Immunology of HIV Infections

Prepared by:
Maha Al-Haloul
Maha Al-Yaqubi
Structure of HIV-1

- The HIV-1 virion is spherical & contains an electron-dense, cone shaped core surrounded by a lipid envelope derived from the host cell.

-- This envelope containing virus – specific glycoproteins (gp120 & gp41)

- The virus core contains a major capsid protein p24 which is the most readily detected viral antigen & is the target for the antibodies used to diagnose HIV infection.
INTRODUCTION

Many researchers are focusing on studies of the immunological concepts involved in the AIDS disease, not only to understand why some individuals remain uninfected, despite repeated exposure to infected individuals, but also to explore various vaccine candidates and concepts that might prevent the disease before exposure to the virus.
The pattern of disease progression

Following infection with the virus, the virus infects cells with CD4 receptors.

During the early phase, individuals may experience a flu-like illness with mild fever, cough, and occasional chills.

The symptoms subside, and the individual may be asymptomatic for many years.

In reality, the disease is progressing, and it is a long battle between the immune response with production of new CD4+ cells and the dying (apoptotic) HIV-infected CD4 cells.

Eventually, the host immune system deteriorates, and the individual succumbs to the complications secondary to loss of the cellular immune system.
Early events in the vaginal transmission of HIV

The binding of the HIV gp120 envelope protein to CD4 T cells results in conformation change in the envelope, interaction with the co-receptor, and fusion of the viral and cell membranes, thus giving the HIV genome access to the interior of the cell. The infected cells are carried first to draining lymph nodes and then spread systemically. HIV specific immune responses, including increases in CD8+ T cells and eventually neutralizing antibodies, only partially control infection. As a result, in the absence of effective vaccination or therapy, a slow and continued depletion of CD4+ T cells ensues and there is a progression to AIDS.
the course of infection in unvaccinated persons. The primary stage of HIV infection (yellow) starts with a burst of viremia, dissemination of the virus, early seeding and destruction of gut-associated lymphoid tissue, and establishment of a viral reservoir with a latent component. HIV levels in plasma then decline to a set point that lasts from months to years. Eventually, in the absence of effective therapy, the virus escapes immune control and AIDS results (red).
the hypothetical course of infection in vaccinated persons. A T-cell vaccine might decrease the burst of viremia and dissemination that occurs in primary infection (yellow), preserving gut-associated lymphoid tissue, diminishing the viral reservoir, decreasing virus levels at the set point, and increasing the length of time that viral levels are controlled (blue).
resistance to HIV

Some individuals especially sex workers with repeated exposure to the virus, are relatively resistant to HIV acquisition.

On examination of CD4+ T-cell immune responses in seronegative sex workers compared with HIV-positive women, CD4+ T cells that produced interferon gamma (IFN-γ) in response to HIV p24 were detected in exposed seronegative sex worker (ESN) women, but at much lower level than in HIV-positive women.

However, ESN women had stronger CD4+ proliferation response to the p24 peptide compared with the HIV positive group.

These data suggest that CD4+ T cells in ESN women recognize HIV and have an enhanced ability to proliferate to the p24 protein.

On examination of the CD8+ cells in these ESN individuals, approximately 40% of ESN women had a CD8+ IFN-γ-positive response, but lower in magnitude than that of HIV-positive women.

In HIV-positive women, lower CD4+ counts influenced the number of CD8+ cells producing IFN-γ, which may undermine the ability to control HIV.
There are several antigens of HIV:

1. GP120 & GP41 (viral envelope glycoproteins)
   *GP120* protrude from the surface & interact with CD4 receptor & a chemokine receptor on the cell surface.
   *GP41* is embedded in the envelope & mediate the fusion of the viral envelope with the cell membrane at the time of infection.

2. P24
   A specific antigen located in the core.
The entry of HIV into the cell

1* Viral envelope gp120 binds to the CD4 protein on the cell surface.

2* Then gp120 interacts with a second protein in the cell surface, chemokine receptors (CCR5-CXCR4).

3* The gp41 then undergoes a conformational change that allows it to insert into the membrane, resulting in fusion of the virus with the cell.

4* After fusion, the viral core containing the HIV genome enters the cytoplasm of the cell.
Pathogenesis of HIV

The two major targets of HIV infections are the immune system & the CNS.

- HIV mainly infects & kills helper (CD4) T cells & result in suppression of the cell mediated immunity.

- It also infects macrophage & monocyte in the brain which producing multifocal giant cells & CNS disorders.
The coreceptors (CCRS – CXCR4) are critical components of the HIV infection process. HIV stains classified into two types (R5**X4):

---R5 virus binds to CCR5 infect macrophage & monocyte lead to CNS disorders.

---X4 strains bind to CXCR4 infect T-cell lead to immunity suppression.
After HIV binds to the CXCR4 & entry of the genome to the cell, the viral genome undergoes reverse transcription, leading to formation of complementary DNA (cDNA).

In dividing T cells, the cDNA enters the nucleus & becomes integrated into the host genome.

After integration, the provirus may remain non-transcribed for months or years & the infection becomes latent.
NEF & its relation to the pathogenesis

One of the earliest markers in the progression of HIV-1 infection was the presence of NEF in the viral strain. A functional NEF protein is important for the development of high viremia & AIDS.

It does this by:

2. Decrease CD4 proteins & class 1 MHC proteins on surface of infected cells, induces death of uninfected cytotoxic T cells & thus favoring HIV replication.
If the HIV has mutations in its Nef protein,,, the HIV individuals has lived for many years without opportunistic infection & without a reduction in the number of their helper T(CD4) cells.

Blocking NEF influence in viral replication may have long-term beneficial effects on therapeutic management of the disease.
One of the key cells in the immune surveillance system is the native DC, which is well equipped for activation of both the innate and adaptive immune response.

HIV virus impair DC functions, thereby enhancing the virus’s ability to persist and escape immune surveillance.

DC are present in the mucosa and skin of humans and are believed to be the first HIV-1 targets following sexual transmission of the virus.

Both myeloid DC and plasmacytoid DC possess the receptors for HIV entry; that is, CD4, CXR4, and CCR5 can be infected but with a lower efficacy than CD4+ cells or macrophages.

The destruction of these cells may be a consequence of direct lytic infection or as targets for specific CTL.

Thus, the number of both myeloid DC (MDC) and peripheral DC (PDC) are significantly decreased in HIV-positive progressors, while remaining unaltered in HIV-positive long-term nonprogression.

depletion, and dysfunction of DCs may contribute to the immunosuppression seen in HIV disease.
The death of HIV infected cells is the result of

1. Immunologic attack by cytotoxic CD8 lymphocytes.

   (effectiveness of the cytotoxic T cells may be limited by the ability of the viral NEF protein to reduce class 1 MHC protein synthesis).

2. HIV act as “a superantigen” which indiscriminately activates many helper T cells & lead to their demise.
Major abnormalities of immune function in AIDS

Lymphopenia
Predominantly caused by selective loss of the CD4 helper T-cells subset; inversion of CD4:CD8 ratio.

Decreased T-cells function in vivo
- Preferential loss of activated & memory T-cells.
- Decreased delayed – type hypersensitivity.
- Susceptibility to opportunistic infections.
- Susceptibility to neoplasms.
Altered T-cell function in vitro

- Decreased proliferative response to mitogens, alloantigens, and soluble antigens.
- Decreased cytotoxicity.
- Decreased helper function for B-cells production.
- Decreased IL-2 & IFN-γ production.

Altered monocyte or macrophage functions

- Decreased chemotaxis & phagocytosis.
- Decreased HLA class II antigen expression.
- Diminished capacity to present antigen to T-cells.
- Increased spontaneous secretion of IL-1, TNF, IL-6.
Bolyclonal B-cell activation

- Hypergammaglobulinemia and circulating immune complexes.
- Inability to mount de novo antibody response to a new antigen.
- Poor response to normal signals for B-cell activation in vitro.
One of the earliest markers in the progression of HIV-1 infection was the presence of NEF in the viral strain.

A functional NEF protein is important for the development of high viremia and AIDS.

In humans some individuals with long-term nonprogressive HIV-1 infection (persons who showed no clinical or immunological signs of immunodeficiency despite being HIV seropositive for over a decade) turned out to be infected with viruses carrying deletion in their NEF gene.
Effects of NEF on our immune system

The selective effects of the NEF protein may markedly enhance viral pathogenesis and progression to disease.

Both exogenous and endogenous NEF down-regulates HLA-ABC molecules critical for the initiation of cytotoxic T lymphocyte (CTL) responses, thus impairing antigen presentation to HIV-specific CD8+ lymphocytes.

NEF and gp120 also are able to down-regulate major histocompatibility complex class I (MHC-I) in dendritic cells (DCs).

Exogenous NEF leads to up-regulation of MHC-II molecules, thereby favoring CD4+ T-cell activation.

This step increases the “pool” of lymphocytes permissive to infection.

However, endogenous NEF does not modulate MHC-II surface expression; rather it induces a loss of co-stimulation.

These results underscore the pleiotrophic action of NEF.

On one hand, exogenous NEF triggers ABC-mediated bystander T-cell activation, ensuring viral spread, while endogenous NEF induces a loss of co-stimulation, favoring immune evasion.

NEF-pulsed DC produces a wide variety of cytokines and chemokines typical of mature DC. This up-regulation of cytokine production might promote T cells to cluster around DC and could enhance HIV-1 replication in CD4+ T cells.
Possible influence of CCL3 and CCL3L1 genotype on the development of adaptive immunity to HIV vaccines and restoration of loss of function in people with deficient production through the provision of CCL3 as adjuvant. CCL3 and CCL3L1 genotypes determine the production phenotype as wild type (WT) or deficient (red arrowheads).

**Left,** wild-type production of CCL3 as the critical component of a rapid innate immune response (red line) that “instructs” the effective development of subsequent adaptive immunity (green line). **Middle,** deficient production of CCL3 “translates” into an ineffective adaptive immune response. **Right,** provision of CCL3 as an adjuvant (blue line) compensates for deficient host production and restores the development of adaptive immunity to wild-type capability (dashed green line).
HIV VACCINES

BY:
Islam Saeed
FOR:
Dr. Mansour El - yazji
HIV-1 virion

- It is composed of two envelope glycoproteins, gp120 and gp41, both of which are required for attachment and entry of the virus into host cells.

- The virus envelope is composed of host-derived cell membrane.

- The HIV-1 genome is composed of 2 single-stranded RNA copies, and the virus also carries its own Reverse Transcriptase enzyme to catalyze the production of RNA to DNA, which is required for viral replication.
HIV Lifecycle

- **Viral attachment.** The major cell surface receptor for HIV-1 is a molecule called CD4, which binds to gp120 in the viral surface.

- **The virus uncoats**

- **Reverse transcribes** its RNA to DNA, integrates its viral DNA into the host cell genome.

- **The viral DNA is transcribed and translated to produce viral protein** used to replicate the virus and increase viral progeny.

- **Newly formed virus can then bud off from the cell and are free to infect neighboring healthy cells.**
HIV is Different

- The natural immune response to HIV is inadequate
- HIV hides from the immune system
- HIV targets and destroys the immune system
- HIV mutates rapidly
• The epitopes of the viral envelope are more variable than those of many other viruses. Furthermore, the functionally important epitopes of the gp120 protein are masked by glycosylation and receptor-induced conformational changes making it difficult to block with neutralising antibodies.

• The ineffectiveness of previously developed vaccines primarily stems from two related factors:

• First, HIV is highly mutable: Because of the virus' ability to rapidly respond to selective pressures imposed by the immune system, the population of virus in an infected individual typically evolves so that it can evade the two major arms of the adaptive immune system; humoral (antibody-mediated) and cellular (mediated by T cells) immunity.
Second, HIV isolates are themselves highly variable: HIV can be categorized into multiple subtypes with a high degree of genetic divergence. Therefore, the immune responses raised by any vaccine need to be broad enough to account for this variability. Any vaccine that lacks this breadth is unlikely to be effective.
Antiviral treatment

Reverse Transcription Inhibitors

Protease Blockers
Goals of an HIV Vaccine

- Prevent infection
- Prevent disease
- Prevent secondary transmission
Challenges in HIV Vaccine Research

- **Viral Genetic Diversity:** HIV is not just one specific virus.

- **Immune Protection:** We don’t know what immune responses are needed, or how strong they need to be.

- **Neutralizing Antibody:** Difficult to generate broadly neutralizing antibodies.

- **Vaccine Testing:** Slow process, very expensive
Antigen Presenting Cells
*“First-line Defense”
*Involved in capturing antigen
*Display ‘foreign’ antigens to activate T Cells

T Cells
*Involved in the ‘killing’ of virus-infected cells
*Adaptive Immunity

B Cells
*Involved in making antibodies
*Adaptive Immunity
three cells primarily involved in a successful immune response:

• **Antigen Presenting Cells (APCs):**
  - normally found in the skin, blood, and mucosal surfaces where pathogens may enter.
  - They are the body’s first line of defense.
  - function to capture antigen (foreign protein) and present these antigens to T cells and cause their activation.

• **T cells**
  - are involved in the killing of pathogen-infected cells.
  - part of the adaptive immune response, meaning that their effector function is specific for a particular pathogen/infection.

• **B cells**
  - are also function in the adaptive immune response to invading pathogens.
  - They are involved in producing specific types of antibodies against the pathogen in order to neutralize the pathogen.
• **So how does the body respond to a viral infection?**

• As the virus begins to replicate within the host cell, the host cell has a defense mechanism where it can take different parts of the virus and present them on the surface of the cell on MHC molecules.

• These MHC molecules present viral antigens to signal to other immune cells that it has been infected.
APCs circulating throughout the body will pick up fragments of the virally-infected cell and present them on their cell surface.
• T cells with specific receptors for the MHC-antigen complex will bind causing the APC to secrete signals to program the T cell to proliferate into cytotoxic T lymphocytes (CTLs) that have the ability to kill infected host cells.
• B cells also have receptors that recognize viral antigens which programs the B cell to produce antibodies which will recognize and neutralize to virus preventing further infection of healthy cells.
• From a vaccine standpoint, researchers want to manipulate the immune system to be programmed to carry out these functions before a ‘real’ infection occurs.
HIV Vaccine Approaches

- Protein subunit
- Synthetic peptide
- Naked DNA
- Inactivated Virus
- Live-attenuated Virus
- Live-vectored Vaccine
HIV VACCINES

- LIVE ATTENUATED..
- INACTIVATED..
- SUBUNIT VACCINES..
- CELLULAR VACCINES..
Live attenuated vaccines

- The positive side is that:
  - although the attenuated vaccine does not prevent infection with a wild-type SIV infection, it does prevent that infection from going on to produce the disease AIDS.
  - HIV-1 superinfection (reinfection) does not always protect against other strains.
• superinfection commonly occurs after the immune response against the initial infection has had time to develop and mature.

• superinfection occurred despite broad CD8+ T-cell responses (twenty-five distinct epitopes) to many HIV viral proteins.

• They conclude that superinfection can occur in the setting of a strong and broadly directed virus-specific CD8+ T-cell response.
They conclude that chronic HIV infection seems to confer protection against superinfection with a second HIV-1 strain. Obviously, more work needs to be done to determine what factors are responsible for superinfection in some individuals and protection in others, both at high risk of reinfection.
Inactivated vaccines

• Although the initial results with inactivated vaccine were negative with high doses of formalin treatment (loss of antigenicity of the viral envelope proteins), it was quickly discovered that by using low doses of formalin, the antigenicity of the envelope proteins was preserved.

• This preparation was capable of inducing viral neutralizing antibodies in both mice and nonhuman primates but the problem will be overcoming the rapidly changing antigens of the wild-type virus.
A second approach has been to inactivate the domains of two nucleocapsid proteins by treating these complexes with mild oxidation or alkylation procedures, which completely inactivates both HIV-1 and SIV but keeps the envelope glycoprotein spikes intact and functional.

Studies in the SIV macaque model revealed that monkeys vaccinated with the inactivated virus were not protected against infection with the wild-type virus, but the levels of SIV viremia were low and there was no depletion of CD4+ T cells.
Subunit vaccines

• Most of the research efforts in HIV vaccines have gone into the subunit vaccines involving the gp120 envelope proteins, which also includes the gp41 domain.

• Both of these proteins do elicit neutralizing antibodies to the homologous vaccine strain but not to heterologous primary isolates in the animal model.
Cellular vaccines

• A strong and specific T-cell immune response in the absence of broadly neutralizing antibodies may blunt the initial viremia, even if the infection is not completely prevented.

• Thus, more recent vaccine efforts have been directed toward stimulating the cellular immune response.

• Particular attention has been paid to those vaccines that induce an HIV-specific CD8+ CTL response whose role in the control of virus load and evolution of disease has been well documented in the macaque model.

• Although the T-cell vaccines do not prevent the HIV infection, they do help vaccinees who get infected to control viral replication and reduce viral loads, thus resulting in less risk of transmission of the disease to seronegative partners.