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Purple Paper

Innate Immunity to HIV

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Overview of HIV

During the span of three decades, the human immunodeficiency virus (HIV) has infected over 50 million people, and despite large international prevention efforts, more than 2 million new infections occur every year¹. However, there have been some successes in prevention (male circumcision²⁻⁴, prevention of mother-to-child transmission) and declines in HIV prevalence have been observed in some countries⁵⁻⁷. There are also promising results not yet ready for widespread clinical use from the Thai vaccine trial⁸ and a female microbicide trial in South Africa⁹. At the same time, antiretroviral treatment (ART) is highly effective and continually improving in its ability to extend the life of HIV-infected individuals. Moreover, there is evidence that ART might decrease HIV transmission from an infected person on ART¹⁰. However, treatment has yet to reach all who need it¹¹, and the idea of combining prevention modalities is taking shape. It is for these reasons that many believe that the realization of an effective HIV vaccine remains a part of the best long-term strategy to limit or stop the HIV pandemic.

Vaccines represent one of the most successful public health interventions of the last century. But despite many attempts, only one HIV vaccine efficacy trial has shown a mildly positive result (called the Thai trial)⁸. While there are many reasons to explain the difficulties of realizing an effective HIV vaccine, the most obvious explanation relates to the biology of HIV infection. In contrast to

Key Points

- HIV infects the cells of the immune system such as T cells, monocytes and macrophages. Whereas adaptive immune responses during HIV infection have been extensively studied, knowledge regarding the innate immune response to HIV is still scarce.
- Very early (days) into HIV infection, innate responses can play an important role in preventing mucosal transmission before HIV infection is established.
- Intracellular restriction of retroviruses has evolved in primates, and HIV has also evolved mechanisms to overcome this restriction and use the host cellular machinery to its advantage.
- Innate immune responses restrict the viral replication and activate adaptive immunity to fight the virus; however the same responses also increase the target cell availability and thereby facilitate further viral replication and contribute to disease progression. Dendritic cell, NK cell, and cytokine responses are prominent in acute HIV infection.
- Chronic innate immune activation is a major contributor of HIV immunopathogenesis and progression to AIDS.
- The failure of previous HIV-1 vaccine trials to induce B and T cell immunity emphasizes the need to look beyond adaptive immunity in order to gain control of HIV infection. It is becoming evident that both innate and adaptive arms of the immune system need to be harnessed in order to develop a successful HIV vaccine.

other viruses for which successful vaccines are available, HIV establishes chronic, latent infection that cannot be cleared (aside from an extreme case in Germany¹²). In addition, while neutralizing antibodies are a main correlate of protection against other viral infections¹³, these are rarely elicited in HIV, and when they are, escape tends to occur rapidly¹⁴. The evolutionary capacity of HIV represents another major challenge, allowing HIV to mutate and avoid immune recognition¹⁵. Furthermore, HIV attacks the immune system (CD4+ T cells), such that by eliciting an immune response

against HIV, the number of cells for HIV to potentially infect increases, particularly in mucosal tissues^{16,17}. Finally, immunity to HIV is rare in nature, confined to small groups of long-term non-progressors (survive >10 years with HIV in the absence of disease), elite controllers (undetectable levels of virus)¹⁸, and HIV-exposed seronegative individuals¹⁹. Further research on these groups may provide important clues that could inform HIV vaccine design.

Innate Immunity

The immune system can be divided into two main arms: innate and adaptive. These arms of the immune system have evolved to combat pathogens, in some cases with a high degree of specificity (adaptive), while in other cases a “less” specific response is directed at portions of HIV common to other microbes (innate). The adaptive immune system has long been the focus of vaccinologists, since its B and T cells exhibit classical immunological memory and specificity. In contrast, the innate immune system comprises cells and tissues that respond immediately to foreign invaders through the detection of danger signals. Natural killer (NK) cells and phagocytes (neutrophils, monocytes and macrophages) are examples of innate cellular immune effectors. The field of innate immunity has expanded rapidly in the past decade, including studies of innate responses to successful vaccines such as yellow fever^{20,21}. This review focuses on innate immune responses to HIV, and how these might assist with development of biomedical prevention modalities.

Initial Events of HIV Infection

The best chance for the innate immune system to control HIV occurs at the time of exposure, before infection is established. For most of the world, this occurs across a mucosal surface, whether it is the penis, rectum or female genital tract. In fact, based on rates of HIV transmission observed in discordant couples²², one can surmise that mucosal surfaces are generally quite effective (>99%) at thwarting HIV infection²³. The most basic innate defenses against HIV include the epithelial layer, vaginal pH, and mucous. In the presence of co-factors that increase the rate of HIV transmission, such as other sexually transmitted infections^{24,25}, the effectiveness of

these defenses can be diminished. Even without pre-existing inflammation due to other infections, semen may also facilitate HIV transmission. Exposure of cervical vaginal epithelium to semen results in production of pro-inflammatory cytokines that recruit dendritic cells, macrophages and lymphocytes into the area, thereby providing target cells for the virus²⁶.

The epithelium itself is more than just a physical barrier that protects against viral invasion. Epithelial cells respond to viruses via Toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns (evolutionarily conserved structures on pathogens). This recognition leads to secretion of molecules called cytokines and chemokines that result in inflammation and recruitment of immune cells such as dendritic cells (DCs). In response, DCs produce interferons, important for initiating antiviral immunity^{23,27}. Release of interferon from virus-infected cells represents an important part of the innate immune response. When a virus invades a cell, the presence of viral nucleic acids triggers the cell to produce interferon. Once released, interferon binds receptors on healthy cells and triggers them to prepare for the potential viral attack by producing host proteins that block the production of the virus.

However this response also leads to influx of susceptible immune cells to the mucosa, providing new targets for HIV and creating conditions for effective cell-to-cell spread²⁸. There are a number of innate mucosal factors that are secreted into the lumen of the female genital tract, many of which have demonstrated anti-HIV activity *in vitro*²⁹. These include α -defensins, SLP-1, Trappin2, and serpin proteases. While the latter two have been associated with HIV-resistance in a Nairobi-based cohort^{30,31}, other molecules with anti-HIV activity can cause inflammation and therefore may increase HIV susceptibility³², and perhaps should be avoided. This hypothesis was recently tested by a microbicide that blocked a chemokine associated with inflammation called CCL20, which prevented cellular recruitment and protected non-human primates from a low-dose simian immunodeficiency virus (SIV) challenge³³.

The exact details of how HIV crosses the mucosal barrier remain poorly elucidated³⁴. However, once

HIV enters the submucosa, it comes into contact with other components of the immune system. It is in these first 4-5 days of infection, referred to as the eclipse period, where in order to survive, HIV must infect enough target cells to establish small foci of infection²³. Since this is prior to the appearance of the adaptive immune response, any chance of ablating HIV infection at this stage is the task of the innate immune system. Preventing HIV spread at this stage is critical; once HIV infects enough target cells in the submucosa, these cells drain through the lymphatic system (where CD4+ T cells are abundant), irreversibly establishing lifelong HIV infection.

Intracellular Restriction of HIV

All viruses require host machinery to replicate, and several of the host factors that HIV requires have been identified³⁵. In addition, humans are equipped with genes called restriction factors that have evolved to inhibit HIV and other retroviruses, and therefore form an important part of the innate response. To date three major antiviral restriction factors have been identified: APOBEC³⁶, TRIM5 α ³⁷, and tetherin^{38,39}. These genes can target a number of HIV-1 replication steps inside the cell, including uncoating, reverse transcription and virus release. APOBEC proteins can be incorporated into newly formed virions and carried to the next cell HIV infects where they induce mutations in the viral genome, preventing further viral replication. TRIM5 α binds to retroviruses and targets them for degradation by the cell machinery before they can replicate. Tetherin causes the retention of viral particles on the cell surface, preventing them from being released and infecting neighboring cells. To counteract these host restriction factors, HIV encodes a number of accessory genes. One of these, called Vif, neutralizes the activity of APOBEC by preventing its packaging into viral particles. Another HIV gene called Vpu mediates the release of viral particles from the cell surface by reducing the expression of tetherin⁴⁰. These examples demonstrate the innate struggle between host and virus, and represent possible therapeutic avenues for treating HIV.

Early Innate Immunity to HIV

Once HIV gains entry into the systemic circulation, the innate response induces adaptive (T and B cell) immune responses. Monocytes, DCs and macrophages are professional antigen presenting cells (APCs) that play an important role in host immune responses by linking innate and adaptive immunity. Since HIV can productively infect macrophages and DCs⁴¹, these cells also serve as viral reservoirs, aiding in viral spread. This is supported by the finding that DC numbers are reduced in HIV infection⁴². Rapid decline of DCs in the blood occurs through both activation and migration of DCs into lymphoid tissues, and by depletion of DCs due to apoptosis and cytopathic effects of HIV. DCs can also transmit the virus without being productively infected⁴³, a process known as *trans*-infection. In this way, DCs act as “Trojan horses”, capturing the virus in the peripheral tissues then migrating into the lymph nodes where HIV can be transferred to CD4+ T cells. This is just one example of how HIV is able to use the immune responses against it to its advantage.

The DC response also leads to activation and recruitment of another important innate cell, natural killer (NK) cells, to the site of infection and lymph nodes^{44,45}. NK cells are elevated in acute HIV infection, but their function decreases as chronic infection is established⁴⁶. NK cells play an important role in HIV immunity due to their ability to kill virally infected cells, particularly those that try to avoid T cell recognition. In addition they produce large amounts of chemokines that block the cellular receptors HIV uses for entry. NK cells express a complex network of receptors on their surface that can either be inhibitory or activating in nature. One major class of receptors is the killer immunoglobulin receptors (KIR). Polymorphisms in the KIR locus have been associated with differential outcomes in various cancers and infectious diseases including HIV⁴⁷. Even though not yet used for viral infections, therapeutic strategies targeting NK cells have been successfully used in cancer and transplantation therapy^{44,48}.

Another important feature of the acute innate response to HIV is the “cytokine storm,” characterized by dramatic increases in the production of cytokines and chemokines by innate

immune cells, including interleukin 15 (IL-15), type I interferons, and others⁴⁹. While some of these cytokines play important roles in antiviral immune response, they also seem to promote viral replication and contribute to immune activation and disease progression⁵⁰. Resolution of this acute inflammation might be one mechanism associated with non-pathogenic SIV infection in sooty mangabeys (monkeys who get SIV infection but rarely develop AIDS)⁵¹.

Chronic Stage Innate Immunity – Immune Activation and Disease Progression

Chronic immune activation is one of the hallmarks of HIV infection, as continued viremia leads to manifestations of immune exhaustion, deregulation, and altered homeostasis. In fact, immune activation is an independent predictor of HIV disease progression⁵². It has been suggested that chronic innate immune activation is an important contributor to impaired adaptive immunity and immune deficiency⁵³. The same immune responses that play a protective role in the initial stages of the HIV infection can prove to be detrimental during chronic infection. Interferon secretion by DCs may contribute to pathogenesis and disease progression by inducing apoptosis of both infected and uninfected CD4+ T cells⁵⁴. The nature of the interferon response has been suggested to account for differences in disease progression between men and women, with women tending to have higher IFN α production and lower viral load initially, but increased T cell activation and disease progression as infection progresses⁵⁵. Decreased immune activation is also associated with non-pathogenic SIV infection, and has been linked to innate immune signaling⁵⁶.

Microbial translocation, or leakage of microbial products from the gut lumen into blood, has been hypothesized as one of the causes of immune activation during HIV infection⁵⁷. Increased plasma levels of lipopolysaccharide (LPS), a common bacterial structure and inducer of innate immunity, have been observed in chronic HIV infection. Levels of LPS and IFN α correlate and may contribute to the hyperactivation of the innate immune system. Many bacterial products signal through pattern recognition molecules, which are elevated in HIV

infection and associated with HIV viral load⁵⁸. Stimulation of intracellular TLRs (TLR7/8/9) results in a strong pro-inflammatory/antimicrobial response. Chronic activation of these receptors in the late stages of HIV infection has been shown to account for functionally impaired virus-specific T cells and T cell exhaustion. Overall, innate immunity in chronic infection is often “too late”, and likely is an important contributor to immune activation and progression to AIDS.

Vaccine and Innate Immunity

Like all immune responses, innate immunity to HIV can have a range of positive and negative effects. For example, depending on the context, innate immunity can both limit and induce HIV replication. Although required to limit viral replication in the initial stages of infection and initiate adaptive immunity, continuous activation of the innate immune system for prolonged periods can result in dysregulated T and B cell responses⁵⁹, contributing to the immune deficiency of chronic HIV infection. The fine balance between protection and harm was shown in a recent study that administered IL-15 during acute SIV infection in rhesus macaques. During this study, NK cell and SIV-specific CD8+T cell numbers were increased, but so was activation and proliferation of CD4+ T cells, with the end result of higher viral loads and accelerated disease progression⁶⁰. However, given the difficulty in inducing protective B and T cell immunity in previous HIV-1 vaccine trials, the need to look beyond adaptive immunity to HIV cannot be ignored. The roles innate immunity plays, particularly at the time of exposure and during the eclipse phase, are critical areas in need of further research and could represent a window in which an effective vaccine could protect. Ideally, a vaccine should induce immune mechanisms that will clear the founder virus before infection is established. Furthermore, the innate immune system can play a key role, in conjunction with the adaptive arm, in clearing HIV infected cells⁶¹. One of the proposed mechanisms of protection of the Thai vaccine, which remains to be confirmed, was through antibody binding and induction of NK cells that killed cells expressing the HIV envelope⁶². Another avenue where innate immunity can contribute to HIV vaccinology is the use of TLR adjuvants. Adjuvants

are compounds that stimulate the innate immune system, leading to enhanced vaccine responses. Currently, BCG is one of the only commercially available vaccines that has been proven to signal through TLRs⁶³. HIV vaccine strategies that stimulate the TLR9 pathway are being developed⁶⁴. Therapeutic vaccines, which during the early stages of infection, adoptively transfer autologous DCs pulsed with inactivated HIV-1, have shown exciting results in primate models and in clinical trials^{65,66}. Unfortunately, such treatments are unlikely to be feasible in developing countries, where HIV vaccines are needed most, since they would need to be made differently for every vaccinated individual. It is also important to reflect on the very definitions of innate and adaptive immunity, since some have suggested there is a bigger overlap between the two arms than was previously appreciated^{67,68}. Of course there is no precedent for vaccines that rely on innate immunity, so the development of one for HIV, if possible, would likely be a long-term venture. A more comprehensive understanding of the immune system seems to be in reach – whether and when this will translate into better rational vaccine design remains to be seen.

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