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Short Communication

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Natural Killer (NK) Cells and Human Immunodeficiency Virus (HIV) Infection

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ABSTRACT

Human Immunodeficiency Virus (HIV) infection has become a serious problem of public health. Recently, it is observed cellular immunity is involved in HIV infection and disease progression, especially the Natural Killer (NK) cells, which are important part of innate immunity. In order to clearly understand the mechanism of HIV infection, we try to figure out the function of NK cells during HIV infection. The article reviews the function of NK cells and the effect of NK cells in HIV infection.

KEYWORDS: Natural Killer (NK); Human Immunodeficiency Virus (HIV) infection; Virus.

The human immunodeficiency virus (HIV) directly targets and devastates the host's immune system, leading to serious infection. Recently, research found innate immunity played very important role in the host's response against viruses, and increasing data indicate that innate immune responses play a key role in the development of effective vaccine-induced immune responses. In particular, Natural Killer (NK) cells represent important early effector cells of the antiviral innate immune defense, which was discovered from 1975 by Herberman.[1] NK cells, which account for up to 15% of Peripheral Blood Lymphocytes (PBL), are classified into three subsets, $CD3^{neg}CD16^{pos}CD56^{dim}$, which is composed of 80%~90% NK cells; $CD3^{neg}CD56^{bright}$, which is composed of 2~10% NK cells; and $CD3^{neg}CD16^{pos}CD56^{neg}$, which is composed of 5~10% NK cells.[2] NK cells can lyse virally infected cells without prior sensitization and participate in the regulation of innate and adaptive immune responses. The ability of NK cells mediating protection against viral infection depends on the relative abundance of each subset. Data from our laboratory and others have demonstrated that the clinical progression of HIV is correlated with changes in the distribution of NK cell sub-populations, namely a decrease in $CD16^{pos}CD56^{dim}$ subsets and an increase in $CD16^{pos}CD56^{neg}$ subsets.

The effects of NK subsets rely on the composition of receptors on the NK cell surface, including inhibitory NK receptors (iNKRs) and activating receptors.[3] These receptors recognize relative ligands of target cells, and induce activating or inhibitory signal. During infections, the binding of NK cell receptors to ligands on the target cell can cause it to overcome inhibitory signals and become activated, culminating in the killing of the target cell. NK cells can be activated by the binding of its receptors (such as CD16) to the Fc portion of antibodies attached to the surface of target cells. We also found increased expression of the activating receptor NKP46, NKG2C and inhibitory receptor NKG2A in patients with deteriorating clinical status. The ratio of NKG2A to NKG2C receptors decreased with advanced clinical progression of disease. Therefore, increased activation of NK cells (through modulated expression of NKG2A compared to NKG2C) may be a marker for identifying the clinical course of HIV-1 infection. Epidemiological studies have shown that particular NK Killer cell immunoglobulin-like receptor (KIR) genes expressed in conjunction with their HLA ligands are associated with significantly slower HIV-1 disease progression and lower viral set-point.[4,5] NK cells expressing protective KIR genotypes are associated with protection from infection, can significantly inhibit HIV-1 replication *in vitro*.[6-9] We observed the inhibitory killer immunoglobulin-like receptor CD158a (KIR2DL1) to be up-regulated in HIV-positive individuals.[6]

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More recently, scientists showed that NK cells are involved in several other pathways to combat HIV infection, such as through secreting degranulated perforin and granzyme B to kill target cells; the Fas-FasL pathway to induce lysis of infected cells; production of cytokines to regulate immunity; and antibody-dependent cell-mediated cytotoxicity (ADCC) to lysis infected cells.[6] NK cells could kill target cells and inhibit HIV-1 replication, at least partly due to antibody-dependent cell-mediated cytotoxicity (ADCC). The mechanism of ADCC against HIV-infected cells is: Fc receptor-positive effector cells bind to gp120 or gp41-expressing HIV-infected target cells *via* gp120 or gp41 specific antibodies of certain Immunoglobulin G (IgG) isotypes and mediate their killing. NK cell is the important effector cell inducing ADCC. However, the roles of NK cells against infection are still under debate, and mechanisms are needed intensive research. Consistent with some other studies, our study also showed that ADCC responses were associated with slower progression of HIV infection. In addition, NK cells are protective against HIV disease progression through combinations of killer cell immunoglobulin-like receptors (KIR) and specific human leucocyte antigen class I (HLA-1) ligands; the studies have shown that particular HLA alleles appear to be associated with stemming the progression of HIV-1 infection.[10] We also demonstrated that ADCC responses are associated negatively with the clinical progression of HIV-1 infection and correlated positively with infected time and specific HLA alleles (HLA-A*30/B*13/Cw*06) in long-term survivors in a uniformly infected cohort.[6] Taken together, these studies suggest that NK cells might play an important role in controlling HIV-1 replication, and that the virus can evade NK cell mediated immune pressure by selecting for sequence polymorphisms in areas targeted by KIR^+ NK cells.

This review briefly summarized the function of NK cells immunity against HIV infection and disease progression, which may provide helpful data into understanding of HIV-1 pathogenesis and immune mechanisms, facilitating anti-virus drugs development and vaccine evaluation.

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