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HIV Toxins: Gp120 as an Independent Modulator of Cell Function

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1. Introduction

Current notions on the pathogenesis of the HIV-induced disease sustain that progressive immunodeficiency results from a combination of the cell cytotoxicity produced by infection and replication of the virus in the target cells, mainly immune system cells, and of the indirect, harmful effects mediated by two main mechanisms: a sustained, chronic activation of the immune system that turns into immune dysfunction with the progressive degradation of lymphoid tissues, and the immunoregulatory and toxic properties of extracellular viral proteins on bystander cells (Choudhary et al., 2007; Moir et al., 2011). Bystander, non infected cells that show altered function and death, include cells with null or low expression of the CD4 receptor, such as CD8^{+} T and B lymphocytes, dendritic cells, neurons and tumor cells.

The HIV-1 Gp120 protein has properties that maintain resemblance with animal toxins. Active forms of free Gp120 can be found at nanomolar concentrations in the plasma of a considerable proportion of HIV infected individuals (Rychert et al., 2010; Gilbert et al., 1991; Santosuosso et al., 2009). A number of in vitro and in vivo activities have been described for the extracellular form of this molecule, indicating that it may contribute to deregulation of immune function and damage to several tissues during HIV infection. Activation, apoptosis, chemotaxis and impaired cellular function are the most frequently reported effects of Gp120 in the absence of HIV infection. Gp120 interacts with chemokine receptors (mainly CXCR4 and CCR5) which are expressed by different cells and tissues, besides the immune system, thus providing a range of possible target cells for toxic effects. However, the high structural variability of Gp120, absorption by host's glycan-binding compounds, and the complexity of the regulation processes involved in chemokine receptor function, have made difficult to asses the actual significance of the free form of this molecule for AIDS pathogenesis. On the other hand, soluble Gp120 or peptides derived of active portions of the molecule may be considered as potential therapeutic agents to target undesirable cells, i.e., tumor cells.

This article provides a review of the main factors influencing the biological outcome of the interaction of the soluble form of Gp120 with cells and tissues, and a selection of recent literature illustrating the diversity of the effects induced by this molecule.

2. Structure-function and evolutionary considerations

The HIV Env protein is synthesized in the form of the gp160 precursor, which processing and folding occur through what is known as the secretory pathway: the Env precursor

protein (gp160) is co-translationally translocated into the endoplasmic reticulum (ER), where 10 disulfide bonds are formed and the molecule starts to fold. Glycosylation of most of the approximately 30 potential N-linked glycosylation sites, with around 25 of them located in the Gp120 region (Zhang et al., 2004), also occurs co-translationally in the ER. Disulfide bond formation and glycosylation, along with interaction with the lectin chaperones calnexin and calreticulin, allows the proper final folding of the gp160 precursor (Earl et al., 1991; Otteken et al., 1996). Then, the molecule forms trimers and is transported to the Golgi complex, where the cleavage into the surface (Gp120) and transmembrane (Gp41) subunits is carried out. Cleavage of the precursor by host proteases generates the N-terminal hydrophobic fusion peptide of Gp41. Gp120 and Gp41 are kept joined by non-covalent interactions on the surface of infected cells and virions.

Binding to cell membranes and disruption of the lipid bilayer integrity are the basic functional properties of the HIV Env complex. Env mediates the fusion of biological membranes that allows the entry of the virus nucleocapsid into target cells, as well as the fusion of infected with non-infected cells. Env-mediated membrane fusion is involved in virus entry, cell-to-cell transmission of virus particles, and syncytia formation. Membrane fusion is a multi-step process which is conducted by Gp120/Gp41 heterotrimers and involves: a) binding of Gp120 to the CD4 receptor on the cell surface, an interaction that is favored by adhesion molecules (Cantin et al., 1997, Bastiani et al., 1997); b) conformational rearrangements allowing Gp120 to interact with a coreceptor molecule, mainly CCR5 and CXCR4; c) projection of a trimer formed by the extended chains of the Gp41 ectodomain; d) insertion of the Gp41 amino-terminal hydrophobic ends, the fusion peptides, into the target membrane and the subsequent packing of the Gp41 molecule into a 6-helix bundle, a structure which formation provides the free energy necessary for membrane fusion (Jones et al., 1998; Melikyan et al., 2000; Sattentau & Moore, 1991; Sullivan et al., 1998; Trkola et al., 1996; Wu et al., 1996; Wyatt & Sodroski, 1998).

Gp120 oligosaccharide moieties greatly influence Gp120 folding, processing, and intracellular transport (Stansell & Desrosiers, 2010), and the ability of the virus to escape from host neutralizing antibodies. N-linked glycosylation sites are main targets of neutralizing antibodies, which exert selective pressure on the viral surface. Thus, it has been postulated that the evolving glycan shield is a mechanism to avoid elimination of the infection by the humoral immune response (Wei et al., 2003; Canducci et al, 2009). Instead, it has been frequently observed that the enzymatic removal of Gp120 oligosaccharides does not greatly affect the interaction of Gp120 with CD4 (Bahraoui et al., 1992; Fenouillet et al., 1989). However, glycosylation is necessary for the acquisition of the proper folding of Gp120 in the ER required for interaction with CD4 (Li et al., 1993). On the other hand, glycans play an important role in the usage of CXCR4 and CCR5 (Polzer et al., 2002; Ogert et al., 2001; Bandres et al., 1998).

Env share a number of structural and biological characteristics with pore-forming protein toxins from widely separated phyla such as bacteria, plants, cnidaria and mammals (Iacovache, et al., 2008): they undergo extensive post-translational modifications, are specific for susceptible structures (acceptor sites), have an hetero-oligomer structure, they tend to aggregate, show variable toxic efficiency among different cell types, act through their pore-forming activity (in conjunction with Gp41), have neurotoxic effects, and present considerable and continuous genetic variation (Butzke & Luch, 2010; Suput, 2009; Kristan et al., 2009). Particularly, a striking similitude exists among the mechanism of pore formation

of the Env complex and that of the pore-forming toxins such as the actinoporins, the sea anemone toxins: 1) attachment of toxin to the cell surface through recognition of specific cellular membrane components; 2) transfer of the N-terminal segment to the lipid-water interface; 3) oligomerization of the toxin on the cell surface followed by the insertion of multiple α-helices monomeres into the membrane to form an ion conductive channel (Kristan et al., 2009; Edwards & Hessinger 2000; Butzke & Luch, 2010). As in the case of Env, the N-terminal portion of the toxin is essential for the final pore formation step (Kristan 2009). Finally, membrane-binding and pore-forming functions relay on different domains in both Env and animal pore-forming toxins.

Early works reported sequence homology between a short portion of Gp120 and the putative actives sites of the snake neurotoxin alpha-bungarotoxin and the rabies virus glycoprotein (Neri et al., 1990; Bracci & Neri, 1995), which interact with the mammals' nicotinic acetylcholine receptor, a member of the ligand-gated ion channel proteins. Later, it was found that Gp120 can bind to the acetylcholine binding site of the nicotinic receptor and the binding can be inhibited by an albumin-conjugated peptide encompassing the 160-170 amino acids of Gp120 (Bracci et al., 1997), which belong to a relatively conserved region of the Gp120 V2 loop. Gp120 can act as competitive antagonist of the nicotinic acetycholine receptors. Although the overall structure of the snake neurotoxins consists of a low molecular weight protein with three beta-strands with finger-like loops (Pawlak et al., 2006; Ackermann et al., 1998), and thus it is quite different to that of Gp120 and the rabies glycoprotein (both belonging to the Class I fusion proteins), the homologous sequence was located in a loop structure in both viral proteins and the snake neurotoxin, suggesting an evolutionary convergence towards the appropriate acetylcholine receptor binding structure.

3. The CXCR4 and CCR5 chemokine receptors

In principle, the biological effects of the interaction of Gp120 with CXCR4 and CCR5 may be conditioned by events similar to those regulating the coreceptor activity after interaction with their corresponding natural ligands. This section presents a general review of the characteristics of these receptors and the main extracellular events regulating their function. Comprehensive reviews of the regulatory pathways involved in CXCR4 and CCR5 signaling can be found elsewhere (Busillo & Benovic 2007; Kucia et al., 2005; Oppermann, 2004; Wu & Yoder, 2009).

CXCR4 and CCR5 belong to the super family of the seven-transmembrane G-protein coupled receptors (GPCRs). CXCR4 has SDF-1 as its sole natural ligand, whereas CCR5 can interact with several chemokines, mainly CCL5, CCL3, CCL4, CCL8 and CCL14 (RANTES, MIP-1alpha, MIP-1beta, MCP-2, and CC-1, respectively). Ligand binding triggers phosphorylation at various sites of the intracellular domains, which act as signals for migration, activation and transcription. Like for others GPCRs, ligand binding induces receptor desensitization and internalization to avoid prolonged activation, followed by degradation or recycling (Marchese et al., 2008). In addition, chemokine receptors can also be subjected to "heterologous desensitization", i.e., inhibition of receptor function by signaling processes triggered by ligand binding to an unrelated GPCR. Thus, cross heterologous desensitization of T cell functions can be induced by CCR5 and CXCR4 ligands, resulting in mutual interference with cellular signaling, adhesion and chemotaxis (Hecht et al., 2003). In another example, it has been shown that activation of toll-like receptor 2 (TLR2) negatively regulates CCR5 on human blood monocytes, inhibiting

monocyte migration after pathogen recognition (Fox et al., 2011). On the other hand, it is clear that that signaling through CD4 by the CD4 ligand interleukin-16 (IL-16) desensitizes the chemokine receptors CCR5, CXCR4, and CXCR3 (Rahangdale et al., 2006; Van Drenth et al., 2000).

CXCR4 is expressed by many tissues and cell types, such as T leukocytes, progenitor cells in the bone morrow, endothelial (Murdoch et al., 1999) and epithelial cells (lung, retina, intestine), and tumor cells. In the brain, CXCR4 has been found in the endothelial cells forming the blood-brain barrier, microglia, neurons, and astrocytes (Berger et al., 1999; Edinger et al., 1997). CXCR4 is important for lymphocyte trafficking and recruitment of lymphocytes and monocytes at sites of inflammation, and plays a role in cell proliferation, organogenesis and vascularization. On the other hand, CCR5 is expressed on resting T-cells with a memory/effector phenotype, monocytes, macrophages and immature dendritic cells (Blanpain et al., 2002). Differentiation of monocytes to macrophages is accompanied by an increase of the CCR5 expression (Kaufmann et al., 2001). Increased CCR5 expression has been found to be induced by interferon-alpha (IFN-alpha) in thymus implants infected by the R5 HIV (Stoddart et al., 2010). Expression of CCR5 in T CD4$^+$ cells is particularly high in mucosa-associated lymphoid tissues (MALT), where the fraction of CCR5$^+$ CD4+ T cells is >50%. It is known that signaling through CCR5 is significantly involved in the induction of an immunological hyporesponsive state that leads to oral tolerance to high doses of antigen (DePaolo et al., 2004) and prevents uncontrolled postinfarction inflammation of myocardium in mice (Dobaczewski et al., 2010). Anti-inflammatory properties of CCR5$^+$ mononuclear cells have been related to the expression of high levels of IL-10 and their ability to recruit CD4$^+$/foxp3$^+$ regulatory T cells (Tregs) (Dobaczewski et al., 2010).

The expression of CXCR4 on the cell surface is increased by several cytokines (IL-4, IL-2, IL-7, IL-10, IL-5, TGF-1), as well as by fibroblast and vascular growth factors, whereas it is reduced by others, mainly those pro-inflammatory cytokines (TNF-alpha, INF-gamma, and IL-1-beta). However this pattern is not absolute and it is thought that mixed signals regulate de expression of CXCR4 signaling in different circumstances (reviewed in Busillo & Benovic 2007). On the other hand, sensitization of CXCR4 (priming to low concentrations of SDF) through its translocation to lipid rafts during inflammatory responses has also been described (Wysoczynski et al., 2005).

Membrane events participating in the regulation of CXCR4 and CCR5 function include dimerization as well as extensive downregulation by endocytosis and/or macropinocytosis. In addition, proteases released by neutrophils cleavage the N-terminus extracellular portion of CXCR4, avoiding ligand interaction (Hezareh et al., 2004; Lévesque et al., 2003).

In the last decade, the CXCR4-SF-1 axis has been increasingly involved in the generation, progression and metastasis of a variety of tumors, so that the expression of CXCR4 is currently considered an important biomarker for identification of the metastatic potential of primary tumors and a potential therapeutic target (Nimmagadda et al., 2010; Muller et al., 2001). CXCR4 was found to be one of the few genes which elevated over expression and function was associated to high osteolytic bone metastatic activity of human breast cancer cells in immunodeficient mice (Kang et al., 2003). In addition, CXCR4 is expressed on normal tissue-committed stem cells, which are currently considered a potential source of transformed cells. There are evidences that the CXCR4-SDF-1 axis can mediate locomotion, chemotaxis, adhesion, and even proliferation and survival of these cells, as well as the secretion of matrix proteases by different cell types (Fernandis et al., 2004; Janowska-

Wieczorek et al., 2000; Spiegel et al., 2004). Studies using RNA interference (RNAi) to reduce the expression of CXCR4 in animal models, have found that this treatment readily reduce growth and inhibits metastasis in a number of tumors, like breast and prostate cancer (Liang et al., 2005; Wang et al., 2011), melanoma (Kim et al., 2010), and neuroblastoma (Wang et al., 2006).

4. In vitro and in vivo effects of extracellular Gp120 on cell function

Although Gp120 interaction with CD4 can induce signaling events in many cell types, a number of effects that were originally attributed to the Gp120-CD4 interaction have been recently found to be explained by binding and signaling events mediated mainly by CXCR4 and CCR5. It should be noted, however, that although signaling intermediates recruited by Gp120 and the natural chemokine receptor ligands are usually the same, the ability of Gp120 to activate those signal transduction pathways may depend on the cell activation status. In general, activated cells are more sensitive to the activity of Gp120 than resting cells (Kinet et al., 2002; Weissman et al., 1997; Schols & De Clercq, 1996).

Gp120 signaling through CXCR4 triggers intracellular events facilitating infection by the HIV. Recently, it was found that Gp120 increases the dynamics of actin by activating cofilin, an actin-depolymerizing factor, which promotes the movement of the viral preintegration complex toward the centre of the cytoplasm. CXCR4-mediated actin rearrangement markedly facilitates viral infection of resting T cells (Yoder et al., 2008). Similarly, CXCR4 signaling after interaction with Gp120 is involved in a variety of other activation events in T cells and macrophages (Table 1). Likewise, it is well known that Gp120 exerts chemotactic effects on T, dendritic cells (DC), and monocyte/macrophages (Table 1). Conversely, it has been also reported that Gp120 can inhibit migration of T (Trushin et al., 2010) and B cells (Badr et al., 2005). It has been suggested that reprogramming of the CD4$^+$ T-cell migration behavior induced by Gp120 may provides a mechanism for lymphadenopathy during HIV infection (Green et al., 2009).

A study using oligonucleotide microarrays showed that tropism of Gp120 for the CCR5 and CXCR4 receptors, along with the cell activation status, are related to the Gp120 biological activity. R5 and X4 HIV envelopes (CCR5 and CXCR4-tropic Gp120, respectively) were found to induce distinct gene expression profiles in primary peripheral blood mononuclear cells (Cicala et al., 2006a). In this study, both R5 and X4 Gp120 activated genes associated with cell proliferation and protein tyrosine kinases, although R5 envelopes were more pronounced in their capacity to activate the p38 mitogen-activated protein kinase (p38 MAPK) cascade. In addition, R5 Gp120 exclusively activated a subset of genes in the resting CD4$^+$ T cell population derived from viremic individuals. p38 is activated in macrophages, neutrophils, and T cells by numerous extracellular mediators of inflammation, including chemoattractants, cytokines, chemokines, and bacterial lipopolysaccharide. Functional responses involving p38 include respiratory burst activity, chemotaxis, granular exocytosis, adherence and apoptosis (Ono & Han, 2000). Activation of p38 kinase has also been associated with HIV replication (Muthumani et al., 2004) and thus, it is proposed that R5 envelopes induce genes that may facilitate replication of virus in resting CD4$^+$ T cells, contributing to the establishment and/or maintenance of viral reservoirs, and the productive infection at mucosal surfaces, favoring transmission (Cicala et al., 2006a). Other studies also shown that R5 and X4 Gp120 can activate NFATs and induce their translocation into the nucleus. Translocation of NFATs is an important signal for HIV transcription, given

that the HIV long terminal repeat (LTR) contains NFATs binding sites which are able to enhance transcription of viral genes (Cron et al., 2000; Cicala et al., 2006b; Kinoshita et al., 1998; Williams & Greene, 2007).

Cell	Mayor finding	Mechanism or concurrent events	Receptor involved	Reference
CD4+ T cell lines	Signal transduction	Protein tyrosine kinase Pyk2 phosphorylation-dependent cell growth, survival and differentiation.	CXCR4 CCR5	Davis et al., 1997
T cell lines	Gp120-CXCR4 co-internalization, cell signaling, and chemotaxis	Translocation of Gp120 and CXCR4 into early endosomes. CD4-independent phosphorylation of Pyk2.	CXCR4	Misse et al., 1999
CD4+ T cell line	Anergy	Inhibition of T cell activation and signaling through the TCR by Gp120/anti- Gp120 complexes, probably by sequestering p56 (lck) to the cytoskeleton.	CD4	Goldman et al., 1997
CHO cell line	Ca2+ mobilization	Coreceptor and CD4-dependent Ca2+ fluxing.	CXCR4 CCR5	Melar et al., 2007
CD4+ T cells, kidney epithelial cell lines and blood CD4+ lymphocytes	Apoptosis and viral replication	Caspase 8 dependent NF-kappaB activation and enhanced HIV replication.	N.D.*	Bren et al., 2009
Intestinal cell line	Functional alterations resembling HIV enteropathy	Activation of GPR15/Bob, presumably in a GalCer-rich membrane subdomain involving PKC activation. Microtubule disruption, perturbation of the transepithelial electrical resistance and decrease of glucose absorption.	GPR15/ Bob GalCer CXCR4	Maresca et al., 2003
Human hepatocyte cell lines and primary hepatocytes	Apoptosis	Gia protein signaling, and independent of caspase cascade activation.	CXCR4	Vlahakis et al., 2003
Blood CD4+ T lymphocytes	Apoptosis	Activation of caspases 3 and 6	CD4	Cicala et al., 2000
Blood CD4+ T lymphocytes	Apoptosis	Activation of the proapoptotic p38 protein	CXCR4	Trushin et al., 2007
Blood CD4+ T lymphocytes	Anergy	Diminished production of IL-2 and IL-4 and reduction of the proliferative responses of stimulated cells Production of high amounts of IL-10, INFγ and TNF-α of unstimulated cells.	CD4	Schols et al., 1996
Blood CD4+ T lymphocytes	Anergy	Dysregulation of the IL-2/IL-2R signal transduction pathway	CD4	Kryworuchko et al., 2003

Cell	Mayor finding	Mechanism or concurrent events	Receptor involved	Reference
Umbilical cord blood CD4+ T lymphocytes	HIV-1 replication in non-dividing cells	Activation of PKCε and its upstream effector PI3K/Akt, involved in HIV-1 replication. Enhancing of expression of the cellular Tat cofactors Tat-Sf1 and SPT5.	CXCR4	Missè et al., 2005
Blood CD4+T lymphocytes	Chemotaxis	Chemotaxis	CCR5	Weissman et al., 1997
Blood CD4+ T lymphocytes	Chemotaxis	CD4-independent signaling through CXCR4 in CD4+ and CD8+ T cells.	CXCR4	Iyengar et al., 1999
Blood CD4+ T lymphocytes	Chemotaxis of unstimulated CD4+ T cells.	Activation of major G protein-dependent pathways: calcium mobilization, phosphoinositide-3 kinase, and Erk-1/2 MAPK activation.	CXCR4	Balabanian et al., 2004
Blood CD4+ T lymphocytes	Inhibition of SDF-1α-induced chemotaxis	Actin cytoskeleton rearrangements Lck-dependent phosphorylation and inactivation of cofilin, a cellular depolymerizing factor.	CD4	Trushin et al., 2010
Blood CD4+ T lymphocytes	NFAT nuclear translocation in resting cells	Facilitation of viral replication in resting cells.	CD4 CCR5 CXCR4	Cicala et al., 2006
Blood CD4+ T lymphocytes	Activation of LFA-1	Binding of gp120 to α4β, an integrin mediating migration of lymphocytes to gut-associated lymphoid tissue, activates LFA-1, favoring formation of virological synapses.	Integrin α4β7	Arthos et al., 2008
Blood resting CD4+ T lymphocytes	Induction of actin dynamics in resting CD4+ T cells	Activation of the cellular actin depolymerizing factor cofilin, which promotes the movement of the viral preintegration complex to the nucleous.	CXCR4	Yoder et al., 2008
Blood CD4+ and CD8+ T lymphocytes	Apoptosis	Reduction of the expression of the proto-oncogene Bcl-2 with induction of apoptosis in CD4+ but not in CD8+ T cells.	CD4	Hashimoto et al., 1997
Blood CD8+ T lymphocytes	Apoptosis dependent of macrophage activation	Activation of macrophages for enhanced expression of TNF and TNFRII. Apoptosis was mediated by the interaction between macrophage TNF-α and the TNFRII on CD8+ T.	CXCR4	Herbein et al., 1998
Blood CD8+ T lymphocytes	Anergy	Synthesis of high amounts of IL-10 by unstimulated PBMC. Reduction of activation and proliferation of CD8+ T cells.	CD4	Schols et al., 1996
Blood CD4+ and CD8+ T lymphocytes	Chemotaxis	CD4-independent signaling.	CXCR4	Iyengar et al., 1999

Cell	Mayor finding	Mechanism or concurrent events	Receptor involved	Reference
PBMCs and monocyte-derived macrophages (MDMs)	Transcriptional program conducive to productive HIV infection.	Modulation of ~300 genes. Induction of the expression of cytokines, chemokines, kinases, and transcription factors associated with antigen-specific T cell activation but not cell proliferation.	N.D.	Cicala et al., 2002
Blood monocytes	Anergy	Induction of IL-10 production	CD4	Schols et al., 1996
Blood monocytes and MDMs	Production of β chemokines	Enhancement of MCP-1, MIP-1β, and RANTES secretion by primary monocytes/ macrophages but not by THP-1 and U937 cells.	CCR5 CXCR4	Fantuzzi et al., 2001
Blood monocytes and MDMs	Aberrant activation	Pertussis toxin-insensitive signal transduction, activation of Ca2+ channels and Pyk2 and MAPK pathways Secretion of the MIP-1β and MCP-1 chemoattractants.	CCR5 CXCR4	Del Corno et al., 2001
MDMs	Production of pro-inflammatory cytokines	Release of pro-inflammatory cytokines. Activation of multiple protein kinases like the Src family kinase Lyn, PI3K and Pyk2.	CCR5	Cheung et al., 2008
Immature DCs derived from monocytes	Migration	Migration of dendritic cells mediated by a novel pathway involving phosphorylation of Pyk2 and activation of the p38 MAP kinase.	CCR5	Anand et al., 2009
Tonsil primary naïve and memory B cells	Apoptosis and inhibition of B cell chemotaxis.	Gp120-induced cleavage of CD62L by a mechanism dependent on matrix metalloproteinase 1 and 3, CD4, CXCR4, G!i, and p38 MAPK. Increase of CD95-mediated apoptosis.	CXCR4 CCR5	Badr et al., 2005
Rat hippocampal neurons	Apoptosis and necrosis	Activation of NMDA receptors with increase of neuronal calcium concentration. Impairment of neuronal calcium homeostasis was prevented by TGF-β1.	NMDA receptors	Meucci et al., 1996
Rat hippocampal neurons	Increase of intracellular calcium concentration.	Dramatic and persistent release of calcium from intracellular stores.	N.D.	Medina et al., 1999
Human neuroblastoma cells	Neurotoxicity Necrosis	Increment of intracellular calcium induced increased cyclooxygenase and 5-lipoxygenase activity. Membrane lipoperoxidation and mitochondrial uncoupling.	CXCR4	Maccarrone et al., 2002
Rat hippocampal neurons	Neurotoxicity and apoptosis	Activation of JNK	N.D.	Bodner et al., 2002

Cell	Mayor finding	Mechanism or concurrent events	Receptor involved	Reference
Rat cerebellar granule cells	Neurotoxicity	Signaling through CXCR4.	CXCR4	Bachis et al., 2004
Rodent dorsal root ganglia and sensory neurons	Neurotoxicity, axonal degeneration and apoptosis	Activation of the mitochondrial caspase pathway.	CXCR4 CCR5	Melli et al., 2006
Rat microglia	Neurotoxicity	Enhancing of outward potassium currents via CXCR4 and cAMP-dependent PKA signaling.	CXCR4	Xu et al., 2011
Rat and human neurons Human monocytes	Neuronal death and monocyte activation	Gp120 and Tat induction of phosphorylation of MLK3 (MAP3K11).	N.D.	Ziye et al., 2006
Rat cerebellar cells	Apoptosis	Caspase-3-mediated apoptosis.	CXCR4	Bachis et al., 2006
Human astroglia	Glutamine metabolism dysfuntion and apoptosis	Imbalanced glutamine synthetase activity accompanied by generation of free radicals.	N.D.	Visalli et al., 2007
Human neuroblastoma cell line differentiated into neurons. Fetal rat neurons	Apoptosis	Pretreatment with platelet-derived growth factor BB reduced gp120-associated neurotoxicity and rescued neurite outgrowth.	N.D.	Peng et al., 2008
Rat brain endothelial cell line	Oxidative stress	Induction of decreased levels of intracellular GSH (reduced glutathione), GPx (glutathione peroxidase), and GR (glutathione reductase) and increased levels of MDA (malondialdehyde)	N.D.	Price et al., 2005
Rat lung metastasis of mammary adenocarcinoma cells.	Tumor retention and enhancing of metastasis	Infusion of Gp120 into the brain enhanced tumor metastasis. Blocked by antagonists of IL-1.	N.D.	Hodgson et al., 1998
Prostate cancer tumor in SCID mice	Apoptosis and inhibition of tumor growth	Tumor regression associated with significant decreases in CD44, CD34, and LYVE-1 and increases in caspase 3 and 9.	CXCR4	Singh et al., 2009
Rats pituitary cells	Supression of growth hormone (GH) release	Gp120 also supressed GHRH release by pituitary cells in vitro. Loss of body weight in chronically treated animals.	GHRH receptor	Mulroney et al., 1998
Rat neuronal progenitor cells from HIV/gp120-transgenic mice	Inhibition of proliferation	Arrests of cell cycle in G1 trough signaling by the p38 MAPK.	CXCR4 CCR5	Okamoto et al., 2007

Cell	Mayor finding	Mechanism or concurrent events	Receptor involved	Reference
Rat brain endothelial cells	Cytotoxicity	Reduction of the expression of ICAM-1- and laminin. Lipidperoxidation.	N.D.	Louboutin et al., 2010
PBMCs in SCID mice	Reprogramming of the CD4+ T-cell migratory behavior	Enhancing of sensitivity to CCL20 and CCL21 and inhibition of migration in response to sphingosine-1-phosphate. Increased accumulation of cells in lymph nodes with a reciprocal decrease in blood and spleen.	CD4	Green et al., 2009

* Not determined

Table 1. *In vitro* and *in vivo e*ffects of soluble gp120

In addition to activation for proliferation, Gp120 can exert a diversity of potent effects in immune system cells in vitro, being apoptosis the most frequently reported, although anergy, and induction of proinflammatory cytokine production are also well known effects. An early review of the influence of Gp120 on the immune system was carried out by Chirmule and Pahwa in 1996 (see reference). Table 1 shows recent studies about the effect of Gp120 on immune system cells, confirming early findings and adding new effects, particularly those related to the induction or inhibition of chemotaxis, and the role of Gp120/anti-Gp120 immune complexes on depletion of bystander lymphocytes. Table 1 also shows the receptor implicated in each case.

Apoptosis is the event more frequently attributed to the interaction of Gp120 with CD4 and coreceptor molecules. The importance of Gp120-mediated apoptosis for AIDS pathogenesis was assessed in an early study performed on lymph-node cell suspensions prepared from three HIV-positive patients. Free Gp120 colabeled with both apoptotic and normal CD4^{+} T lymphocytes, although it was more often identified on apoptotic than on normal CD4^{+} T lymphocytes but not on CD8^{+} T lymphocytes or B cells. HIV particles were not found associated either with normal or apoptotic lymphocytes. This study pointed out that free Gp120 can bind to CD4^{+} T cells in lymph nodes of HIV-infected individuals and potentially mark them for premature death by apoptosis (Sunila et al., 1997).

Holm and cols., demonstrated that the affinity of native, virion-associated Gp120, for the CD4 and CXCR4 or CCR5 receptors was important for induction of apoptosis on primary human CD4^{+} T cells with an activated phenotype. In this study, virions expressing a mutant Gp120 defective for CD4 binding induced apoptosis, whereas mutants defective for CXCR4 binding did not. These observations indicated that the Gp120-CD4 interaction did not induce apoptosis, but seems to promote it by enhancing the exposure of the CXCR4 binding site on Gp120 (Holm et al., 2004). Gp120 expressed by *env*-transfected, non-infected cells, also induced CXCR4-dependent apoptosis in umbical cord CD4^{+} CXCR4^{+} cells; apoptosis was inhibited by SDF-1 (Roggero et al., 2001).

As for virion-associated Gp120, studies performed with recombinant Gp120 showed that Gp120 induced apoptosis through Fas-dependent and Fas-independent mechanisms and that not all lymphocytes were equally sensitive (reviwed in Cicala et al., 2000). Induction of apoptosis by soluble Gp120 was characterized by Thrushin and cols., whose shown that

binding of soluble Gp120 to CD4 facilitate apoptosis of primary human CD4^{+} T cells, but that it was caused primordially by the Gp120-CXCR4 interaction, since apoptosis was prevented by the CXCR4 inhibitor AMD3100 and by the anti-CXCR4 antibody 12G5 (Trushin et al., 2007). Similarly, soluble Gp120-induced apoptosis mediated by CXCR4 was demonstrated in adult human hepatocytes, which lack CD4 (Vlahakis et al., 2003). Binding of Gp120 to CXCR4 is also able to induce apoptosis of CD8^{+} T cells by upregulating the expression of TNF and TNF-receptor II on interacting CD8^{+} T cells and macrophages (Herbein, et al., 1998). Thus, the expression of CXCR4 or CCR5 may restrict the cell sensitivity to Gp120 and explain the differential response of T cells subsets.

Recent studies have shown that the expression of CXCR4 on cancer cells makes them susceptible to apoptosis induced by the HIV-1 envelope. Endo et al. (2008) observed that apoptosis of breast cancer cell lines induced by HIV-1 particles was dependent on Gp120 and CXCR4 but not CD4. In addition, a Gp120 mutant with low CD4 binding ability induced apoptosis in breast cancer cells but not in T-cells. Importantly, conformational heterogeneity of CXCR4 in breast cancer cells in comparison with CXCR4 in T cells was related to the ability of Gp120 to induce apoptosis mediated by CXCR4 (Endo et al., 2008, 2010). Likewise, it has been shown that the Gp120-CXR4 interaction mediated apoptosis of prostate cancer cell lines but not of normal prostatic epithelial cells (Singh et al., 2009).

Anergy is a state of inhibition of proliferation and/or effector functions normally induced in T cells after encounter with antigen; the cell stay alive and functional inactivation is reversible upon antigen removal. It is induced by incomplete stimulation though the TCR and co-stimulatory molecules, and by the normal stimulation in the presence of IL-10 (Schwartz, 2003). Studies addressing the anergic effect of Gp120 use activation with anti-CD3 or mitogen-activation to simulate the effect of antigen stimulation. The contribution of anergy to the reduced immune function induced by X4 Gp120 in peripheral blood lymphocytes (PBMC) was early described by Schols and De Clercq (Schols & De Clercq, 1996). The addition of low concentrations of Gp120 was able to inhibit the proliferative response and the production of interleukin-2 (IL-2) and interleukin-4 (IL-4) in PBMC previously stimulated with an anti-CD3 antibody and concanavalin-A. In contrast, Gp120 induced the production of high amounts of IL-10, gamma interferon (IFN-g), and tumor necrosis factor alpha (TNF-a) in unstimulated PBMC. The induction of IL-10 by Gp120 was found to be important for the inhibitory effect of Gp120 on PBMC proliferation. Thus, X4 Gp120 can reduce the function of T lymphocytes by directly inducing anergy or by stimulation of the production of anergy-inducer immunosupressive cytokines. Importantly, the activation status played an important role in the cytokine pattern induced by Gp120 in PBMC (Schols & De Clercq, 1996).

Evidence of the participation of chemokine receptors in the induction of anergy by Gp120 has been obtained in studies of the long-lasting hypo-responsiveness to antigen stimulation caused by Gp120 in naive T lymphocytes. Gp120 was found to induce anergy by stimulating the activity of the cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA), which causes the progressive accumulation of the phosphorylated form of the cAMP-responsive element binding, a pathway which is also activated by the ligation of CXCR4 by SDF-1 (Masci et al., 2003).

It should be noted that although there is an association between circulating Gp120 and the induction of proinflammatory and immunoregulatory cytokines like IL-6, IL-10, and TNF-alpha in some HIV infected individuals (Rychert et al., 2010), this effect can not be necessarily induced by direct cell interaction with Gp120, since cytokines could be induced

also by deposition of Gp120-anti-Gp120 immune complexes, which has been associated with disease progression (Daniel et al., 2001; Gerencer et al., 1998).

Evidences indicate that Gp120, Tat and Nef may be largely involved in the events allowing the initial entry of HIV into the brain and in the injury and apoptosis of neurons. HIV gains entry into the brain at the asymptomatic stage of the infection trough infected circulating monocytes or as free virus. It is thought that entry is favored by a subclinical, early loss of the functional integrity of tight junctions of the brain endothelium, the brain blood barrier (BBB) (Strazza et al., 2011; Annunziata, 2003). Once in the brain, monocytes can repopulate the resident macrophage population and become a productive source of virus, extending the infection to microglia, astrocytes and endothelial cells, where it can establish a protected reservoir and give rise to the production of cytokines and chemokines (An et al., 1999). Inflammatory soluble factors like IL-1 and TNF-alpha, along with high amounts of viral proteins like Gp120, Tat and Nef, likely released by a particular kind of monocytes (CD14^{low}CD16$^+$) (Thieblemont et al., 1995), may cause a continuous activation of the brain endothelium, leading to the attraction and diapedesis of more virus and activated cells. Increased numbers of CD14^{low}CD16$^+$ monocytes in the circulation associates with HIV-associated neurocognitive disorders (HAND) (Thieblemont et al., 1995; reviewed in Gras & Kaul, 2010) and are abundant in brain autopsies from patients with HIV encephalitis (Fisher-Smith et al, 2001).

Perturbation of the brain blood barrier (BBB) may be induced by the HIV non-productive infection of brain endothelial cells by micropinocytosis or adsorptive endocytosis of the virus mediated by Gp120 (Banks et al., 2001). The transit of free virions by a paracellular route favored by TNF-alpha has been also observed (Fiala et al., 1997). Another explanation is the increase of BBB permeability by the activity of viral proteins. It has been found that soluble forms of Tat, Nef and Gp120 proteins, which circulate in the blood of HIV infected patients, alter the expression of cell junction proteins and thus disrupt the integrity of the BBB (reviewed in Toborek et al., 2005; Kanmogne et al., 2005). Gp120 is also able to increase monocyte migration through a brain microendothelial cells monolayer and to reduce the transendothelial electric resistance (Kanmogne et al., 2007). The presence of functional CD4 and chemokine receptors on discrete regions of brain microvessels derived from children has been demonstrated (Stins et al., 2004). In the presence of interferon (IFN)-gamma, children brain microvessels, but not adult brain microvessels, suffer cytotoxicity induced by Gp120. The effect associated with an increase of the expression levels of CCR3 and CCR5 induced by IFN-gamma. Several Gp120 peptides and RANTES, but not SDF-1, inhibited the Gp120 cytotoxic effect. Authors also showed that Gp120-mediated endothelial cell cytotoxicity involved the p38 MAPK pathway. Thus, a blood-brain barrier dysfunction induced by Gp120 in the brain of HIV-1-infected children may explain the higher incidence of HAND in this population (Khan et al., 2007).

Besides its potential role in BBB damage, chemokine receptors have been involved in direct and indirect Gp120-induced neuronal damage. Macrophages and microglia, the resident immunocompetent phagocytic cells in the brain, are the main cellular reservoirs of HIV in the central nervous system. Activated microglia produces free radicals and proinflammatory cytokines and chemokines which can damage neurons. Gp120 and Tat activates human fetal microglia in vitro, the resident phagocytes of the brain, to induce the expression of CD40 and MHC class II, and the secretion of inflammatory mediators, like cytokines, chemokines, and neurotoxins favoring the recruitment of cell from the circulation (reviwed in D'Aversa

et al., 2005). The progressive increase in the immune activation with increased expression of cytokines is suggested to cause neuropathological changes and neuronal and axonal damage. A recent report shows that Gp120 is able to activate rat microglia and cause neurotoxicity by inducing an increase in the expression of the voltage-gated K^+ channels (K_V), enhancing the cell outward K^+ currents. The Gp120-associated enhancement of K^+ current was blocked by a CXCR4 receptor antagonist or a specific protein kinase A (PKA) inhibitor. This data suggest that interaction of Gp120 with CXCR4 may underlay the microglia activation leading to neurotoxin production and neuronal apoptosis (Xu et al., 2011). In other study, Gp120-mediated neurotoxicity was found to involve signaling trough the p38 MAPK in macrophages, microglia and neuronal cells. Gp120-mediated p38 MAPK activation and neuronal death was prevented by CCL4 (MIP-1beta), one of the CCR5 ligands (Medders et al., 2010). On the other hand, soluble Tat is able to cross the BBB and to induce the production of chemoattractive factors by astrocytes and monocytes (mainly MCP-1, which is considered one of the most important chemokines in HIV infection and HAND), and the expression of CCR5 on monocytes (Weiss et al., 1999).

5. Relevance of extracellular Gp120 to HIV pathogenesis

It is known that molecular diversity produce a variety of ligand-receptor interactions, which in turn, induce signaling events that diverge from the optimal agonist effect (Edwards & Evavold, 2011). Thus, an important issue to be considered in the studies of the biological activity of Gp120 is its extreme heterogeneity at the amino acid sequence and glycosylation levels. A survey of the HIV sequences contained in Los Alamos database in the year 2000 showed that, of 566 full-length Gp120 protein sequences, protein lengths varied from 484 to 543 amino acids because of the insertions and deletions found in hypervariable regions. Main factors contributing to Env variation are: base-substitution due a lack of proofreading during the reverse transcription of the HIV genome, large insertions and deletions, and recombination. These processes are accelerated by the viral high replication rate, the rapid viral turnover and the pressure to change imposed for the immune response of the HIV infected individuals (Korber et al., 2001). Many of substitutions at the hypervariable regions of Gp120, as well as insertions and deletions involve glycosylation sites, so that the number of N-linked glycosylation sites ranges from 18 to 33 (Korber et al., 2001).

Another source of Gp120 molecular variation is the non-uniform content of carbohydrate units. The addition of oligosaccharides and oligomerization of the Gp160 precursor are both co-translational events that take place in the ER (reviewed by Land & Braakman 2001). It is known that incomplete or "immature" glycosylation is present in trimeric Gp120, due to steric limitations imposed to the glycan-modifying enzymes in the Golgi apparatus. Numerous Gp120 glycosylation variants can be produced even within a single cell population, as has been shown in the H9 lymphoblastoid cell line (Pal et al., 1993; Mizuochi et al., 1990). Instead, recombinant monomeric Gp120 is believed to contain fully mature glycans (Eggink et al., 2010; Binley et al., 2010). Thus, monomeric and native, trimeric Gp120 derived from virus and infected cells, may differ in their pattern of glycosylation (Means & Desrosiers, 2000; Mizuochi 1990). A recent study of the expression of a model oligomeric Gp120 showed that N-glycosylation of varied depending on the cell type used for expression (Raska et al., 2010). Cell-dependent addition of oligosaccharides may explain the observation that HIV laboratory strains exposed a higher proportion of high-mannose glycans that HIV primary isolates (Astoul et al., 2000).

The actual amount of Gp120 in tissues and fluids of the HIV infected individual is another important consideration regarding the role of free Gp120 in AIDS pathogenesis. The Gp120 Env subunit can shed from viral particles and infected cells in vitro to adopt a water-soluble form (McKeating et al., 1991; Smith-Franklin et al., 2002; Layne et al., 1992; Schneider et al., 1986). As described in the previous section of this review, a myriad of biological activities has been described for soluble Gp120, and thus the potential of this molecule to account for a significant portion of the physiological dysfunction observed during the HIV-1 infection is considerable. However, few studies have estimated the extension of the presence of Gp120 in the organism of HIV-infected subjects. Gp120 has been detected in the circulation of about on third of HIV-infected subjects at concentrations of 4-130 pM (Rychert et al., 2010) and 2-20 pM (Gilbert et al., 1991) in early and chronic HIV-infected subjects, respectively. A different study by Oh and cols. (1992) reported a higher concentration in plasma, although the methodology used has been questioned (Klasse & Moore, 2004). The amount of Gp120 bound to tissues can be relevant to the understanding of the dynamics of this molecule in the body. A recent study by Santosuosso and cols. (2009) showed that concentration of Gp120 in secondary lymphoid tissues obtained from autopsies of HIV-infected subjects can be high (up to 9007 pg/ml, or 75 pM), even when Gp120 is not detected in plasma. Although a distinction among the amount of soluble Gp120 and virus or cell-associated Gp120 was not clear in this study, it was shown that Gp120 can accumulate in lymphoid tissues early in the HIV infection, and that levels of viral protein in these tissues can exceed significantly those found in plasma.

The presence of physiologically significant amounts of soluble Gp120 in vivo is still a matter of debate. Klasse and More (2004) have discussed several factors that may limit the effective concentration of Gp120 in fluids and tissues, like the capture of Gp120 by antibodies and serum lectins (Daniel et al., 1998), and the absorption of Gp120 by proteoglycans on cell surfaces (Mbemba et al., 1999;). The soluble mannose binding lectin (MBL), a innate immunity molecule present in the human serum, is able to capture HIV particles probably through the high-mannose glycosylation sites of the Gp120/Gp41 complex (Saifuddin et al., 2000). It has been proposed that MBL can participate in the clearance of HIV, since it activates complement and opzonise particles for binding to phagocytic cells (Mass et al., 1998; Pastinen et al., 1998). Soluble Gp120 could be also cleared or inactivated by MBL.

6. Conclusion

Gp120 is a molecule with remarkable properties, some of which are related to a probable evolutionary relationship with animal toxins, and others to its interaction and adaptation to the human immunological and physiological environment. The Gp120 primary role in viral entry using CD4 and chemokine receptors, allow it to induce signaling events which final outcome depends on the particular cell physiological status, thus leading to activation, altered function or death. The high mutation rate of the *env* gene, combined with a rapid replication and viral turnover rates and the pressure to change imposed for the immune response, allow HIV (and the secreted Gp120 molecule) to extent its range of functional capabilities and cellular tropism. Along with other viral proteins such as Nef and Tat, which also have a spectrum of biological effects as soluble proteins, Gp120 may be an important mediators of the bystander CD4^{+}-T-cell death and chronic inflammation that are hallmark of the disease leading to AIDS.

In the recent years, the interaction of Gp120 with chemokine receptors, enabled by the initial interaction with CD4, as been identified as the origin of many of the effects of Gp120 on the function of immune system cells and other tissues. By reviewing the recent literature, a general picture emerges that indicate that properties of Gp120 strongly associate with its chemokine receptor specificity and the activation status of the target cells. R5 Gp120 is able to activate resting cells, where X4 Gp120 seems to induce mainly anergy and apoptosis. On the other hand, X4 Gp120 is able to enhance the activation phenotype in cells that have been previously stimulated. A proper understanding of the influence of cell status on the effect of particular forms of Gp120 on cell viability and function is necessary to get an integrated view of the significance of free Gp120 for the HIV disease.

Several studies indicate that CD4 is not required for apoptosis of tumor cells induced by Gp120, since it can be mediated by CXCR4. In particular, the importance of CXCR4 expression for development and metastasis of breast cancer cells has been demonstrated, as well as for the Gp120-mediated apoptosis of these cells. Interestingly, HIV infected individuals do not present an increased incidence of this type of tumor, whereas they develop others (Amir et al., 2000; Herida et al., 2003; Pantanowitz & Dezube, 2001). Although other factors may determine this effect, participation of Gp120 can not be discarded. The complex structure and variability of Gp120 provides a substrate for the search of active molecules targeting chemokine receptor-expressing tumor cells.

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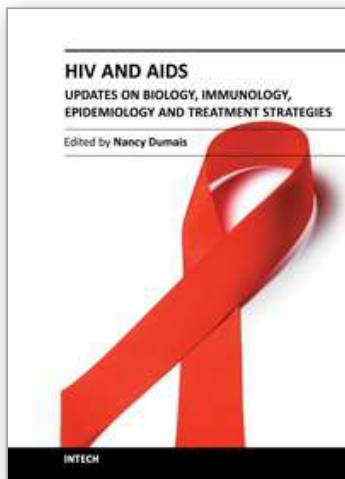
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