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Role and Relative Effectiveness of Immune System for Combating Small Pox and AIDS

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***Abstract*—**The human body has a complex system of innate and adaptive mechanisms for combating infection. This article discusses the role and relative effectiveness of these mechanisms in relation to small pox and AIDS.

***Keywords*—**AIDS, Immune System, Small Pox, Viral Infections.

I. Introduction

A wide range of viruses infect humans and can cause disease. The human body has evolved an immune system to combat these pathogens. The main function of Human immune system is to recognize foreign material (antigens) within the body and arrange for its elimination. To achieve this purpose immune system has developed effectors mechanisms such as Innate and adaptive responses. Human Immunodeficiency virus (HIV) is a positive single stranded RNA enveloped retrovirus. HIV infection destroys the immune system ultimately leaving the body susceptible to infection with a wide range of bacteria, viruses, fungi and protozoa – a condition known as Acquired Immunodeficiency syndrome [1] AIDS is described clinically by the emergence of major opportunistic infections or by a decline in the CD4 T cell count to less than 200 cells/ul of blood [2]. HIV requires not only CD4+ receptors mainly found on CD4 T cells but also chemokine co-receptors on the host cell surface to allow entry of virus into the cell [3], [4]. Small pox displays many biological similarities to HIV. The aim of this article is to discuss the role and relative effectiveness of these mechanisms in relation to small pox and AIDS.

II. Materials and Methods

Literature Review was performed by searching articles using online databases as well as library resources including text books.

III. Innate Immunity

Innate Immunity is a non specific phylogenetically ancient immune system that is present in all organisms to prevent infection. It is innate because it exists before infection [5]. It is the initial line of defense against invading pathogens and is especially vital in preventing bacterial and viral infections presenting at mucosal cell surface [6]. Innate immune system works during early phase of infection allowing adaptive immune system enough time to launch an effective protective response [7]. Innate immunity is different from adaptive immunity as cells of innate immune system do not use cell surface immunoglobulins or T cell receptors (antigenic sequence) to recognize a pathogen or microbial product, they are not MHC restricted, lack memory which is essential in vaccination and speed of innate response is faster than adaptive immune response [8], [9]. Cells of the innate immune system recognize pathogens by using a system of receptors which identify molecular patterns expressed by pathogens. Such receptors on cells of innate immune system are called Pattern Recognition receptors (PRRs). These molecular patterns are conserved (not likely to mutate), shared by a large group of pathogens and clearly distinguishable from self patterns [10].

Pattern recognition is a straightforward method by which a limited number of cellular receptors can differentiate a large subset of potential pathogens. Innate immune system has both cellular and soluble components and innate immune system can be divided into cellular, extracellular and intracellular elements (see Table I).

TABLE I
Components of Innate Immune System

Cellular Components	Soluble Components	Physical Barriers
Macrophages [11]	Complement System [6]	Skin [11]
Dendritic Cells [11],[12]	Chemokines [6]	
Interferon Producing Cells (IPCs) [11],[12]	Cytokines [6]	Epithelial cells of Mucous Membranes [6], [11]
Cytotoxic Natural Killer Cells (NK) [11],[6]	Cathelicidins and pentraxins [11]	Digestive enzymes and acid in stomach
Neutrophils [11], [12]	Defensins [6]	Intestinal mucus
Eosinophils [11], [12]	Lectin binding proteins or Collectins [17]	
γδ T-cells [13]		
CD8+ T-cells with non Cytotoxic antiviral activity [14], [15]		
B1 Cells [16]		

Cells that bridge these two immune system and contribute to both very rapid (innate) and delayed (Adaptive) immune responses include Dendritic cells (DC), macrophages and some T cells.

Systematic and Mucosal Components of Innate Immunity can be divided into cellullar (DC, NK Cells, γδT-cells, CD25 T Reg), Extracellular (Cytokines; IL-2, 4, 10, 12, 15, IFNγ) and Intracellular (APOBEC3G, TRIM-5a) categories. [9]

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IV. Innate Immune Responses against HIV

In this section components of innate immunity in relation to protection against HIV infection are discussed.

A. Cellular Components

1. Interferone Producing Cells

IFN producing Plasmacytoid DCs ($_p$DC) are first line of defense against viral infections including HIV [18]. They produce type 1 IFNs (IFN-α, IFN-β). Type 1 IFNs are also produced by a number of other cells soon after viral infection and include macrophages, fibroblasts, lymphocytes, endothelial and epithelial cells. IPCs have a number of antiviral activities against HIV/AIDS. By acting in autocrine and paracrine manner IFNs induce antiviral state within the cells that produce them and in uninfected neighbouring cells.

Type 1 IFNs directly inhibit HIV replication and also stimulate a wide range of immune cells such as NK cells [19], monocytes, T cells etc [20]-[22]. Type 1 IFNs allow the synthesis of two new enzymes , first an endonuclease called RNA se enzyme which degrades viral and host mRNA and the other a protein kinase which phosphorylate protein synthesis initiation factor eIF2, resulting in inactivation of eIF2 and inhibition of viral protein. Virus induced Type1 IFNs also activate human NK cell cytotoxicity and lysis of infected cells [19].

Type II IFN (IFN-γ) is produced by lymphocytes, NK cells, CD4+ T cells and CD8+ T cells. IL-12 (produced by activated macrophages and DCs) stimulates production of IFN-γ by T-cells or NK cells. IFN-γ in turns activate CD4+ T cell differentiation into Type 1 helper T cells (Th1), which in turn are involved in the generation of TCs and DTH reactions and promote some classes of antibodies. CD4+ T helper cell responses include expression of cytokines such as IL-2, IFN-γ, TNF-β that result in launching multi-cellular cell mediated response against invading virus [8].

Clinical studies clearly highlight the importance of IPCs in HIV infection. For instance a lack of IPCs and IFN-α production has been associated with elevated HIV RNA levels and AIDS [23]. Circulating IPC count was inversely related to HIV viral load and opportunistic infections. This suggests a role of IPC in control of HIV replication and development of AIDS. Moreover HIV infected individuals (for > 10 years) remain healthy despite low CD4+ T cell counts due to normal IPC numbers and IFN-α production. These patients were not getting any anti HIV treatment.

Another study showed negative correlation between circulating IPC and HIV viral load after primary HIV infection where a transient decrease in IPC counts is associated with viral replication [24]. Type I IFNs can enhance the identification of HIV by the specific immune system by enhancing MHC Class I and B7 expression on APCs [25]. These studies show that IPCs protect HIV infected individuals from AIDS and cancer via IFN production and through the induction of innate and adaptive immune responses. More over innate immune system has the capacity to provide protection against viral infection even after the loss of an adaptive immune cell function. Table II lists anti-viral activities of IPCs.

TABLE II
Anti-Viral Activities of IPCs

Functions of IPCs	Studies
Type 1 IFN inhibits HIV replication.	[23],[24]
Type 1 IFN inhibits opportunistic infections even in the presence of low CD4+ cell count	[23]
Activates other cells of the immune system e.g. NK cells	[19]
IFN α also prevents activated T cells from undergoing apoptosis	[21]
Type 1 IFNs can increase the identification of HIV by the specific immune system by enhancing MHC Class1 and B7 expression on APC.	[25]
Type 1 IFNs activate STAT 4 Transcription factor to induce IFNγ and promote Th1 cell development	[26], [27]

Studies [26], [27] are in contrast to other studies [20], [28] that show that Type 1 IFNs reduce IFN-γ production by reducing IL-12 from DCs and inhibit Th1 development.

2. NK Cells and Neutrophils

NK cells provide defense against human viral infections including HIV. Soon after viral infection IFN α/β is produced to activate NK cell mediated cytotoxicity and blastogenesis and IL 12 production by activated macrophages or DCs causes NK cell induced IFN-γ production contributing to antiviral defense [19], [29]. Besides eliminating HIV infected cells directly NK cells also remove infected cells through antibody directed cellular cytotoxicity (ADCC). Neutrophils are the most abundant innate immune cells not only exhibit phagocytic activity but also produce a number of proteins and cytokines to control microbial infection. They are the major component of inflammatory responses induced by viral infection.

3. CD8+ Non Cytotoxic anti-HIV T cells

CD8+ T cells have anti-HIV role in both innate and adaptive immune system. In innate immune system CD8+ T-cells control HIV replication through a CD8 T cell non cytotoxic antiviral response–CNAR. This CNAR activity is mediated primarily by release of soluble suppressive factor/s termed CAF-CD8 antiviral factor [30].

Studies of healthy HIV infected individuals showed that addition of CD8+ T cells to the virus producing CD4+ T cells suppressed virus replication without eliminating virus infected cells. However virus could be recovered from isolated PBMCs after removal of CD8+ T cells [31]. CNAR is attributed with a long term asymptomatic state of HIV and the response deceases as the disease progresses [31], [32].

4. γ^{δ} T Cells and B1

γδ T cells are involved in innate immunity and mucosal protection as they are commonly found at mucosal surfaces such as rectal and vaginal epithelia [33]. They generally do not recognize peptide antigens presented by MHC molecules but instead interact directly with non peptide antigens or with cellular stress proteins [34]. These cells can lyse HIV-infected

cells [35] and in some in-vitro studies have repressed HIV replication via chemokines and other soluble antiviral factors.

Anti Tat natural IgM antibodies found in all normal human sera produced by B1 cells represent an innate anti HIV response. These natural antibodies bind to epitopes in Tat protein thus retarding HIV viral entry and intracellular replication there by contributing to resistance to HIV pathogenesis in early Post HIV infection [16].

5. DC and Macrophages

These cells act as antigen presenting cells presenting viral antigens to CD4+ and CD8+ T and B cells thus initiating specific immune responses against HIV virus. DCs and can also activate other arms of innate and adaptive immune system by secreting a number of cytokines. Similarly Macrophages suppress HIV replication by secreting cytokines such as Type 1 IFNs, TNF-α, IL-10, Leukemia Inhibitory Factor, LIF etc [30]. DCs and macrophages can directly destroy invading pathogens or infected cells by phagocytosis [30].

B. Soluble Components

1. Chemokines and Defensins

Chemokines play an important role in determining both innate and adaptive responses. Chemokine co-receptors such as CCR5 and CXCR4 considerably contribute to HIV disease progression as these receptors are required by HIV virus to enter host cells. Hence chemokines such as CCL3 (MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES) produced by CD8+ T cells show anti viral activity by binding to HIV-1 co-receptors. These chemokines compete with the virus for binding to the co-receptor CCR5 thereby inhibiting infection by R5 HIV strains. Similarly chemokine CXCL-12(SDF-1) binds to co receptor CXCR4 confers antiviral activity against X4 HIV-1 strains. They are antibiotic peptides that show antiviral activity [36]. Neutrophils are major producers of α-Defensins [37]. α-Defensins seem to act at two levels: First is the inhibition of viral replication cycle by blocking proviral DNA import. Secondly α-Defensins bind specifically to not only CD4 receptor but also HIV virus envelop glycoprotein gp120. Thus they inhibit binding of gp120 to CD4 preventing entry of HIV virus into target cells [38]. More over human β-defensins originating in oral epithelium also prevent HIV infection by directly interacting with virions and via modulation of CXCR4 co receptor [39].

2. Complement System

Activation of Complement system results in 3 main antiviral functions i.e. opsonization of micro-organisms for uptake by phagocytic cells, stimulation and chemotaxis of phagocytic cells, and lysis of micro-organisms [40]. During HIV infection the complement system is highly activated as revealed by high levels of complement products in blood [41]. In infected individuals HIV virus is coated with complement activation product (C3 fragments) and this result in destruction and opsonization of some of the virus [42], [43]. Complement system also has a role in adaptive immunity. For instance based on mouse models complement system is found to be involved in the development and maturation of antibody responses to HIV in humans [40].

Moreover HIV gp120 surface glycoprotein also activates innate response by providing the site for interaction with MBL (the initiating protein for lectin pathway complement) thus activating complement system [40].

A retrospective study of HIV infected persons showed significantly higher frequency of subjects with low serum MBL that had pneumonia than a group without pneumonia, indicating that in immunocompromised persons, MBL helps protect against some opportunistic infections [44].

3. APOBEC3 (A3G)

It is an intracellular antiviral human enzyme which inhibits HIV replication in new target cells by incorporating into budding HIV virions [1]. It acts as cytidine deaminase (hydrolytic deamination of cytidine to Uradine) inducing numerous dC to dU mutations in the negative strand of HIV DNA formed during the reverse transcription of the next target cell [45]. This negates viral replication by enhancing the accumulation of a damaging level of G to A mutations in the complementary plus strand cDNA [46]. This results in inviable virions. Hence A3G is part of innate cellular antiviral response factors that reduce the damage caused by HIV virus to their host cells. It is important to note that HIV uses Vif protein to counter the antiviral activity of A3G. Hence A3G is active against HIV-1 mutants lacking functional Vif gene. However there is another human protein APOBEC3B that is effective against both vif deficient and wild- type HIV-1 with equal efficiency.

V. Adaptive Immunity

High levels of total and HIV specific IgG along with IgA (lower quantities) antibodies are found in all body secretions of HIV exposed and HIV infected individual. These antibodies in urogenital secretions e.g. vaginal and seminal fluid provide mucosal protection against HIV infection in humans.

Cellular immunity generates cytotoxicity mediated by T lymphocytes. CD8+ T cells contribute to cellular immunity by lysis of infected cells in an antigen specific HLA restricted manner. During acute HIV-1 infection virus specific cytotoxic T-lymphocyte (CTL) responses are generated which result in temporary initial decline in viremia [47], [48]. During asymptomatic phase of HIV disease both humoral and cellular immune response continues to limit viral replication. CD4 counts remain high and viral load is low. During symptomatic phase (AIDS) HIV in lymphoid foci causes a decline in immune competence. This weakens CTL responses by enhanced concentrated generation of immunosuppressive viral proteins. Despite high number of HIV Specific CD8 T cells disease progression occurs because virus is able to develop anti immune strategies to avoid T cell recognition [49]. See Table III.

TABLE III
ANTI-IMMUNE STRATEGIES OF HIV

Mutational Escape
Latency
Masking of antibody binding sites on viral envelope
Downregulation of Class 1 MHC molecules on surface of infected cells
Upregulation of FAS ligand surface of infected cells

Source: Data taken from [49]

VI. IMMUNE RESPONSES AGAINST SMALL POX

A. Genetic Mutations and Resistance to Small Pox

Small pox displays many biological similarities to HIV. For Instance both HIV and Small pox are viruses and have high mortality rate. Furthermore there is some evidence that like HIV, Variola Major and a distant relative of small pox, myxoma virus uses chemokine receptors such as CCR5 to enter cells. Mutations of CCR5 receptor gene in humans (lack of one or both alleles that produce CCR5 receptor) confer resistance against HIV infection [50]. Research by University of California scientists has shown that this resistance to HIV or CCR5 gene mutation is caused most likely by small pox. Small pox and not plague exerted enough selection pressure for the upsurge of CCR5 Δ 32 allele mutation [51].

As small pox used these receptors to enter immune cells in doing so it might have imposed the selective pressure for protective mutation to persist and later this mutation provided immunity against HIV in some people.

In other words the human immune system developed polymorphism or gene mutations to resist and clear small pox and this mutation persisted as it provided the survival advantage. Hence small pox that once attacked human cells by exploiting CCR5 receptor and at the same time it mediated evolution of life saving CCR5 receptor mutation [51].

B. Immune Responses

Studies on VarV have been limited since its eradiation due to limited animal models (as small pox specifically infects humans) restricted access to virus and viral DNA as well as reduced interest in an extinct pathogen. Hence there is limited literature discussing pathogenecity and immune responses against VarV in humans.

Human innate immune responses discussed above are also active against Variola virus (VarV). This is because innate immune system is a generalized response of human body against most pathogens including small pox. Hence components of innate immune system such as IFNs, ILs, TNF-α, Complement System show anti-viral activity against VarV.

This is demonstrated by the fact that VarV has developed a number of immune evasion strategies to counteract the antiviral activity of human immune response. Some of the VarV anti immune strategies are summarized in Table IV.

TABLE IV
ANTI-IMMUNE STRATEGIES OF SMALL POX

Anti-Immune Strategies of Small Pox (VarV)	Studies
VarV gene D7L encodes a functional IL-18 binding protein (IL-18BP) capable of inhibiting biological activity of IL-18	[52]
VarV encodes CrmB (a homologue of TNF receptor) that exhibit anti TNF and anti chemokine activities by binding to TNF and several chemokines to stop recruitment of immune cells to mucosal surfaces and the skin, site of viral entry and replication	[53]
Human IFN-γ Receptor like proteins are produced by VarV. They have high neutralizing activity for Human IFN-γ and Human IFN-α	[54]
Inhibitor of Complement system. Two secreted VarV proteins, SPICE and CKBP-II help VarV evade host mediated complement Actiation.	[55]

A study of VarV in non human primates revealed gene expressions that seem to represent increased IFN response (IFN-α,β,γ regulated genes), cell proliferation immune response (associated with lymphocyte activation) and viral modulation of host immune response as a result of small pox infection [56]. The study also showed a lack of TNF-ακβ activated transcriptional program in the presence of an overwhelming systemic infection. This suggests that VarV gene products may ablate this response. This supports the immune evasion strategies of variola virus as discussed in Table III. The lack of TNF-α during small pox infection may denote the first proof for variola CrmB activity and disruption of host immune system. There was decrease in transcript abundance of T and B lymphocytes during infection reflecting a decrease in the relative abundance of lymphocytes and Immunoglobulin responses.

A study [57] has shown that in the absence of B cells or antibody production complete virus clearance and host recovery is not achieved in ectromelia virus primary infection. This study clearly showed that first CD8 T cell effector function and then B cell function is required to clear the virus in early and late stages of infection respectively.

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