immune response, the adaptive immune system. Each type of cells in the innate immune system has a unique distribution and function in the body and therefore differs in their ability to induce adaptive immune arms according to the stimuli. Any functional defect or alteration in the innate immune system can affect the adaptive arms of the immune system in terms of failure to overcome the battlefield with the invader. This review focuses on the relevant function of each member of the innate immune system and sheds the light on detailed mechanisms about how this smart virus invades and evades the immune system which opens new insights into the immunology and therapeutic targeting of HIV-1 infection.

1. Introduction

Human immunodeficiency virus (HIV)-1 is a unique invader of the immune system that eventually leads to acquired immunodeficiency syndrome (AIDS) [1] if not treated. HIV has affected over 71 million people around the world since its emergence according to UNAIDS reports [2]. The vast majority of HIV-1 infections are due to the exposure of mucosal surfaces to the virus during sexual contact [3]. Unfortunately, there is no protective vaccine yet available and the disease is not curable by the available therapeutic strategies [4]. There seems to be some gaps in knowledge regarding how the virus can invade our bodies, overcome the immune system and escape/impair the immune responses, particularly the innate immunity.

The innate immune system represents the primary sentinel of our bodies against invaders. Indeed, the innate immune system of its both arms, the humoral and cellular components, collaborate either to eliminate invaders or to activate a more specific branch of the immune system, namely the adaptive immune system [5–9]. The mediation of specific arm of the adaptive immune responses has been shown to be substantially dependent on the participant arm(s) of the innate immune system. Hence, the potential role of innate immune system to determine the subsequent adaptive immune responses underscores its important role in primary and secondary defense responses [5–9]. Thus, alteration or impairment of the innate immune system components will remarkably affect the immune responses in total.

In the case of HIV-1 infection, there is strong evidence that the maintenance of sufficient and efficient innate responses play a

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis inducing ligands; DC, dendritic cells; NK, natural killer; MAC, membrane-attack complex; FH, factor H; Gp, glycoprotein; CR, complement receptor; FDC, follicular dendritic cell; MHC, major histocompatibility complex; BM, bone marrow; KIR, killer-cell immunoglobulin-like receptor; SHIV, Simian-Human Immunodeficiency Virus; MICA, MHC class-I polypeptide-related sequence A; ULBP, UL16 binding protein; ADCC, antibody dependent cellular cytotoxicity; LTNP, long-term non-progressors; APC, antigen presenting cells; DC-SIGN, Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin; GALT, gut associated lymphoid tissues; mDC, myeloid dendritic cells; pDC, plasmacytoid dendritic cells; TLR, Toll-Like Receptor; MDDC, monocyte derived dendritic cells; Th, helper T cells; Treg, regulatory T cells; IDO, indolemine 2,3-dioxygenase; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; CNS, central nervous system; Ig, immunoglobulin; Nef, negative factor; Tat, Trans activator.

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principal role in disease controlling as seen in a small group (<1%) of patients who are naturally able to control HIV-1 disease progression [10–18]. Therefore, targeting innate immune system components could be a novel therapeutic in management of HIV-1 infection [11–13]. In this review, we addressed new advances in our understanding of HIV-1 invasion and evasion strategies of the innate immune system to further clarify how the virus can overcome the battlefield with the immune system in HIV-1 progressors. In our discussion, we considered the complement system, natural killer (NK) cells, dendritic cells (DCs), basophils/mast cells, and monocytes/macrophages. In addition, we made future recommendations regarding exploiting some ignored members of innate immune system to be further studied and used in the management of this grim infectious disease.

2. Complement system

2.1. Complement system and HIV

The complement system is a set of about 40 soluble and membrane-bound proteins that play a critical role in defense as part of innate immune system that mediate humoral adaptive immune response [5,19]. Activation of complement components is crucial to the development of inflammatory reactions as one of the earliest defense lines against invading pathogens including viruses [20]. The threshold for B cell activation in the presence of both complement and antigen is lowered due to the increased immunogenicity compared with a naive antigen [19]. This illustrates the important role of complement system as a humoral arm of the innate immune system that participates in priming and boosting the adaptive immune response.

There are three pathways of complement activation: the classical, lectin and alternative pathways. The end product of complement activation of all three pathways is cell lysis as a result of membrane-attack complex (MAC) formation [21]. Although complement proteins lack the specificity to discriminate between self and non-self-targets, host cells express several membrane proteins (complement regulatory proteins) that inhibit complement activation and MAC formation at several stages of complement cascade, thus preventing self-damage [22–27]. These complement regulatory proteins include CD59, CD55, and CD46 [22–26], in addition to the fluid phase of complement regulatory protein factor H (FH) [27]. Worthy to note that complement activation or downregulation is tightly regulated process, once the complement activation exceeded the capacity of complement regulatory proteins to inhibit its action, then the activation process keeps continuing, and vice versa.

2.2. HIV-1 invasion and evasion of complement system

After exposure to HIV-1 (most commonly via sexual transmission), the virus might succeed to cross the epithelial layer of the mucous membrane via different mechanisms [28]. These include but not limited to transcytosis, dendritic cells (DCs), and complement system contribution (Fig. 1) [29]. In fact, the complement system is activated against HIV-1 (even in the absence of antibodies) through direct interaction of viral envelope glycoproteins (Gp) Gp120 and Gp41 with complement proteins that might lead to viral inactivation [30–32]. It has been shown that complement system activation against HIV-1 is responsible to destruct and clear a portion of plasma HIV-1 in vivo [32]. The observed susceptibility of some of HIV-1 particles in plasma to complement-mediated lysis in this study may be due to the low complement regulatory proteins incorporation onto HIV-1 envelop or to the excess exposure to complement activating proteins, since HIV-1 particles with sufficient complement regulatory proteins on their surfaces are resistant. These data suggest a potential role for complement activating proteins in activating complement system and provide evidence for the important role of the complement system in priming and boosting the innate and adaptive immune responses even in HIV-1 infection.

In a recent study by Tjomsland et al. [33], it has been shown that complement-opsonization of HIV-1 particles could affect the antigen presentation process in DCs. In this study, both mature and immature DCs were significantly enhanced to present complement-opsonized HIV-1 particles via MHC class-I by 63% and 72% respectively, compared to non-opsonized HIV-1 particles, indicating that complement-opsonization routes more HIV-1 particles toward presentation via MHC class-I [33]. Conversely, another more recent study by Ellegård et al. [34] has shown that complement-opsonization of HIV-1 particles decreases the antiviral responses in immature DCs, and this process is entirely dependent on the engagement of complement receptor 3 (CR3) that expressed on DCs with opsonized HIV-1 particles and abrogation of TLR-8 mediated responses. Several studies have demonstrated that HIV-1 has established several mechanisms to evade complement-mediated lysis at both free virus and infected cell level. As described earlier, human cells constitutively express variety of complement regulatory proteins. The virus incorporates different cellular membrane complement regulatory proteins on its envelope during budding process [35,36]. In addition, it incorporates FH via its glycoproteins (Gp120 and Gp41) thereby HIV-1 establishes a way to resist complement-mediated lysis [37]. Of note, the complement activation or downregulation on HIV-1 envelop heavily depends on the amount of recruited complement regulatory proteins. Interestingly, if the complement activation fail to mediate HIV-1 lysis, the virus can hijack the complement system and exploit it to enhance its infectivity toward cells that express CRs [38–40], including monocytes/macrophage, DCs [39,40], thymocytes [41], as well as other non-immune cells such as erythrocytes [38]. In turn, this may facilitate *trans*-infection of CD+ T cells. For instance, complement-opsonization of HIV-1 results in 2- to 3-fold enhancement of *trans*-infection of CD4+ T cells via DCs [40]. In another instance, erythrocytes might facilitate wide dissemination of opsonized HIV-1 particles seeding in lymphoid organs where the HIV-1 can be trapped by target cells [42]. Moreover, trapping of HIV-1 and *trans*-infection of T cells by B cells [43] and follicular dendritic cells (FDCs) [44] using complement receptor 2 (CR2) have been reported. On their surface, FDC can trap opsonized-HIV particles with complement or complement-antibody complex without being infected for several months. These trapped virions have been shown to be highly infectious to CD4+ T cells and resistant to antiretrovirals and neutralizing antibodies [45,46]. In fact, opsonized HIV-1 particles accumulate in blood and lymphatic tissues among other complement-enriched compartments thus, providing several mechanisms for viral transmission [47]. Collectively, these information provides evidence about the possible mechanisms of how HIV-1 can escape the complement system and utilize it to invade other tissues which requires an important attention when considering complement system activation as a solid arm in management of HIV-1 infection.

There are two types of antibodies that could develop during HIV-1 infection: neutralizing and non-neutralizing antibodies. After few weeks of HIV-1 infection or as less as 13 days, HIV-1 envelope-specific antibodies (non-neutralizing antibodies) start developing [48,49]. In fact, these antibodies amplify complement activation and deposition on viral envelope [50]. Even with this amplification after seroconversion, these antibodies however fail to induce complement mediated lysis of the infected cells or even the free virus due to the complement regulatory proteins [51]. Moreover, the presence of both complement and non-neutralizing anti-HIV antibodies that arise during the early phase