

HIV-Host Cell Interactions

Subjects: **Infectious Diseases**

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The development of antiretroviral drugs (ARVs) was a great milestone in the management of human immunodeficiency virus (HIV) infection. ARVs suppress viral activity in the host cell, thus minimizing injury to the cells and prolonging life. However, an effective treatment has remained elusive for four decades due to the successful immune evasion mechanisms of the virus.

HIV

AIDS

immunity

cells

T- cell exhaustion

CCR5

CXCR4

sex

1. Introduction

The human immunodeficiency virus (HIV) is a Lentivirus belonging to the *retroviridae* family, responsible for the HIV/acquired immune deficiency syndrome (AIDS) pandemic ^[1]. Although discovered and declared a pandemic in the 1980s, there is evidence that pre-epidemic strains of HIV existed as far back as the 1920s ^{[2][3][4]}. Based on genetic and antigenic variations, HIV is divided into two types: HIV-1 and HIV-2. HIV-1 is the most virulent and widespread ^{[5][6]}. HIV-1 is responsible for the global pandemic, whereas HIV-2 is mainly confined to West Africa ^{[7][8]}.

HIV targets and infects Cluster of Differentiation 4-positive (CD4⁺) cells, predominately CD4⁺ T helper lymphocytes ^[9]. To mount a successful invasion, HIV requires the presence of the CD4 receptor and the C-C chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4) co-receptor on the host cell ^{[10][11]}. Infection terminates in the death of the host cell; thus, infection invariably leads to the depletion of CD4⁺ T lymphocytes ^[12]. Since CD4⁺ T lymphocytes are the regulators of the adaptive immune system, their depletion effectively weakens the immune system, leading to the acquired immune deficiency syndrome (AIDS) stage of the infection ^[9]. Two biological phenotypes of HIV-1 exist, and these differ in terms of receptor tropism: X4 HIV-1 has an affinity for the CXCR4 receptor, whereas R5 HIV-1 has an affinity for the CCR5 receptors ^{[13][14]}.

The most common mode of HIV transmission is unprotected sexual intercourse with an infected person ^{[15][16]}. Other modes of transmission include mother-to-child transmission, the use of contaminated needles and transfusion with infected blood ^{[17][18][19][20][21]}. Men who have sex with men and injectable drug users are at a higher risk of HIV infection ^{[22][23][24][25]}. Body fluids such as semen, vaginal fluids and blood of infected persons contain free-floating viruses and virus-infected CD4⁺-positive cells that facilitate the transmission of infection to the next cell or host ^{[26][27][28][29]}.

Tremendous progress in the understanding of the HIV molecular interaction with the host cell, the host cell responses to the virus and potential therapeutic implications of this interaction has been made since its discovery [30][31]. Vigorous research heralded the development of antiretroviral drugs a very important milestone in controlling the HIV pandemic [32]. Despite much progress in understanding the HIV–host cell interactions, the cure for HIV infection has remained elusive for four decades now [31][33].

2. Structure of HIV

The HIV-1 virion is spherical, with viral glycoprotein spikes (glycoprotein 120 (gp120) and gp41) that protrude from the viral envelope (env) [34]. The other structures include the Group antigens (Gag) responsible for directing the formation of virions from productively infected cells and the Pol protein containing enzymes critical for viral replication such as reverse transcriptase, protease and integrase [35][36]. The viral proteins such as viral protein R (vpr), viral protein U (vpu) and virion infectivity factor (Vif) are important for regulating nuclear import, replication, the degradation of CD4 molecules, virion release from cells and enhancing viral pathogenesis [37].

3. HIV Life Cycle

The HIV life cycle consists of 11 phases and includes binding/attachment, fusion, trafficking, nuclear import, reverse transcription, integration, transcription/translation, assembly, budding and release [38][39] (Figure 1).

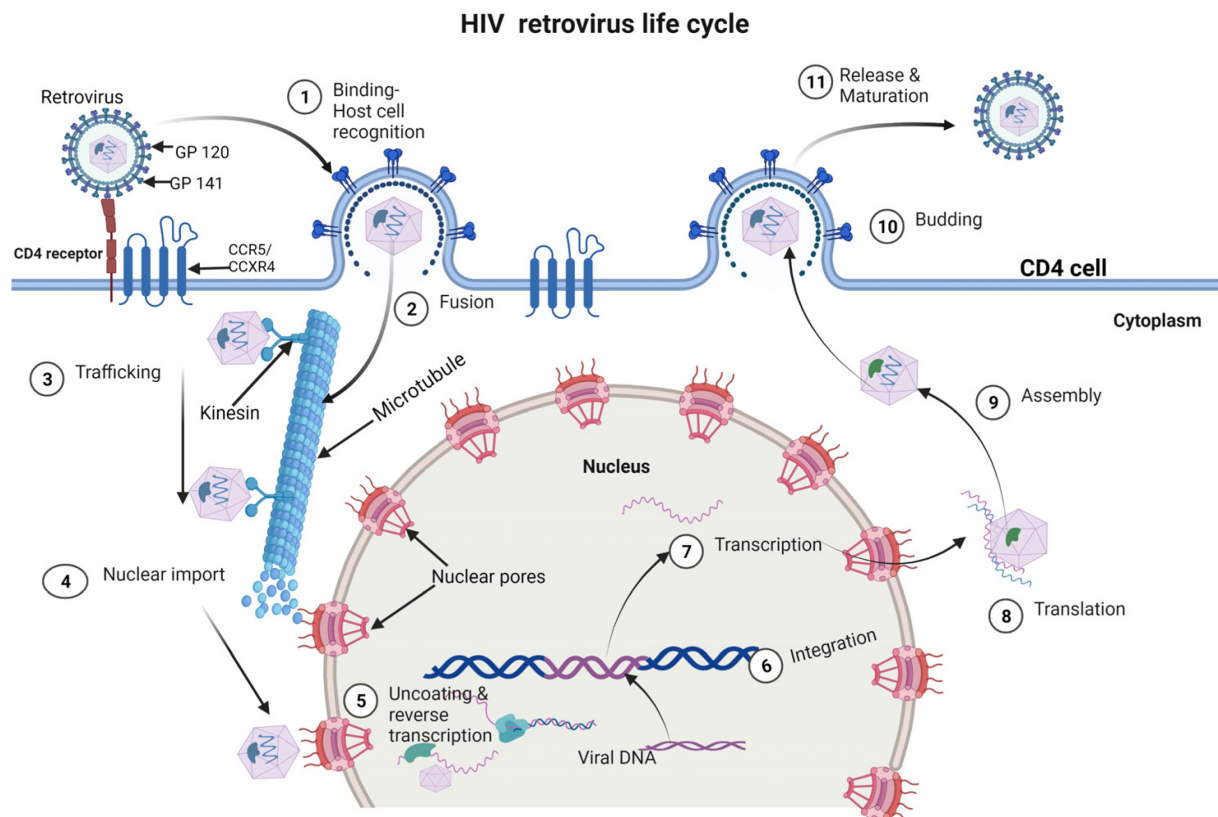


Figure 1. The life cycle of HIV-1. The early stage begins with virus interaction with the host cell receptors (1), which causes the virus to fuse and release its viral core into the host cell's cytoplasm (2). Following this, the core is transported across the cytoplasm (3) as reverse transcription and nuclear import start to occur (4). The viral components are brought into the nucleus at the nuclear pore, where they are localized to transcriptionally active chromatin while uncoating and reverse transcription are carried out (5). Integration follows (6); then, viral genes are transcribed (7) and translated (8) into the Gag polyproteins, which assemble (9) and localize to the host membrane, followed by the occurrence of the budding of an immature virion (10). The viral protease cleaves the Gag polyprotein into its component, functional proteins during the last stage of the HIV-1 lifecycle, known as maturation (11).

The initial step of HIV infection is the attachment of the virus to the CD4⁺ T cell receptor and co-receptor. The viral envelope glycoprotein, gp120, interacts with the CD4 receptor on the T cell surface, which triggers a conformational change in gp120, allowing it to bind to the co-receptor, either CXCR4 or CCR5 [40][41][42][43]. This binding leads to the exposure of the gp41 subunit, which mediates the fusion of the viral and cellular membranes [40][41][42][43]. After the viral envelope fuses with the host cell membrane, the core containing the viral genome and enzymes such as reverse transcriptase (RT), integrase (IN) and protease (PR) is released into the host cell cytoplasm and transported to the nucleus. The RT converts the viral RNA genome into double-stranded DNA (dsDNA), which is subsequently integrated into the host cell genome by the integrase enzyme with the aid of the Pre-integration Complex (PIC), a nucleoprotein complex comprising host and viral proteins, and the viral genome [44][45][46]. The integrated viral DNA is called a provirus, which remains dormant until activated by the host cell [47][48].

4. HIV-Related Factors Promoting Infection and Immune Evasion

4.1. Downregulation of MHC Class I and II

HIV can evade the host immune system by downregulating the expression of MHC class I and II molecules, which are proteins that are essential for antigen presentation and recognition by immune cells [49][50]. This occurs at a molecular level through several mechanisms, including the ability of HIV to interfere with the transcription and translation of MHC class I and II genes, which reduces the overall expression of these molecules on the surface of infected cells [51][52]. This effect is mainly mediated by the HIV-1 accessory protein Nef [53], which is essential for viral pathogenesis and hence a potential target for antiretroviral drug discovery [37].

Nef interacts with the cytoplasmic tail of MHC I and II molecules and redirects them to the endocytic pathway for degradation [54][55]. One proposed mechanism for the HIV-1 Nef-mediated downregulation of cell surface MHC-I molecules is that Nef and Phosphofurin Acidic Cluster Sorting Protein 1 (PACS-1) combine to usurp the ADP ribosylation factor 6 (ARF6) endocytic pathway by a phosphatidylinositol-3 kinase (PI3K)-dependent process and downregulate the cell surface MHC-I to the trans-Golgi network [56].

The HIV Vpu protein also facilitates the degradation of MHC class I molecules. Vpu targets MHC I molecules for degradation by interacting with the host protein beta-TrCP, which recruits the E3 ubiquitin ligase complex to tag MHC I for degradation in the proteasome. The Vpu protein [57][58] interferes with the transport of newly synthesized MHC I molecules to the cell surface, where they are required for recognition by immune cells [59][60][61] by sequestering MHC-I intracellularly in the early stages of endocytosis and recycling [62].

4.2. Production of Non-Neutralizing Antibodies

The viral envelope glycoprotein, gp120, is highly variable, and it can quickly mutate to escape recognition by neutralizing antibodies that target specific regions of the protein, thus leading to the production of non-neutralizing antibodies that can bind to gp120 but are unable to block virus entry [11][41].

Non-neutralizing antibodies can still play a role in HIV immune evasion. By binding to gp120, they can prevent the recognition of viral epitopes by neutralizing antibodies or T cells, effectively shielding the virus from immune surveillance [63]. Non-neutralizing antibodies can also trigger Fc receptor-mediated signaling, which can downregulate immune effector cells, such as Natural Killer (NK) cells and macrophages, leading to decreased antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis of infected cells [64][65].

4.3. Induction of Immune Exhaustion

HIV can induce immune exhaustion, which is a state of functional impairment of T cells, at a molecular level by several mechanisms. First, persistent antigen stimulation caused by HIV infection leads to T cell activation and proliferation, eventually leading to T cell exhaustion [12]. Second, HIV upregulates inhibitory receptors on T cells, such as programmed cell death receptor 1 (PD-1), cytotoxic T lymphocyte antigen-4 (CTLA-4) and T-cell immunoglobulin domain- and mucin domain-containing protein 3 (TIM-3), which negatively regulate T cell activation and function [12]. Third, HIV downregulates the expression of key transcription factors and cytokines, such as the T-Box protein expressed in T cells (T-bet), interferon-gamma (IFN- γ) and IL-2, that are necessary for effector T cell function [12][66].

4.4. Destruction of Virus-Specific T Helper Cells

HIV can evade the host immune system by destroying virus-specific T helper cells, which are important for coordinating the immune response against the virus [67]. This occurs at a molecular level through several mechanisms [68]. First, HIV can directly kill infected T helper cells by inducing apoptosis or programmed cell death [69]. Second, HIV-infected cells can also cause the bystander killing of uninfected T helper cells through the release of viral proteins, such as Tat, Nef and gp120, which activate apoptosis pathways in nearby cells through several mechanisms such as the upregulation of Fas, FasL and TNF α expression [70], the reduced expression of Bcl-2 and the activation of p53 [71]. Third, HIV proteins can induce cell death pathways by disrupting the normal functioning of cellular proteins and organelles, such as the mitochondria, which can lead to the death of infected and uninfected T helper cells [67][72][73].

4.5. The Emergence of Antigenic Escape Variants

HIV can evade the host immune system through the emergence of antigenic escape variants, which are viral strains that have mutations in the viral proteins that are recognized by the immune system [74]. Several mechanisms favor this. First, HIV replicates at a high rate, which results in the generation of a large number of viral particles that can potentially acquire mutations [75]. Second, the HIV reverse transcriptase, the enzyme responsible for copying the viral genome, is highly error-prone, which increases the likelihood of mutations occurring during replication [76]. Third, the immune system exerts selective pressure on HIV by targeting specific viral proteins, which can result in the emergence of variants that are less recognizable by the immune system [67].

4.6. Expression of an Envelope Complex That Minimizes Antibody Access

HIV can evade the host immune system by expressing an envelope complex that minimizes antibody access, which refers to the outer surface of the virus that is recognized by the immune system [77]. The envelope protein of HIV undergoes molecular-level changes through various mechanisms. The envelope protein of HIV is covered in sugar molecules, making it highly glycosylated, and this can prevent antibodies from binding to and neutralizing the virus by shielding vulnerable regions of the envelope protein from antibody recognition [78].

4.7. Dysregulation of the JAK/STAT Pathway

Interferons are primarily produced and released by host cells such as immune cells (macrophages, dendritic cells, T cells) and non-immune cells (fibroblasts, epithelial cells) in response to viral infections, certain bacterial infections or other immune triggers [79]. Upon detecting viral particles, the host production of interferons creates an antiviral atmosphere which suppresses viral replication through the mechanism of inducing the expression of antiviral proteins and activating immune cells [80][81][82][83].

4.8. Other Factors That Promote HIV Infection

The HIV-1 viral infectivity factor (Vif) is a 23-kDa protein found within the HIV-1 virion that plays a crucial role in the survival/invasion of host tissue by HIV [84]. It counteracts the APOBEC3 family of proteins, which are host cellular defense mechanisms that can mutate the genetic material of viruses, including HIV. Vif targets Apolipoprotein B mRNA Editing Catalytic Polypeptide-like (APOBEC3) proteins for degradation, allowing the virus to continue to replicate and spread [85]. Without Vif, HIV is much less able to infect and replicate in host cells [85]. Additionally, the Elongin–Cullin–SOCS (ECS) box site is involved in several HIV-related factors that promote infection and immune evasion [86][87]. The HIV-1 Vif can interact with the ECS box site on SOCS proteins, leading to the dysregulation of cytokine signaling pathways and promoting viral replication and immune evasion [86][87]. The ECS box site is also involved in the regulation of interferon signaling pathways, and the dysregulation of these pathways by HIV can contribute to immune evasion and pathogenesis of the virus [86][88][89].

5. Host Cell Mechanisms That Control Infection and Replication

HIV-1 infection progression is determined by both the virus and the host cells, with pattern recognition receptors (PRRs) playing a vital role in initiating the host immune response [90]. Early HIV-1 infection, the first hours to days after infection, in which the virus replicates in the cells such as the dendritic cells and macrophages/monocytes and is not detectable in the blood, is referred to as the “eclipse phase” [91]. The characteristics of early/recent infection include a high viral load and immune cell depletion. This eventually leads to immunodeficiency, and without treatment, individuals die of AIDS [92]. However, at the onset of infection, innate immune cells such as dendritic cells, NK cells, NKT cells, $\gamma\delta$ T cells and B1 cells macrophage/monocytes respond to infection and also induce the cells of the adaptive immune system, the CD4⁺ and CD8⁺ T lymphocytes [93]. The innate immune response, requiring no gene rearrangement, is non-specific and uses pattern recognition receptors to recognize the HIV infection and induce other innate related factors against HIV [94]. These innate immune components include skin mucosal epithelial cells, phagocytes and NK cells, as well as a series of soluble factors, such as cytokines, chemokine and small molecular substances, such as complement and mannose-binding lectin [95].

The secreted IFNs produce an antiviral effect by autocrine and paracrine ligation to interferon-alpha/beta receptors (IFNAR) on cell surfaces [96]. This activates the downstream Jak/STAT signaling pathway through receptor-associated Jak1/TyK2 (tyrosine kinase) [97]. The phosphorylated STAT1 and STAT2 then form a heterodimer that interacts with IFN-regulatory factor 9 (IRF9) to form an IFN-stimulated gene factor 3 (ISGF3) transcription complex. ISGF3 translocate to the nucleus, where it binds to IFN-stimulated response elements (ISREs) in gene promoters, leading to the expression of IFN-stimulated genes to establish the host antiviral status that impairs viral replication and promotes the maturation of dendritic cells, promoting the activation of adaptive immune response [98].

Sentinel dendritic cells and macrophages are powerful, professional antigen-presenting cells that not only play a significant role in the initial response to infection but also activate adaptive immunity [95]. While sentinel dendritic cells are the first cells in response to infection, macrophages are the main effector cells involved in the late innate immune response and support the recruitment of inflammatory cells by secreting cytokines such as IL-1 and TNF- α [99]. Other cytokines, such as IFN- α and IL-15, which are secreted by dendritic cells and monocytes are significant in the activation of NK cells [100].

5.1. Pathogen Recognition Receptors (PRRs)

Pathogen Recognition Receptors (PRRs) are immune receptors that recognize conserved molecular patterns on pathogens, such as bacteria or viruses [101]. PRRs are differentially expressed by various immune cells including macrophages and dendritic cells [102]. PRRs are an essential component of the innate immune system and initiate downstream signaling that leads to the production of cytokines, chemokines and molecules capable of activating the adaptive immune response [103].

PRRs can be divided into several classes, such as Toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-I-like receptors (RLRs) and C-type lectin receptors (CLRs), among others [104]. TLRs (**Figure 2**) are the most studied and characterized PRRs and recognize a broad range of pathogen-associated molecular patterns (PAMPs), including lipopolysaccharides, lipoproteins and viral nucleic acids [105]. Once bound to their specific ligands, TLRs

activate multiple downstream signaling pathways, including the NF- κ B pathway and the interferon regulatory factor (IRF) pathway, leading to the expression of genes that drive the inflammatory and antiviral immune response [106][107].

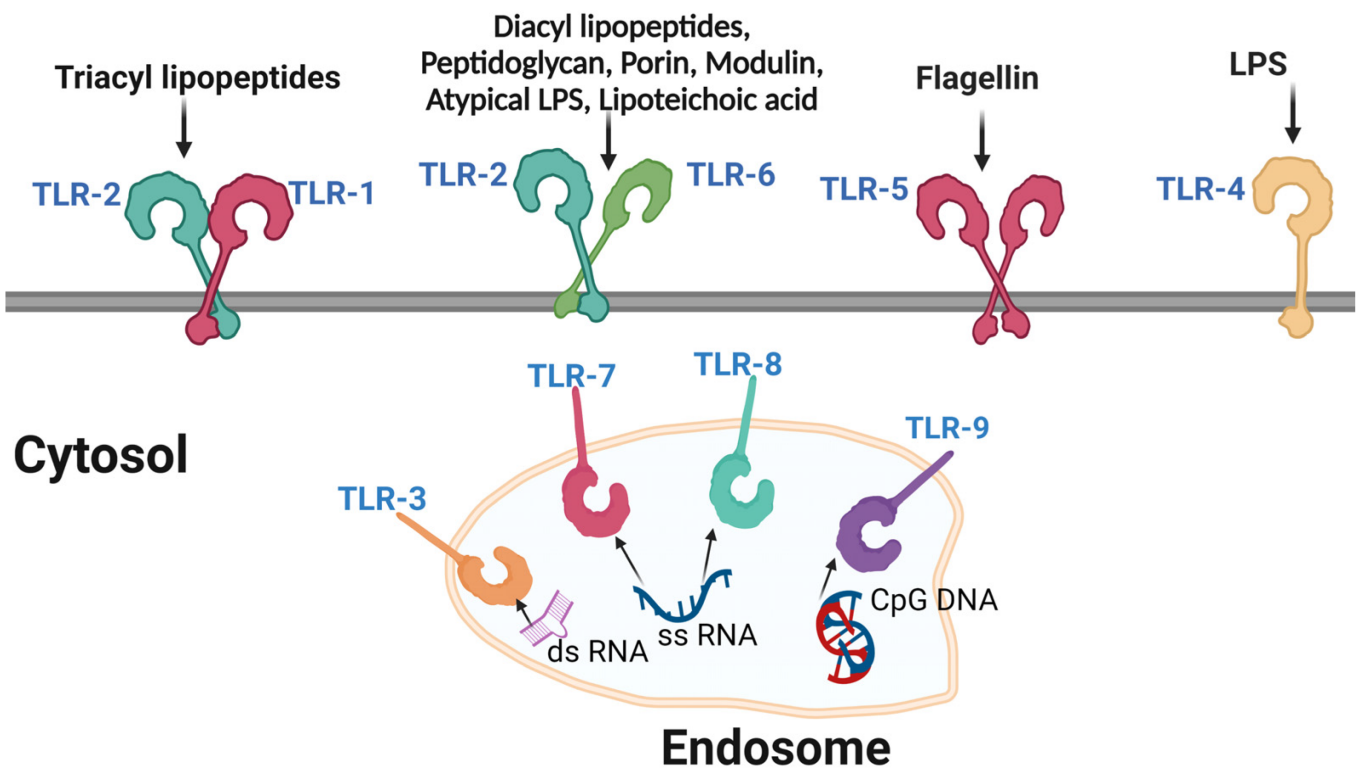


Figure 2. Toll-like receptors. Toll-like receptors act as antigen sensors for the immune system. They recognize a wide range of foreign antigens and thus help the immune system mount an appropriate response.

5.2. Dendritic Cells

Dendritic cells (DCs) are among the first cells that encounter HIV, and being antigen-presenting cells, they are significant in the fight against the virus and the stimulation of the adaptive response [93][108]. While patrolling in the tissue, they can recognize antigens, process them and present them to T cells in secondary lymphoid organs, thereby activating the adaptive immune system. DCs can also secrete several diverse cytokines intended to upregulate the immune response by the secretion of cytokines; the exact type of cytokines secreted is dependent on the DC cell subtype and specific stimuli [94][109].

5.2.1. Plasmacytoid Dendritic Cells (pDCs)

The most characteristic feature of the pDCs is the production of the type 1 interferon that promotes a strong antiviral immune response [110]. Plasmacytoid DC expresses TLR7, which enables it to recognize the virus after uptake by endocytosis and activate a signaling cascade that leads to the maturation of pDCs, the production of IFN- α , IFN- β and TNF- α and the expression of chemokine receptors such as the CCR5, CD40, CD80 and CD86 co-stimulatory molecules [94].

5.2.2. Conventional Dendritic Cells (cDCs)

Conventional DCs function mainly as specialized APCs; however, they also produce several cytokines upon recognition of an antigen, mainly inflammatory cytokines including IL-6, IL-12, IL-15, IL-23, TNF and IL-1 β all, of which are significant in restraining HIV-1 infection as compared to pDCs, which are known for the secretion of a large amount of type I interferons [93]. Conventional DCs are important in bridging innate immunity and adaptive immunity by presenting antigens to T cells [93]. Whereas cDCs1 are distinguished by their effective MHC class I-mediated priming of CD8⁺ T cells, cDC2 have a broad variety of factors generated and high cross-presenting abilities, promoting a potent activation of T_h1, T_h2 and T_h17 as well as CD8⁺ T cell responses [93][95][99][109].

5.3. Macrophages

Macrophages are key players in innate immune responses to pathogens, and their ability to destroy a wide range of pathogens while doubling as APCs makes them a vital component of the innate immune system [111]. Unlike most cells of the myeloid lineage, macrophages have a longer life span, ranging from months to years [112]. Macrophages are widely distributed in the body and reside in almost every tissue of the body [113]. While initially thought to be incapable of self-renewal, there is evidence that tissue macrophages can and do replenish themselves [114][115][116].

Viral interaction with macrophages is very important in the HIV disease course [117]. In the sexual transmission of HIV, macrophages encounter HIV in the genital mucosa along with CD4⁺ T cells and DCs [118][119]. Macrophages play a crucial role in the immune response to HIV infection in the early stages of the disease, as their primary function is to engulf and clear viral particles and infected cells [120][121].

5.4. CD4⁺ T Cells

CD4⁺ T cells are crucial components of the immune system and play a key role in mounting an effective response against viruses such as HIV [9]. However, HIV specifically targets and infects CD4⁺ T cells, leading to a gradual depletion of this cell population and ultimately resulting in the onset of AIDS [122].

The mechanisms underlying the CD4⁺ T cell response to HIV infection involve a variety of signaling pathways and biochemical interactions [123]. Upon the initial encounter with HIV, CD4⁺ T cells become activated and initiate a series of intracellular signaling events, including calcium flux and protein kinase C activation [84][124][125].

5.5. CD8⁺ T Cells

CD8⁺ T cells recognize and directly eliminate virus-infected cells. In the acute phase of HIV infection, there is an increase in CD8⁺ T cell activity due to APCs and CD4 T cell stimulation, resulting in CD8⁺ T cells killing virus-infected cells by releasing granzymes, which can induce apoptosis in the target cell and a pore-forming protein called perforin, which perforates the cell membrane of the target cell, thereby killing the cell [126].

CD8⁺ T cells recognize infected cells through the presentation of viral peptides on major histocompatibility MHC 1 molecules [\[127\]](#). Once they encounter an antigen on MHC 1 molecules, they become activated, gain cytotoxic activity and additionally secrete a variety of cytokines including IFN-γ, which inhibit viral replication and create an antiviral environment [\[67\]\[128\]](#).

6. Influence of Sex on HIV Transmission and Immune Responses

There are notable sex differences in HIV infection transmission and progression. HIV infection in females is marked by a stronger initial immune response, characterized by a high CD4⁺ T cell count, low viral load and high CD8⁺ T cell activity, while infection in males is marked by high viral load, a lower CD4⁺ T cell count and low CD8⁺ T cell cytotoxic activity [\[129\]\[130\]](#). However, there is early immune exhaustion in females, accelerating the progression to AIDS at a rate comparable to that of males, and progression to AIDS occurs at a lower viral load compared to that of males [\[131\]](#).

Both the foreskin and the vaginal mucosa contain CD4⁺ T cells, which can be infected by HIV during sexual intercourse with an infected person; however, male CD4⁺ T cells express higher CCR5 receptors when compared to females, which implies that males are more likely to be infected in one sexual encounter with higher viral particles, thus partially explaining the higher viral loads in males in primary HIV infection [\[132\]\[133\]](#). Furthermore, the Langerhans cells in the vagina and foreskin transport viral particles to the local lymphatics, where they present the viruses to the CD4⁺ T cells in the process of infecting them and spreading the infection [\[134\]](#). Therefore, males who undergo circumcision have up to 60% reduced chances of contracting HIV because of the loss of the foreskin, which significantly reduces both CD4⁺ T cells and Langerhans cells [\[135\]\[136\]\[137\]](#).

It is a well-established fact that females generally mount stronger immune responses to both self and non-self-antigens, including viral infection: therefore, females are more prone to autoimmune disease than males [\[138\]](#). While the mechanisms behind the sex differences are not fully understood, several genetic and physiological mechanisms are thought to be responsible for the stronger immune responses mounted by females compared to males in response to HIV infection and for how this may influence disease progression [\[139\]](#).

The first mechanism that can explain the stronger immune responses in females is the presence of X chromosome-linked genes that contribute to the higher expression of TLRs in females [\[140\]](#). TLR7, which is higher in females, is located on the X chromosome, and females have two copies of the X chromosome, as opposed to males, who only have one [\[141\]](#).

The differences in immune response between sexes could also be attributed to sex hormones. Sex hormones have been shown to regulate the expression of TLRs, particularly TLR7 and TLR8, which recognize single-stranded RNA viruses such as HIV; this can lead to a stronger innate immune response against HIV and may help to control viral replication [\[142\]\[143\]\[144\]](#).

Estrogen has also been shown to stimulate immune response by increasing the number and activity of immune cells such as T cells and B cells, and it achieves this by stimulating the secretion of cytokines from a variety of cells, including immune cells such as monocytes, macrophages, dendritic cells and T cells [145][146][147]. Estrogen modulates the production of cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), TNF-alpha and IFN- γ , among others [148][149][150][151][152][153]. These cytokines are important in regulating immune responses and play a role in inflammatory and autoimmune diseases [154][155][156][157]. Estrogen stimulates cytokine release by binding to the Estrogen receptors (ERs), ER-alpha (ER α) and ER-beta (ER β), which are expressed on the surface of immune cells [158].

Estrogen can also bind to membrane-associated estrogen receptors (mERs), such as G protein-coupled receptor 30 (GPR30), which activate intracellular signaling cascades, such as the mitogen-activated protein kinase (MAPK) pathway [159][160][161]. These signaling pathways regulate cytokine production by immune cells [162][163]. The MAPK pathway can activate the c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) and p38 MAPK sub-pathways, which regulate different aspects of immune cell activation [163].

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