Chapter 1

Immune Responses and Cell Signaling During Chronic HIV Infection

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Additional information is available at the end of the chapter

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1. Introduction

The immune response can be defined by the reaction of the immune system to a particular antigen to which it is exposed. In order to understand immune responses against an infectious agent such as human immunodeficiency virus (HIV) and their regulation during the course of chronic HIV infection, we will provide a brief overview of HIV and its proteins and attempt to shed light on this disease process. We will also review the immune system, its components and describe how these components interact at the molecular levels to fight an invading pathogen such as HIV.

2. Human immunodeficiency virus (HIV)

AIDS (Acquired Immuno-Deficiency Syndrome) in patients was discovered in 1981 and characterized by the appearance symptoms including persistent lymphadenopathy and opportunistic infections such as Kaposi sarcoma, *Pneumocystis carinii* pneumonia. In addition, it was found that all of these patients shared a common defect in cell-mediated immunity characterized by a significant decrease in CD4+T lymphocytes, later revealed to be a principal target of infection [1-3]. Three years later, the causative agent of AIDS was identified as HIV [4, 5]. HIV was classified under the *lentivirus* genus and the *Retroviridae* family. It is an enveloped virus with a size of about 100 nm in diameter. Its genome consists of two identical copies of positive-sense single stranded RNA (ssRNA) that are reverse transcribed into cDNA in infected cells [2, 5]. Each ssRNA is about 9,500 nucleotides in length, and encodes three structural genes called gag, pol, env, and a complex of several other nonstructural regulatory

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genes known as tat, rev, nef, vif, vpr, and vpu [2, 5]. The gag gene encodes the viral structural proteins including p24 (capsid), p17 (matrix), p7 (nucleocapsid). The pol gene, on the other hand, encodes viral enzymes including p32 (integrase), p66 and p51 (reverse transcriptase), and p10 (protease). The env gene encodes the coat glycoproteins gp120 (surface) and gp41 (transmembrane), which play a major role in viral attachment and fusion with host target cell membranes. The nonstructural genes including transactivator of transcription (Tat), regulator of virion protein expression (Rev), negative regulatory factor (Nef), viral infectivity factor (Vif), viral protein R (Vpr), and viral protein U (Vpu) proteins, respectively, are also essential for viral replication and pathogenesis [2, 5].

3. The immune system and its cellular components

The immune system is a very complex and dynamic network, which can be broadly divided into innate and adaptive components [4,6,7]. The cellular components of innate immunity include dendritic cells, natural killer (NK) cells, NK T cells, macrophages, and granulocytes, whereas, the adaptive immunity is mediated by B and T lymphocytes [4,6-8]. The components of both branches act in conjunction and are regulated by soluble mediator proteins known as cytokines and chemokines in order to fight, clear, and protect the host from a wide variety of pathogens [4,6-8].

3.1. The innate immune system

The innate immune system is the first line of defense against invading pathogens. Viral infections including HIV induce the interferon (IFN) response that is characterized by the production and secretion of pro-inflammatory cytokines including type-I IFN (IFN-α/β). These cytokines have antimicrobial and anti-proliferative properties and serve to propagate the adaptive immune responses [9]. In humans, cellular RNA molecules are short stem secondary structures. In contrast, RNA viruses produce long dsRNA molecules in the infected cells as a part of their life cycle. Thus, the long dsRNA can be recognized as a foreign molecule and triggers both cellular and humoral innate immune responses [10]. There are two well characterized ways in which a cell can recognize pathogens. Distinct extracellular pathogen components are recognized by different Toll- like receptors (TLR) expressed on the cell surface or in the endosome such as TLR2, TLR3, TLR4, TLR7, TLR8, and TLR9 [11]. Intracellular replicating pathogens however, are recognized by RNA helicases, which are encoded by the retinoic acid-inducible gene I (RIG-I) and/or melanoma differentiation-associated gene 5 (MDA5) [12]. Following viral recognition, the activation and translocation of the transcription factor nuclear factor κB (NFκB) and interferon-regulatory factor (IRF)-3 to the nucleus occurs and promotes the transcription of IFN type I [13]. Production of type-I IFN stimulates the surrounding cells to produce a wide range of antiviral proteins including protein kinase R (PKR), myxovirus resistance factor, 2'-5' oligoadenylate synthase/RNaseL and dsRNA adenosine deaminase 1, which subsequently leads to the activation of eukaryotic initiation factor (eIF)-2, and translation inhibition of both host and viral mRNAs [14].

Monocytes, which are the precursors of macrophages, as a part of the innate immune system, play a major role in controlling and clearing pathogens. They exhibit antimicrobial, antifungal, and antiparasitic properties [4,6-8]. They possess phagocytic and endocytic activity. In addition, they act as antigen presenting cells by uptaking, processing, and presenting antigen in the context of major histocompatibility complex (MHC) class II to CD4+ T cells. Moreover, they secrete inflammatory cytokines such as IFN type-I (IFN-α/β), interleukin (IL)-1, IL-6, IL-12, and chemokines such as IL-8 [4,6-8]. This stimulates the adaptive immune system and leads to the activation and differentiation of B and T lymphocyte populations. These important monocyte/macrophage (M/M) functions are largely driven and regulated by the responsiveness of these cells to numerous cytokines such as IFN-γ, IL-10, and Tumor Necrosis Factor (TNF)-α, and signals delivered to them via the TLR family through recognition of different microbial products such as bacterial lipopolysaccharide (LPS) and viral proteins and nucleic acids including those of HIV [4,6-8].

3.2. The adaptive immune system

B and T lymphocytes form the arm of the adaptive and antigen-specific immune response. B lymphocytes are antigen presenting cells, upon antigenic and cytokine stimulation they differentiate into plasma cells which produce antigen-specific antibodies. While T lymphocytes are divided into two distinct populations: helper and cytotoxic cells which are differ in their function T helper lymphocytes express the CD4 surface receptor, recognize antigens presented as peptide epitopes bound to MHC class II molecules expressed on the surface of antigen presenting cells, and function mainly as cytokine producing cells to 'help' the development of the immune response. Activated CD4+ T cells differentiate into T helper (Th)-1 and Th-2 effectors, and memory cell sub-populations. The Th-1 and Th-2 subsets of CD4+ T cells were originally defined by their polarized cytokine production patterns [15,16]. Th-1 cells produce IFN-γ, IL-2, IL-12 and lymphotoxin-α, which enhance antigen presentation, phagocytosis, and cell-mediated cytotoxicity. On the other hand, Th-2 cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13, promoting more of an antibody response [16-18]. Cytotoxic T lymphocytes however, express the CD8 surface receptor, and recognize antigenic peptide epitopes presented on cell surface MHC class I molecules. Antigen-activated CD8+ T cells also proliferate and differentiate into effectors and memory cell populations, largely in response to cytokines that share the common γc receptor, such as IL-2, IL-15, and IL-7. Cytotoxic T cells secrete IFN-γ, which inhibits virus replication, as well as perforin, and granzymes in order to kill virus-infected cells.

3.3. HIV and the cellular immune response

HIV is commonly transmitted by sexual contact, and thus it initially interacts with and activates the innate immune system and antigen presenting cells including macrophages and dendritic cells at the mucosal surfaces [5,19,20]. Importantly, these cells then migrate to the lymphoid tissues and thereby also deliver the virus to other susceptible cells located at these sites. In the lymphoid tissues, HIV interacts and infects other cells such as CD4+ T cells and is able to disseminate to other areas such as the brain and gut [5,21]. Subsequently, inflammatory cells

and cytokines accumulate during chronic infection and immune activation causing severe reactions and tissue pathology. This includes destruction of regulatory immune cells, mainly CD4+ T cells, and overall impairment of immune functions, which are the hallmarks of chronic HIV infection [5,22-24]. Studies have shown that M/M and T lymphocyte functions are impaired over the course of HIV infection, thus contributing to the overall immune dysfunction and appearance of the opportunistic infections observed in HIV-infected patients. Several *ex vivo* and *in vitro* studies have reported that many M/M defects arise during chronic HIV infection including poor phagocytic activity [25-27], altered cytokine and chemokine secretion [24,28-31], impaired antigen uptake and MHC class II molecule expression [32,33]. Other studies have shown defects in T lymphocyte effector functions including impairment of CD4 T lymphocytes to produce IL-2 and to proliferate in response to recall antigens (influenza, tetanus toxoid), alloantigens (mixed lymphocytes reaction), or exogenous mitogens (phytohemagglutinin) [34,35]. Also, CD8 T lymphocytes exhibit an altered differentiation and proliferative phenotype and impaired capacity to kill virus-infected cells and clear the virus [36]. However, the molecular mechanism by which HIV impairs these cellular functions remains unclear. One possible mechanism by which chronic HIV infection may adversely affect immune cell function is through the modulation of cell signaling molecules, as observed in several cell types including M/M, CD4+ and CD8+ T cells, and neuronal cells [37-42]. This may occur by the direct action of HIV and its different immunomodulatory proteins such as Gp120, Nef, Tat, and Vpr, or indirectly via its effects on the cytokine secretion profile induced during the course of the disease as discussed in more detail below [43-46].

4. Cytokines

As mentioned above, cytokines are small secreted proteins with molecular weights of about 10-40 kDa [18,47,48]. These proteins function as mediators to regulate both the innate and adaptive immune responses [4,6,7]. They transmit the biochemical message from the extracellular environment to the nucleus of the targeted cell via cytokine-cytokine receptor interaction and subsequent triggering of complex intracellular signal transduction [49,50]. They can affect cell function in a paracrine as well as an autocrine manner. There are many cytokines produced by the immune system. Certain cytokines are associated with the initial response to an infection or inflammation and are referred to as inflammatory cytokines. Other cytokines are induced according to the nature of the infectious agent and the type of immune responses produced against them. For instance, infection with *Influenza virus*, *Vaccinia virus*, or *Listeria monocytogenes* is known to induce a Th-1 immune response [51]. This type of immune response is associated with the production of cytokines such as IL-2, IFN-γ, and IL-12, which regulate cell-mediated immunity including delayed hypersensitivity reactions, activation of macrophages and leukocyte cytolytic processes, and result in the protection and elimination of intracellular pathogens [16,50,52]. On the other hand, infection with *Nippostrongylus barsiliensis* or *Leishmania major* is known to induce a Th-2 response [51]. This immune response is characterized by secretion of cytokines such as IL-4, IL-5, IL-9, IL-10, and IL-13 that predominantly regulate antibody-mediated immunity and generally lead to the protection and

clearance of extracellular antigens/pathogens [16,50,52]. During chronic HIV infection, both types of immune response and their associated cytokines are dysregulated, which may result in altered M/M and lymphocyte functions and increased susceptibility to programmed cell death (PCD) [53-56].

The following section will focus on cytokines that play an important role in regulating M/M as well as T lymphocytes effector functions and cell survival. These cytokines include IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-10, IL-4, IL-2, IL-7, and IL-15 (summarized in Table 1).

Cytokine	Producer cells	Effects on M/M, T cells	STAT signaling in viremic patient
IFN-γ	Th1 lymphocytes, activated NK cells, and CD8 T cells	Upregulates the activation of MHC class I and II, and activates pathogen killing.	Increased STAT1 activation
IFN-α	Leukocytes, and virus-infected cells	Upregulates the activation of MHC class I.	Decreased STAT1 activation
GM-CSF	T cells, Macrophages	Stimulates growth and differentiation of myelomonocytic lineage cells. Enhances phagocytosis.	Not significantly affected
IL-10	T cells, Macrophages	Potent suppressor of monocytes/ macrophage function (e.g. inhibits MHC class II activation, antigen presentation, and phagocytosis).	Not significantly affected
IL-4	Th2 lymphocytes	Induces activation of MHC class II, induces endocytosis, and mannose receptor activation.	Not significantly affected
IL-2	Activated T lymphocytes and dendritic cells	Promotes T cell proliferation and T reg development	Decreased STAT5 activation
IL-7	Bone marrow and stromal cells in lymphoid organs	Maintains thymocytes survival.	Decreased STAT5 activation
IL-15	M/M, dendritic cells, mast cells, epithelial cells, and fibroblast	Induces survival and proliferation of CD8 T cells, NK cells and NK T cells.	Not significantly affected

Table 1. Cytokines and their effects on monocyte/macrophage and T lymphocyte functions

4.1. Cytokines that affect monocytes

Cytokines such as IFN-γ and GM-CSF affect mainly M/M, while, IL-10 and IL-4 act on both M/M and lymphocytes. IFN-γ is an 18-kDa potent pleiotropic cytokine produced by NK cells, NK T cells, Th-1, and CD8+ T cells. It has a critical role in the regulation of both innate and adaptive immunity [57,58]. It inhibits Th-2 and promotes Th-1 cell polarization and differen-

tiation. Also, it inhibits viral replication and regulates cell death [57,58]. Moreover, it activates monocytes and macrophages, increases MHC class II expression, promotes antigen processing and presentation, and enhances their phagocytic, antimicrobial, and tumoricidal activities [59-64]. For instance, it has been shown that treatment of M/M with IFN-γ enhanced phagocytic activity against many pathogens including *Aspergillus fumigatus, Cryptococcus neoformans, Listeria monocytogenes, Mycobacterium avium, Toxoplama cruzi and gondii* [26,61,65]. Other studies have revealed that the lack of IFN-γ responses, such as in IFN- γ, IFN-γ receptor (IFN-γR), or STAT1-deficient mice, or in patients with mutations in the IFN-γ-R gene, lead to impaired immunity and increased susceptibility to infection [66-70]. GM-CSF is a 22-kDa protein secreted by macrophages and T cells. It facilitates growth and differentiation of monocyte and granulocyte lineages. It also enhances M/M effector functions including phagocytic, antimicrobial and antiparasitic activities [71,72].

IL-10 is a potent immunosuppressive and anti-inflammatory cytokine produced by macrophages and T cells. It downregulates MHC class II molecule expression and antigen presentation to CD4+ T cells [73,74]. It also inhibits the expression of co-stimulatory molecules, B7.1/B7.2, on monocytes and macrophages as well as the production of various cytokines such as TNF-α, IL-1, IL-2, IFN-γ, IL-3, and GM-CSF [73,75,76]. In addition, it suppresses macrophage nitric oxide production, and anti-fungal activity [77]. Moreover, it stimulates proliferation and differentiation of B cells, and polarizes T cells towards a Th-2 type response [17,78].

IL-4 is a 20-kDa cytokine secreted by Th-2 lymphocytes that promotes a Th-2 immune response. It has dual immunoregulatory functions [18]. It activates B cell differentiation and antibody production. Also, it enhances macrophage cytotoxicity and their expression of MHC class II and mannose receptor [79-84]. On the other hand, it inhibits cytokine secretion such as TNF-α, IL-1, IL-6, IL-18, GM-CSF and granulocyte colony-stimulating factor (G-CSF) [85-94]. It also suppresses cytokine-induced macrophage activation, oxidative burst, and intracellular killing [62,95]. Moreover, it downregulates monocyte adhesion and CD14 expression [96,97], monocyte-mediated cytotoxicity, nitric oxide production, and anti-fungal activity [77,98].

4.2. Cytokines that affect lymphocytes

Cytokines that share the γ-chain receptor, such as IL-2, IL-7, and IL-15, play a critical role in lymphocyte growth and differentiation [36,99]. IL-2 is a protein produced mainly by activated CD4 but also CD8 T lymphocytes and dendritic cells. It is a T cell growth factor and plays a critical role in regulating the immune response. It plays a major role in activating the immune system in the presence of antigenic stimulation, but also in downregulating this response following pathogen clearance. IL-2 stimulates T cell proliferation and is essential for developing regulatory T cells. In addition, IL-2 has been shown to upregulate expression of Tumor Necrosis Family death receptor ligand, FasL, in activated T cells thereby enhancing their susceptibility to activation-induced cell death [100,101].

IL-7 is a pleiotropic cytokine secreted by bone marrow and stromal cells of lymphoid organs. It stimulates the growth and maintains the survival of thymocytes (B and T lymphocyte progenitor cells) by increasing the expression of the anti-apoptotic molecule Bcl-2 and down-

regulating the expression of the pro-apoptotic molecule Bax [102-105]. Thus, it is an essential element for T cell survival, proliferation, and optimal effector function.

IL-15 is a cytokine that is produced by different cell types including M/M, dendritic cells, mast cells, epithelial cells, and fibroblasts. It plays an important role in growth and homeostasis. It provokes adaptive and innate immune responses. For example, it shares several biological effects with IL-2 such as mediating survival and proliferation of naïve and memory CD8 T cells. It also stimulates NK T cell expansion and regulates the development of NK cells and its cytotoxicity [36,99,106].

It has been reported that during the course of chronic HIV infection, many inflammatory and anti-inflammatory cytokines such as TNF-α, IFN-β, IFN-γ, IL-18, IL-2, IL-10, and IL-4 are increased in patients serum [77,107-115], and thus may play a role in the alteration of M/M and T lymphocyte functions and signaling pathways (Table 1) [38-42]. Several studies have also proposed and used cytokines such as IFN-γ, GM-CSF, IL-4, IL-2, IL-7 and IL-15 as therapeutics in clinical trials for diseases including HIV and myeloma in an attempt to compensate for impairments in the cytokine network [36,99,116-118].

4.3. Cytokine signaling pathways

Cytokine signaling pathways can be defined as biochemical signaling cascades that are triggered within minutes to relay the information required to mediate various cytokine-dependent cellular functions [119-123]. Most cytokines share general mechanisms of signal transduction in which cytokine-cytokine receptor binding causes the assembly of the specific receptor subunits. Subsequently, a number of tyrosine kinases from the Src and Syk families are activated leading to signal transduction through mainly three major signaling pathways: (i) Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT), (ii) Phosphoinositide 3-kinase (PI3K), and (iii) Mitogen-activated protein kinase (MAPK) [124-126]. These signaling pathways form a very complex and evolutionarily conserved network.

A general overview of these cascades is illustrated in Figure 1. Briefly, when the ligand-receptor interaction occurs, subsequent events are activated based on the nature of these ligands and receptors. For example, a receptor with intrinsic kinase activity (e.g. epidermal growth factor receptor) is usually autophosphorylated directly leading to the creation of a docking site for an adapter protein complex called Grb2/SOS (son of sevenless) [36]. As a result, SOS is recruited to the plasma membrane where it encounters and activates a small G protein named Ras [36,127,128]. Activated Ras induces the activation of several downstream signaling molecules, including a serine/threonine kinase called Raf, which in turn activates the MAPK and PI3K signaling pathways [36,127,129]. PI3K signaling molecules can also be activated directly via the p110α catalytic subunit of the PI3K [127]. A receptor with no intrinsic kinase activity (e.g. cytokine receptors) generally requires activation of receptor-associated kinases such as JAKs for its phosphorylation. Subsequently, activated JAKs can activate the STAT signaling pathway directly and also interact with and activate Grb2/SOS, which in turn activates PI3K and MAPK signaling [36,122,130,131].

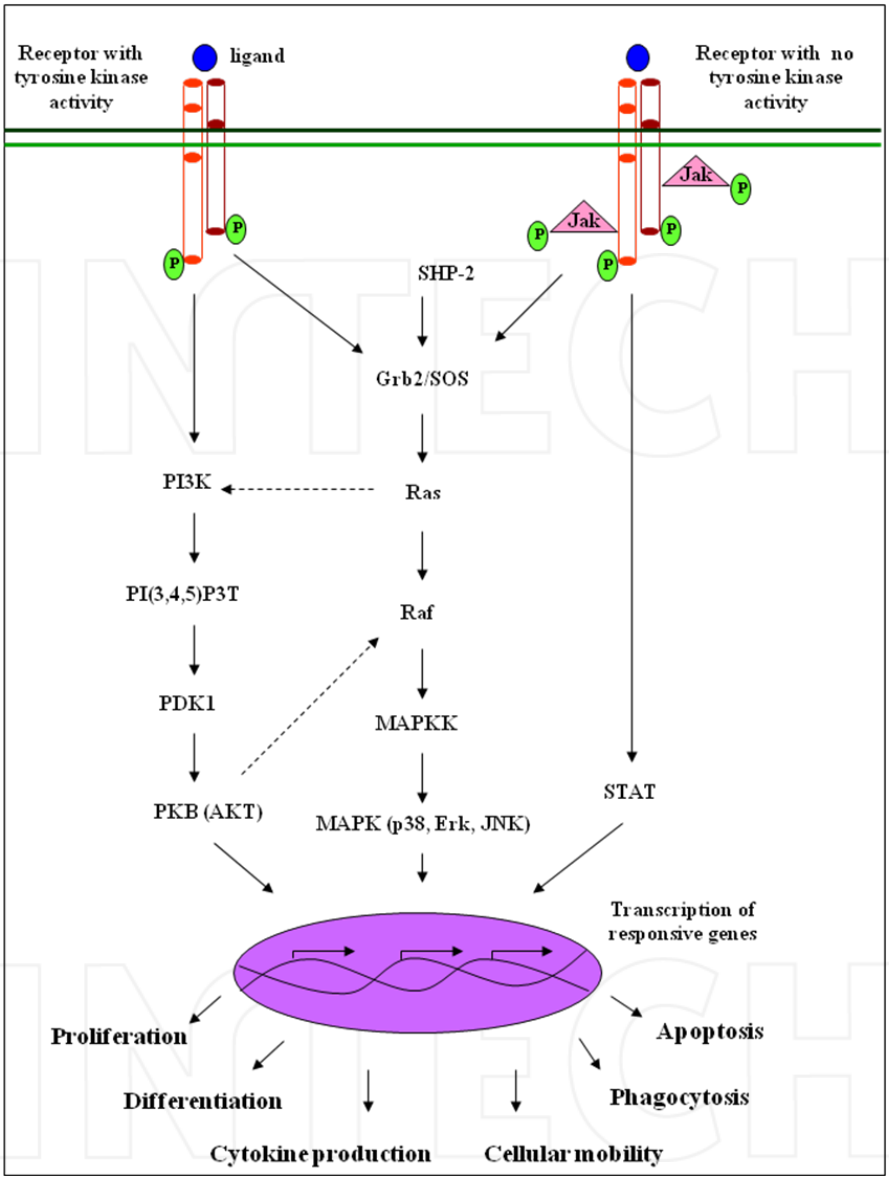

Figure 1. Overview of the major intracellular signaling pathways Upon ligand-receptor binding, signal transduction triggers takes place based on the type and nature of the receptor. If the receptor has intrinsic tyrosine kinase activity, autophosphorylation of the tyrosine residues of the receptor will occur and thus creates docking sites for a variety of different signaling molecules that have SH2 and PTB domains. Grb2/SOS complexes bind to docking sites and lead to recruitment of SOS (son of sevenless) to the plasma membrane where they interact with Ras. Subsequently, activated Ras molecules activate several downstream molecules including Raf, MAPKK, and MAPK. The PI3K signaling pathway can be activated directly via the p110α catalytic subunit of the PI3K. Phosphorylated receptors also

activate phospholipase Cγ (PLCγ), which activate Protein Kinase C (PKC) and calcium-dependent signaling pathways. If the receptor has no intrinsic kinase activity, activation of the Janus Kinase (Jak) or other receptor-associated kinase occurs. Subsequently, activated Jaks phosphorylate the receptor and thus create docking sites for various signaling molecules including members of the Signal Transducers and Activators of Transcription (STAT) family. Signal transduction culminates in the transcriptional activation of STAT responsive genes that influence cellular proliferation, differentiation, cytokine production, mobility, phagocytosis, and survival [modified from [187]].

Evidence has also demonstrated the presence of a complex crosstalk between these pathways. For instance, it has been shown that Jak2 is responsible for the activation of STAT, Erk MAPK, and Akt signaling pathways in response to growth hormone in hepatoma and preadipocyte cells [132]. Another report has demonstrated a role for Akt in serine phosphorylation of the STAT1 transcription factor and upregulation of gene expression in response to IFN-γ [133].

HIV-induced perturbation of the JAK/STAT, PI3K, and MAPK signaling pathways in immune cells including M/M and T lymphocytes has been documented (summarized in Table 1, 4) [41,134-146]. These effects appear to be to the advantage of the virus. On one hand, it may help the virus to replicate and establish infection. On the other hand, it may also help the virus to escape the immune system. In the following subsections, we will provide a brief overview of cytokine signaling and where HIV infection appears to target these cascades.

4.3.1. JAK/STAT signaling pathway

The JAK/STAT pathway is one of the major signaling pathways involved in cytokine responses. Studies have shown that many ligands such as epidermal growth factor (EGF), receptor tyrosine kinases (RTK), G protein-coupled receptors (GPCR) and several cytokine families including interferons and interleukins are the main triggers of the JAK/STAT signaling cascade [147-149]. An overview of the JAK/STAT signal transduction pathway is illustrated in Figure 1. Initially, cytokine-receptor interaction triggers tyrosine transphosphorylation of receptor-associated JAKs. This is followed by phosphorylation of receptor cytoplasmic domains by JAKs and recruitment of latent STAT proteins via their Src homology 2 (SH2) domains to the activated (tyrosine phosphorylated) receptor. This is followed by STAT tyrosine phosphorylation. Activated STATs form dimers via their SH2 domains and are translocated into the nucleus where they bind STAT responsive elements [119,120,123], and thus promote transcription of STAT responsive genes such as cytokine-inducible SH2-containing protein (CIS), members of the IRF family, and numerous other genes [150-153].

In mammalian cells, four JAKs (Jak1, Jak2, Jak3 and Tyk2) and seven STAT proteins (STAT1, 2, 3, 4, 5a, 5b, and 6) with their different isoforms have been identified. [147,154]. Through IL-6-induced signaling, Jak1 is the principal kinase in the downstream signaling cascade. It has been shown in many cell lines that down regulation of Jak1 would lead to impaired signal transduction. Activated JAKs lead to phosphorylation of STAT proteins. However, JAK kinases do not appear to show specificity for a particular STAT protein [147,154]. STAT proteins play an important role in regulating and maintaining both innate and adaptive immune responses (summarized in Table 2) [119-121,123]. For instance, studies have suggested that impairment of JAK/STAT signaling may increase susceptibility to many infections including HIV [65,67,70,155].

STAT gene	Activating cytokines	Examples of STAT responsive genes	Phenotype of knockout mice
STAT1	IFNs,IL-6,IL-10	IRF-1, ISG54, MIG, GBP, CIITA	Impaired IFN and innate immune responses, increase susceptibility to tumors, opportunistic and viral infections
STAT2	IFNs	IRF-1, ISG54	Impaired Type-1 IFN responses
STAT3	IL-2,IL-6,IL-10	JunB, SAA3, JAB, C-reactive protein, Bcl-xL	Embryonic lethal
STAT4	IL-12	IFN-γ, IRF-1, MHC class II, CD23, Fc-γRI	Defect in IL-4 and IL-12 responses, and impaired Th1 differentiation.
STAT5 a, b	Numerous (e.g. IL-2,IL-7,IL-15, GM-CSF)	CIS, IL-2R-α, β-casein, osm, pim1, p21	Impaired proliferation, growth and survival, defect in IL-2 responses, impaired growth.
STAT6	IL-4,IL-13	IL-4R-α, C-γ-1, C-γ-4	Defect in IL-4 responses, and impaired Th1 differentiation.

Table 2. STATs proteins and their role in the immune system

A number of reports have suggested that defects in cytokine responsiveness arise in different cell types during chronic HIV infection and these defects could be due to the direct effects of HIV and/or its proteins, or due to indirect effects associated with alterations of the host cytokine profile [38-42,139,141-143,156]. In M/M, it has been revealed that GM-CSF-induced STAT5 activation in monocyte-derived macrophages (MDM) is inhibited by *in vitro* HIV-1 infection [156]. Other *in vitro* reports have suggested that HIV and its Gp120 and Nef proteins are capable of activating STAT1 and STAT3 in monocytic cell lines and MDM [141-143]. Recently, the HIV matrix protein p17 has been shown to induce STAT1 and pro-inflammatory cytokines in macrophages [139]. Moreover, in *ex* vivo studies, we found that among the responses to cytokines tested (IFN-γ, IFN-α, IL-10, IL-4, and GM-CSF) in terms of STAT induction in monocytes, only IFN-γ showed a significant upregulation of STAT1 activation in HIV+ patients that were off antiretroviral therapy (ART) compared to HIV- controls and patients on ART [39]. Furthermore, this potentiation of IFN-γ-induced STAT1 activation was associated with increased total STAT1 expression levels and monocyte cell death [39]. Another *ex vivo* study has shown a defect in IFN-α induced STAT1 activation in monocytes obtained from a similar set of HIV patients, and this defect was due to the decreased IFN-α receptor expression levels on these cells [42].

In lymphocytes, we and others have shown that both IL-7Rα expression and IL-7-induced STAT5 activation was impaired in CD8 T cells from HIV+ patients [36,40,41]. STAT activation in response to IL-4 and IL-10 did not appear to be similarly impaired [40]. We also found that IL-2-induced STAT5 activation was inhibited in CD8+ T cells from a subset of HIV-infected patients naive to therapy, but was restored, at least in part, after ART [38]. Somewhat similar results have been observed in other *in vitro* studies in which activation of STAT5 in response to IL-2 was inhibited by HIV-1 infection through prior Gp120-CD4 interactions in CD4+ T cells [37,144].

4.3.2. PI3K signaling pathway

Phosphoinositide 3-kinases or phosphatidylinositol-3-kinases (PI3Ks) belong to a family of enzymes that have serine/threonine kinase activity. These enzymes can be activated by various stimuli including growth factors, antigens, cytokines [157,158], and are capable of phosphorylating the third position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns) [157,159]. This family is composed of four classes, which differ in their structure and functions (known as Ia, Ib, II, and III). However, all of them contain at least one catalytic domain and one regulatory domain [157,159]. Many PI3K cellular functions rely on the ability of PI3Ks to activate protein kinase B (PKB, also known as Akt) (Figure 1). In humans, three Akt genes have been identified named *akt1*, *akt2*, and *akt3*.

PI3-kinases have been shown to play a major role in diverse cellular functions, including cell growth, proliferation, differentiation, survival, and migration [160-163]. Thus, dysregulation of this pathway may influence different cellular responses that are associated with immunity as well as carcinogenesis (Table 3) [157,164]. It has also been reported that there is a basal activation of the PI3K/Akt pathways in macrophages that is required for their survival [165]. Certain reports have suggested a critical role for PI3K signaling in chronic immune activation by promoting cell survival [166]. For instance, an *in vitro* study has revealed that HIV infection and its protein Tat was sufficient to activate the PI3K/Akt pathway in macrophages [166]. Interestingly, PI3K/Akt inhibitors including Miltefosine, an antiprotozoal drug known to inhibit PI3K/Akt pathway, significantly reduced HIV-1 production from infected macrophages and increased susceptibility to cell death in response to extracellular stress, as compared to uninfected cells [166]. Another study has shown that inhibition of Akt phosphorylation is required for TNF related apoptosis inducing ligand (TRAIL)-induced cell death in HIV infected macrophages [167].

Target Gene	Phenotype
$p85^{\alpha}$	Decreased B cell development and activation, increased antiviral responses
$p85^{\beta}$	Increased insulin sensitivity
$p110^{\alpha}$	Embryonic lethal and defective proliferation
$P110^{\beta}$	Embryonic lethal
$P110^{\gamma}$	Decreased T cell development and activation, decreased inflammation, chemotaxis, and oxidative burst
PTEN	Embryonic lethal, autoimmune disease, decreased T cell development, increased T cell activation, and chemotaxis
SHIP1	Increased myeloid cell proliferation and survival, increased B cell activation, chemotaxis, and mast cell degranulation
SHIP2	Perinatal lethal

Table 3. Characteristics of PI3K knockout mice

Viral protein	Effects on M/M	Effects on lymphocytes
gp120	Stimulates STAT1 activation	Stimulates STAT1 activation
p17	Stimulates STAT1 activation	No report
Tat	Stimulates MAPK, Akt activation	Stimulates Akt, MAPK activation
Nef	Stimulates STAT1 & 3, MAPK activation	Stimulates Erk & p38 MAPK activation
Vpr	Stimulates MAPK activation	No report
HIV infection	Inhibits STAT5 activation, Stimulates STAT1, Akt activation	Inhibits STAT5 activation, Stimulates STAT1, MAPK activation

Table 4. HIV viral proteins and their effects on monocytes/macrophages and lymphocytes

4.3.3. MAPK signaling pathway

Mitogen-activated protein kinases (MAPKs) are also a family of enzymes that have serine/threonine kinase activity [168]. This family of kinases is generally activated in response to various extracellular stimuli such as growth factors and inflammatory signals, as well as cellular stress. They regulate different cellular processes including mitosis, proliferation, differentiation, and cell death [168]. The MAPK family is composed of three major subfamilies of kinases known as the extracellular receptor kinases (ERKs), the c-Jun N-terminal kinases/stress-activated protein kinases (JNK/SAPK) and the p38 MAP kinases [169]. Activation of a specific MAP kinase requires activation of a small GTP binding protein (e.g. Ras) which results in the phosphorylation of a series of downstream kinases (Figure 1) [128]. Activation of the MAPK kinase kinase (MAPKKK) (e.g. Raf) leads to the activation of downstream MAPK kinase (MAPKK), and finally, specific MAPK (p38, Erk or JNK) [170,171]. The Erk MAPK family is found in two isoforms called Erk1 and Erk2. Both isoforms are phosphorylated by members of the MEK family, which are often activated by extracellular stimuli such as growth factors, LPS and chemotherapeutic agents [129,172,173]. The JNK family is found in three isoforms named JNK1, JNK2, and JNK3 [174], while the P38 family is found in five different isoforms called p38 (SAPK2), p38β, p38β2, p38γ (SAPK3), and p38δ [175,176]. Both JNK and p38 MAPKs are phosphorylated by SAPK/Erk kinases (SEKs) and mitogen-activated protein kinase kinases (MKKs), which are usually induced by inflammatory cytokines as well as other stressors such as endotoxins, reactive oxygen species, protein synthesis inhibitors, and ultraviolet (UV) irradiation [174,177-179]. MAPKs have been shown to activate various downstream transcription factors such as activator transcription factor (ATF)-2, SP-1 (a member of Specificity Protein/Krüppel-like Factor family) and activator protein (AP)-1, and even STAT3 [178,180-182].

Several reports have shown that activation of the MAPKs resulted in phosphorylation of HIV Rev, Tat, Nef, and p17 proteins and enhanced viral replication [140,183]. Other studies have demonstrated a role for MAPK in regulating monocyte and lymphocyte functions and cell death during HIV infection. For example, in monocytes, it has been shown that the HIV Tat protein stimulates IL-10 production via activation of calcium/MAPK signaling pathways in human monocytes [134,135,184]. Another report has suggested that HIV Vpr is capable of inducing programmed cell death in primary monocytes and the monocytic cell line THP-1 cells [185]. Further, it has been shown that HIV and its protein nef induced FasL, Programmed Death-1 expression and apoptosis in peripheral blood mononuclear cells (PBMCs) and the Jurkat T cell line through activation of the p38 MAPK signaling pathway [138,186].

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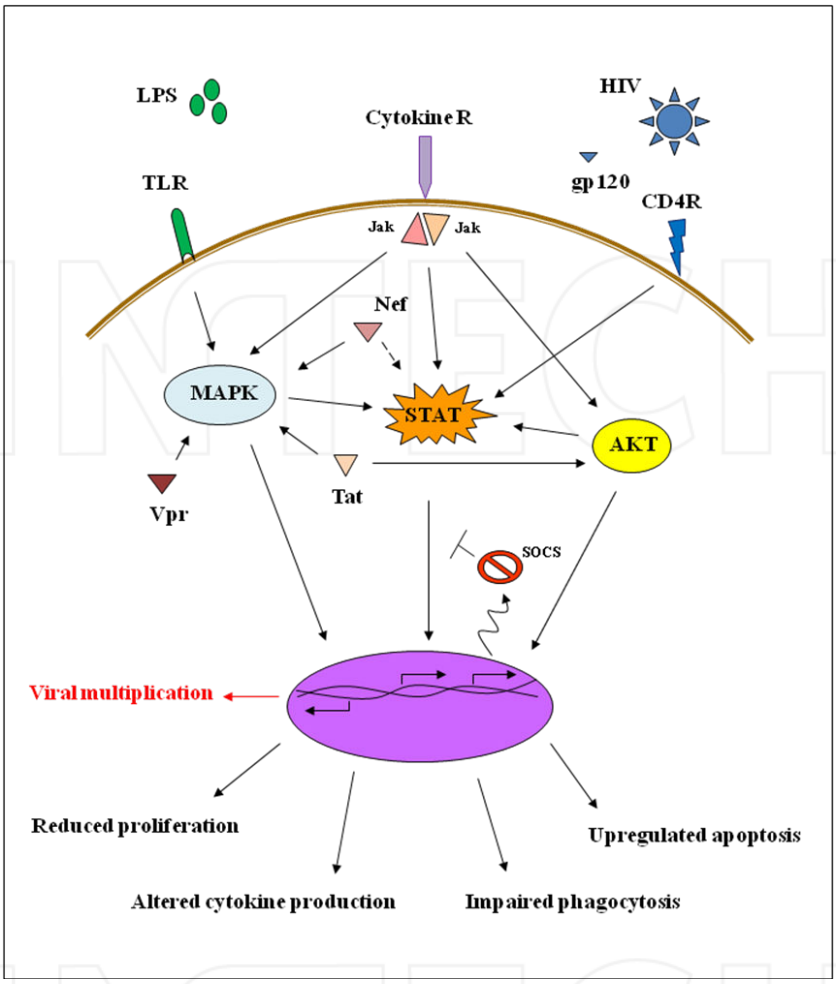

Figure 2. A model for the effect of chronic HIV infection on cellular signal transduction Cell signaling molecules may be regulated directly or indirectly during chronic HIV infection. In the direct setting, HIV and its proteins (Gp120, Nef, Tat, Vpr), through the binding of cellular receptors or internalization by endocytosis, alter signaling pathways including JAK/STAT, PI3K, and MAPK. In the indirect scenario, HIV infection may adversely affects the host cytokine network, which may in turn affect signal transduction. Both scenarios may thus promote viral replication and defective host immune effector functions and reduce immune cell survival [modified from [187].

5. Conclusion

It is well established that HIV targets the immune system and mainly immune cells that express the CD4 surface receptor, but the virus is not exclusive to these cells. Thus, through the course

of chronic HIV infection the immune system becomes progressively impaired and unable to protect the body from opportunistic pathogens. This impairment not only includes CD4 T cell depletion, but also the dysregulation of immune cell effector functions, and a skewed cytokine/chemokine expression profile. These effects may be due to the disruption of the described signaling pathways as a result of direct HIV infection, through the action of numerous viral proteins and/or the chronic, but defective state of host immune activation, as summarized in Figure 2. Understanding the molecular mechanisms and identifying the key molecules involved in this impairment may provide important insight towards developing new therapeutic strategies aimed at prolonging the life span of HIV infected individuals and clearing HIV from the host.

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