Chapter 4

Inhibition of HIV Replication by Host Cellular Factors

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1. Introduction

Human immunodeficiency viruses 1 and 2 (HIV-1 and HIV-2) infection leads to immunological failure and Acquired Immunodeficiency Syndrome (AIDS). During transmission and dissemination within a new host, HIV must overcome several cellular mechanisms aiming to inhibit or restrict its infection and its spread to other host cells. Not surprisingly, as a well-adapted human pathogen, HIV has evolved in order to counteract and subvert these cellular inhibitory factors. Defining how viral and cellular proteins interact remains a critical area of research with direct implications in the knowledge of transmission, pathogenic mechanisms, vaccine design and molecular targets for therapeutic intervention.

In this chapter, the mechanisms involved in the inhibitory activity of some cellular proteins and the way HIV evades those host cell restrictions will be focused on. Particular attention will be given to the tripartite motif 5 (TRIM5) protein family, involved in viral uncoating; the retroviral protection factors, apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) and Tetherin, involved in the reverse transcription and viral release respectively; and to the sterile alpha motif [SAM] and histidine/aspartic acid [HD] domain-containing protein 1 (SAMHD1), which mediates the restriction of HIV-1 replication in dendritic cells. This review will also delve into the mechanisms of two recently described factors: MxB, which restricts HIV nuclear import and integration, and cholesterol-25-hydroxylase that converts cholesterol to a soluble antiviral factor (25-hydroxycholesterol) that blocks HIV fusion with target cells.

2. Brief overview on HIV replication cycle

The replication cycle of HIV can be divided into five major steps: (i) virus-receptor interactions and fusion; (ii) reverse transcription and proviral integration; (iii) HIV genomic DNA transcription; (iv) HIV mRNA splicing, nuclear export and translation; and (v) viral assembly, release and maturation (Figure 1).

The first step of the cycle begins with the binding of the virion gp120 surface subunit (SU glycoprotein) to CD4 receptor present in T-cells, macrophages and dendritic cells. The SU glycoprotein and the gp41 transmembrane subunit (TM glycoprotein) remain associated by non-covalent binding. Both SU and TM are proteolytically cleaved from the envelope (Env) precursor protein by a cellular convertase, furin, within the endoplasmatic reticulum (ER). The SU glycoprotein allows viral binding to cellular receptors – CD4 and a coreceptor belonging to the chemokine receptor's family – while the TM protein is involved in the fusion between the viral envelope and the host cell membrane [1]. After initial binding to CD4, SU undergoes structural changes that lead to the exposure (or formation) of the coreceptor-binding site. Although several chemokine receptors were identified as mediators of HIV entry *in vitro*, CCR5 and CXCR4 seem to be the two major coreceptors [2, 3]. After SU glycoprotein binding to co-receptor additional conformational changes are observed, exposing the N-terminal region of TM (dubbed the "fusion peptide"), which mediates the fusion between the viral and host membranes (reviewed in [4, 5]). This viral fusion process may occur through a direct pH-independent fusion mechanism with plasma membrane [6], or via endocytosis and fusion with endosomes [7].

After viral fusion, the viral capsid enters the cytoplasm and the viral RNA is converted to double-stranded DNA, a reaction mediated by the viral reverse transcriptase (RT), that occurs in a cytoplasmic complex named the reverse transcriptase complex (RTC). RT has three essential activities for virus replication: RNA-dependent DNA polymerase (i.e. reverse transcriptase), RNase H activity that cleaves the genomic RNA in RNA/ DNA hybrids during cDNA synthesis, and DNA-dependent DNA polymerase activity (for synthesis of the second strand of the proviral DNA). The result is a double-stranded DNA replica of the original genomic RNA. The double-stranded viral DNA, as part of the preintegration complex (PIC), penetrates the host cell nucleus through the pores in the nuclear membrane. Another viral enzyme, integrase, inserts the double-stranded viral DNA in the host cell chromosomal DNA (reviewed in [8]). The PIC is composed of several cellular and viral components, e.g. viral DNA, RT, integrase (IN), capsid (CA), matrix (MA) and Vpr proteins. In activated cells, the proviral DNA is transcribed, acting as a template for mRNA synthesis. The viral mRNA exists as three distinct classes: multiply spliced (~2kb), single-spliced (4-5kb) and unspliced (9kb). The multiply spliced transcripts are the first to accumulate soon after infection and encode the regulatory proteins Tat, Rev and Nef. The accumulation of Rev protein enables the efficient nuclear export of single-spliced and unspliced mRNA and to an increase in the levels of these mRNAs (reviewed in [9]).

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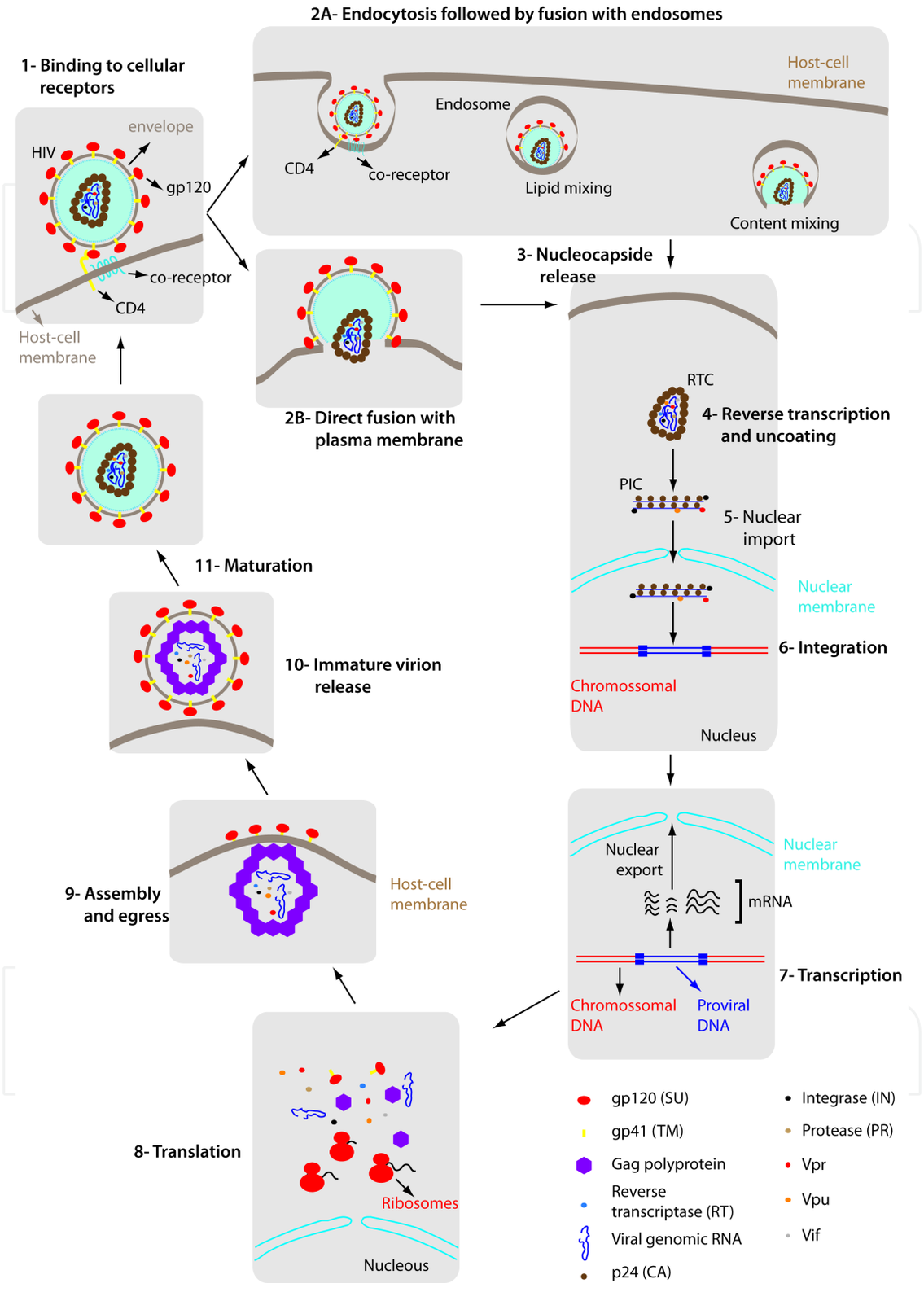

Figure 1. Schematic representation of HIV replication cycle. HIV initiates infection by attaching (1) to cellular receptors: CD4 and a chemokine receptor (co-receptor). The interactions with both receptors trigger the fusion between viral envelope with cellular membrane, either after endocytosis (2A) or by direct fusion with plasma membrane (2B). The release of viral nucleocapside into the cytoplasm (3) precedes the formation of the reverse transcriptase complex (RTC)

where the reverse transcription takes place (4). The RTC transforms to the preintegration complex (PIC), composed by several cellular and viral components, that is imported to the nucleus where viral DNA is integrated into cellular chromosomal DNA (5 and 6). The proviral DNA is then transcribed (7) and mRNA migrates to the cytoplasm and translated to viral proteins (8). Assembly of different components of viral particles occurs at plasma membrane (9). After egress and release of immature virions (10), the proteolytical cleavage of Gag polyprotein takes place leading to mature virions (11).

After replication, transcription and translation, the viral genome information is ready to proceed to the final step: the viral assembly, the release and maturation of recently formed virions. The nucleocapsid assembly occurs through protein-protein interactions mediated by the uncleaved Gag polyprotein – through the capsid (CA) domain [10] – that also recruits the viral genomic RNA, through the interaction between the nucleocapsid (NC) domain and the RNA packaging signal (*Psi* sequence) [11]. The NC domain also mediates the formation of the RNA dimer via a palindromic sequence in the dimer linkage structure (DLS) sequence, which is located in the *Psi* sequence. In addition, specific cellular tRNAs are packaged. The assembly of the virus particle, which final steps occur at the plasma membrane (reviewed in [12]), is partly regulated by the Vpu and Vif proteins, which play an important role in the assembly of the virus. At the cell membrane, the immature viruses are released and maturation takes place through polypeptide cleavage mediated by the viral protease. The mature virus is now able to infect other cells.

3. Organization of viral genome

The majority of replication competent retroviruses depend on three genes: "group specific-antigen" (*gag*), "polymerase" (*pol*) and "envelope"(*env*) genes. The "classic" structure of a retroviral genome is: 5'LTR-*gag-pol-env*-LTR 3 ' (Figure 2). The non-coding LTR ('long terminal repeat") represents the two ends of the viral genome and they are linked to host cell DNA after integration. The *gag* and *env* genes encode the core and the viral envelope glycoproteins respectively. The *pol* gene encodes for the RT, IN and protease [13]. In addition, HIV contains in its 9.749 kb RNA, six additional genes: *vif, vpu* (only in HIV-1), *vpr, vpx* (only in HIV-2), *tat, rev, and nef*) which contribute to their genetic complexity and helps virus in several steps during replication cycle [14].

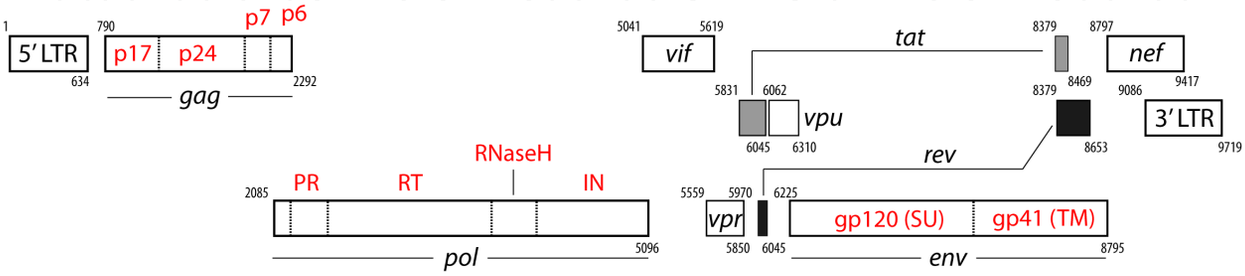

Figure 2. HIV-1 genome organization. The major viral proteins encoded by *gag*, *pol* and *env* genes are indicated in red. Numbers indicate the beginning and ending of each gene according to nucleotide numbering of HXB2CG HIV-1 strain (GenBank accession number: K03455).

The *vif* gene codes for Vif, a protein that increases the infectivity of the HIV particle. This protein is found inside HIV-infected cells, and its main function is to interfere with one of the innate immune system's defenses - a cellular protein called APOBEC3G [15].

The "Viral protein U", (coded by *vpu* gene), enhances the release of new viral particles, helping them to bud from the host cell. Vpu also works within the infected cell to enhance the degradation of CD4 protein. This has the effect of reducing the amount of CD4 present in plasma membrane, therefore reducing the likelihood of superinfection [16].

The "Viral protein R", (coded by *vpr* gene), is incorporated into viral particles through a specific interaction with Gag proteins. It has several functions during intracellular steps of viral replication. For instance, Vpr is present in the PIC and has been shown to influence the reverse transcription and the nuclear import of viral DNA; it also modulates cell cycle progression and apoptosis of infected cell [17].

Tat and Rev are regulatory proteins coded by *tat* and *rev* genes. They are present in the nucleus of infected cells and bind to defined regions of the viral DNA and RNA. These proteins enhances the transcription of proviral DNA into mRNA, promote the RNA elongation, stimulate the transport of HIV-1 mRNA from the nucleus to the cytoplasm and also are essential for translation [9].

Tat is a regulatory transactivator protein, which enhances the activation of HIV long terminal repeat (LTR) increasing the efficiency of HIV genomic transcription. This enhancement is also the result of additional interaction between Tat and cellular transcription factors such as NF-κB and SP-1. Furthermore, Tat also plays a crucial role in AIDS pathogenesis, especially in the development of HIV-associated dementia, dysregulation of cytokine expression and induction of apoptosis [9]. As referred earlier in this chapter, Rev facilitates the nuclear export of single-spliced and unspliced viral mRNAs (~4 kb and ~9 kb mRNAs respectively). The molecular mechanism underlying Rev activity involves a direct interaction between Rev protein and a *cis*-acting sequence-specific target named RRE (Rev-responsive element). RRE is found within the *env* gene in all incompletely spliced mRNAs [9, 18]. It has been shown that Nef protein has several functions. It induces down-regulation of CD4 [19] and the HLA class I and II molecules from the surface of HIV infected cells [20], which may represent an important escape mechanism for the virus to avoid recognition by CD4+ T cells. Nef may also interfere with T cell activation, as a result of selective binding to various proteins that are involved in intracellular signaling [21].

4. Cellular factors with inhibitory activity on HIV replication and implications in viral pathogenesis

Innate immunity had evolved as a mechanism to defend eukaryotes from bacterial and viral infections. These mechanisms rely on different cellular restriction factors that suppress the replication of the pathogens, namely retroviruses [22].

During HIV-1 infection, incoming viral RNA triggers a TLR7/8-mediated innate immune response, resulting in the production of type I interferon (IFN). In particular IFNα has been shown to be up-regulated after TLR sensing during acute infection with HIV-1 or SIV [23-25]. Accordingly, initial observations *in vitro* revealed that pre-treatment of macrophages with type-I IFN inhibited the replication of HIV-1, indicating that potent inhibitory factors were induced after IFN exposure [26, 27]. Most of them are still uncharacterized.

The identification of cellular restriction factors and the viral proteins that antagonize those restrictions have stimulated an active area of research that explores crucial mechanisms underlying HIV interference with cellular restriction factors and innate immunity. In this subchapter specific cellular factors with inhibitory activity on HIV replication are discussed including how viral-encoded proteins counteract these factors.

4.1. TRIM5α

The search for the mechanisms underlying the innate cellular resistance to retroviral infections shown by different non-human primate species, has led to the identification of a cytoplasmic factor that prevented infection of Old World monkeys by HIV-1 [28]. This factor – TRIM5α – was identified as a member of the tripartite motif (TRIM) family of proteins, a large family of cellular proteins with distinct biological activities including innate immune signaling [29]. After its initial identification in rhesus macaques (rhTRIM5α) [28] and owl monkeys (TRIM-Cyp) [30], TRIM5α was also identified as a retroviral restriction factor in humans [31, 32] that is induced by both type I and type II IFN [33].

Different models have been proposed for retroviral inhibition mediated by TRIM5 proteins [34]. They suggest that these proteins mediate restriction by directly binding to specific determinants in the viral CA protein, blocking HIV replication soon after viral release in host cell cytoplasm. The TRIM proteins family is defined by three domains (RING, B-Box2, and Coiled- Coil), which are present in all members of this family. The N-terminal RING domain possesses E3 ubiquitin ligase activity that is crucial for retrovirus restriction [35, 36]. The B-Box2 and Coiled Coil (CC) domains are thought to contribute to the higher and low order multimerization of TRIM5α, respectively. The TRIM5α also possesses a C-terminal capsid binding domain that mediates specific recognition and restriction of certain retroviruses [37]. The recognition of viral capsid determinants (CA protein) relies on three variable regions present in the C-terminal domain of TRIM5α, and apparently they are equally involved in retrovirus recognition and restriction [38-41].

Several studies have addressed the mechanisms by which TRIM5α protein prevents viral infection and different models have been proposed to explain this restriction. The "accelerated uncoating" model was based on the observation that cytosolic CA protein was specifically dissociated in rhTRIM5α-expressing cells [42] leading to the proposal of a "proteasome independent capsid degradation" mechanism. This model suggests that the stripping of capsid protein prevents viral RTC to proceed to subsequent steps in infectious replication cycle, namely the reverse transcription and nuclear import [42]. An alternative model was primarily based on the observation that proteasome inhibitors allows reverse transcription and integration, without affecting the TRIM5α-mediated restriction [43, 44]. Accordingly, a "two-step

restriction mechanism" was proposed, suggesting that restriction activity of TRIM5α occurs by both proteasome-dependent and -independent pathways. The relative contribution of each pathway is apparently dependent on host cells-viruses combinations [45].

4.2. APOBEC3

One important form of intrinsic immunity against retroviral infections is provided by apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) family proteins, and particularly by human APOBEC3G (A3G) and APOBEC3F (A3F) [46-49]. These two proteins are cellular antiretroviral factors that possess inhibitory activity against HIV-1 replication [22, 48, 50].

APOBEC proteins act on single-stranded DNA or RNA substrates and their main function is to induce alterations in the nucleotide sequence through cytidine deamination, converting cytidines to uridines (C to U) or deoxycytidines (dC) to deoxyuridines (dU).

The A3G protein, which expression seems to be regulated at a transcriptional level through NFAT and IRF binding to specific sites located in A3G promoter region [51, 52], is packed inside newly formed HIV-1 virions by a specific interaction with the amino-terminal region of NC domain of HIV-1 Gag polyprotein [53-57]. As expected due to the interaction with NC, A3G is present in viral core as a ribonucleoprotein complex together with genomic RNA, NC, IN and Vpr [58]. Interestingly, binding of A3G to HIV genomic RNA led to inactivation of deaminase activity, while the action of HIV RNase H, which degrades the RNA chain during reverse transcription activates its enzymatic activity [58]. After viral entry into a new cell and during reverse transcription, the released A3G targets the minus-strand DNA product and induces a dC to dU deamination resulting in a dG to dA hypermutation in the HIV-1 double-stranded DNA genome of the replicating virus. This hypermutation activity ultimately introduces mutations and stop codons that disrupt the normal expression and function of viral proteins [46, 59]. A3G can also interfere directly with viral reverse transcriptase preventing RT-dependent cDNA elongation independently of deaminase activity [60]. Finally there is also evidence suggesting that A3G reduces the integration of HIV-1 DNA by interfering with PIC functions [61, 62]. In addition to A3G, also A3F seems to exhibit inhibitory activity against HIV-1 replication [47, 49, 63, 64].

Despite their ability to hinder HIV replication, these proteins only show their potent inhibitory effect with HIV-1 mutants lacking a functional *vif* gene, since the Vif protein expressed by wild-type HIV-1 blocks the function of these host cell proteins [50, 65-70]. Basically, Vif binds to A3G in the cytoplasm of infected cell and directs it for polyubiquitination and proteasomal degradation, preventing its inclusion into the newly formed virions thus overcoming the inhibition of viral replication mediated by A3G [67-69, 71]. A cellular E3 ubiquitin ligase complex consisting of cullin5, elonginB, elonginC and RING finger proteins that binds an E2 ubiquitin-conjugated enzyme, induces the polyubiquitination of A3G. This complex is recruited by Vif that connects it to its substrate inducing the polyubiquitination of A3G [67-69, 71-73]. Additionally, Vif also interferes with the translation of A3G mRNA, reducing its intracellular pool [72, 74].

Besides A3G and A3F proteins, the human genome also contains genes encoding five others members of the APOBEC3 family. However, of these five additional genes, apparently only three (APOBEC3A, APOBEC3B and APOBEC3C) are expressed in human cells. Recent data shows that APOBEC3A is recruited at post-entry HIV-1 replication complexes [75-79]. Its expression is induced in monocyte-derived macrophages (MDM) by interferon-alpha (IFN-α) and it seems to promote resistance to HIV-1 infection in MDM [75]. The APOBEC3C protein is a weak inhibitor of wild-type or *vif*-deficient HIV-1 [63, 64, 80] although it was described, together with APOBEC3B, as a potent inhibitor of simian immunodeficiency virus (SIV) replication [81]. As for A3G, the APOBEC3B protein is also packed inside HIV-1 virions due to a specific interaction with the NC protein. It induces a potent inhibition of HIV-1 replication and it seems to be resistant to HIV-1 Vif protein [82]. However, APOBEC3B is expressed at very low levels in human tissues, in contrast to A3G and A3F [82].

4.3. Tetherin/ BST-2

In early 2008, an additional restriction factor dubbed Tetherin, previously referred to as BST-2, CD317 or HM1.24, was described [83, 84]. The main function of this IFN-induced protein [85, 86] remained elusive until it was identified as an intrinsic antiviral factor that restricts the egress of HIV and other enveloped viruses by tethering mature virions to the host cell membrane [83, 84, 87-91]. Tetherin is a type II membrane protein highly expressed at the plasma membrane of B cells at all differentiation stages, bone-marrow CD34+ cells and T-cells [92]. It has an unusual topology consisting of an amino-terminal cytoplasmic tail (CT), followed by a transmembrane region that anchors tetherin to the plasma membrane and a coiled-coil extracellular domain that is also linked to the plasma membrane by a carboxy-terminal glycophosphatidylinositol (GPI) anchor [93, 94]. Due to the presence of this GPI anchor, tetherin is mainly located in cholesterol-rich microdomains also referred as "lipid rafts". Tetherin is involved (through the CT domain) in the organization of subapical actin cytoskeleton in polarized epithelial cells [95] and unlike other GPI-anchored proteins, is endocytosed from lipid rafts in a clathrin-mediated pathway [96].

Coincident with the identification of tetherin as an antiviral factor, it was also found that it was the target of the HIV-1 accessory protein Vpu, providing a plausible mechanism for the well-established but ill-defined, virus-release function of Vpu [83]. The Vpu is a small transmembrane (TM) protein encoded by the *vpu* gene present in the genomes of HIV-1 and some SIV strains, but absent in HIV-2. It is anchored to the plasma membrane of the infected cell by its amino-terminal region. Initial studies showed that Vpu protein besides its ability to degrade CD4 protein [97], was also required for efficient replication of HIV-1 in some cell types and that the restriction factor counteracted by Vpu was a protein located at cell surface [16, 98-101]. This factor was found to be IFNα-inducible and showed the ability to block the release of Vpu-defective virions by directly tethering them to the plasma membrane of virus-producer cells. The trapped virions are subsequently internalized by endocytosis and probably degraded in lysosomes [83, 85]. Remarkably, the lipid rafts localization of tetherin is coincident with the preferential site for budding and egress of enveloped viruses [102, 103], providing further explanation for the mechanism by which tetherin blocks virion release. Several aspects of the Vpu-mediated antagonism of tetherin are still controversial. It was initially proposed that Vpu

impairs the transport of newly synthetized tetherin by sequestering it within the trans-Golgi network [104-106]. Additionally, Vpu might block the recycling of tetherin after its internalization from the lipid rafts [104, 106, 107]. Finally, it was also proposed that Vpu might directly internalize tetherin from cell membrane [108-110]. Interestingly, it was observed that treatment with proteasomal inhibitors lead to increased levels of tetherin and loss of Vpu-mediated enhancement of HIV-1 release. These results suggest that the Vpu-induced down-regulation of tetherin might at least in part involve proteasomal degradation of the restriction factor [111-113]. The exact mechanisms of tetherin down-modulation from cell surface, intracellular sequestration or degradation remain to be determined. These three distinct mechanisms may act cooperatively counteracting tetherin to varying degrees in different cellular contexts. Regardless the model that is preferentially observed, binding of Vpu to tetherin through TM-TM interaction seems to be crucial for Vpu antagonism of the restriction factor [108, 111, 114, 115].

Despite the wide cellular distribution of tetherin and the need to counteract its viral restriction action, most primate lentiviruses do not contain a *vpu* gene. Some (e.g. SIVsmm, SIVmac, and SIVagm) use their Nef proteins to antagonize tetherin function [116-118]. This is not surprising since Nef protein - a myristoylated protein coded by *nef* gene essential for HIV replication *in vivo* - is known to act as an adaptor protein interacting with different cellular proteins. Through these interactions Nef manipulates cellular trafficking, signal transduction and gene expression in HIV infected cells (reviewed in [119]). Apparently, Nef targets the cytoplasmic tail of tetherin reducing its expression at host cell membrane [116, 118]. In alternative to Nef, HIV-2 relies on its envelope glycoprotein Env to antagonize tetherin. The proposed mechanism suggests that Env interacts directly with the ectodomain of tetherin, sequestering it away from sites of virus budding and targeting it to clathrin-mediated endocytosis [120].

Besides the referred lentiviruses, the antiviral activity of tetherin was also demonstrated against a broad range of unrelated viruses, such as filoviruses [87, 88], arenaviruses [88] and herpesviruses [121, 122]. For some of these viruses specific viral encoded antagonists has been described. For example, human herpesviruses 8 (HHV-8, also known as Kaposi's Sarcoma herpesvirus) uses K5/MIR2 - a viral protein belonging to the membrane-associated RING-CH ubiquitin ligase family - to ubiquitinate tetherin and target it for degradation [121]. In Ebola virus - a filovirus associated with hemorrhagic fever outbreaks - the tetherin-mediated restriction is counteracted by viral envelope glycoprotein [123] in a process similar to the described sequestration of tetherin by HIV-2 Env.

4.4. SAMHD1

Myeloid-lineage cells, including monocytes, dendritic cells (DCs) and macrophages, play a multifaceted role in HIV-1 initial infection and viral dissemination during acute infection. In particular, the interactions between HIV and DCs are connected with all aspects of HIV infection *in vivo*, including transmission, pathogenesis and immune control (recently reviewed in [124]). DCs exposed to HIV during sexual transmission help viral dissemination and systemic infection by two distinct mechanisms: by becoming productively infected or by transferring HIV to CD4+ T cells during immunologic synapse (IS), even in the absence of DCs infection [125-127].

Although DCs can be infected, HIV replication is generally less productive compared with CD4+ T cells. Nevertheless, extensive viral replication takes place once DCs come into contact with CD4+ T cells in lymphoid tissue in the context of IS [128]. This implies that HIV must be able to evade DC's innate immune sensing and endolysosomal degradation and then make use of DC maturation and migration to draining lymph nodes to be transmitted to highly susceptible T cells during antigen presentation process within lymph nodes (reviewed in [129]).

Infection by DNA or RNA viruses triggers innate immune responses when host recognizes specific viral molecular structures (e.g. nucleic acid and surface glycoprotein), called pattern-associated molecular patterns (PAMPs) [130-132]. These PAMPs are recognized by pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs), RIG-I-like helicases (RLH), and cytosolic DNA sensor proteins. Inside the cytoplasm, viral nucleic acid can be detected by different PRRs depending on the cell type. For example, TLR7 and TLR9 are responsible for detection of viral RNA and DNA, respectively, in plasmacytoid dendritic cells (pDCs), whereas RLHs detect viral RNA in conventional DCs, macrophages and fibroblasts [133, 134]. The recognition of PAMPs by the PRRs activates several transcription factors, namely nuclear factor-κappa binding (NF-κB) and IFN regulatory factors (IRFs). This activation leads to the production of pro-inflammatory cytokines and type-I IFNs (IFN-α and IFN-β), respectively (reviewed in [130]). The production of type-I IFNs induces the expression of hundreds of interferon-stimulated genes (ISGs) [135], providing crucial mechanisms of antiviral defense by inhibiting viral replication and spread. For example, during HIV Infection, viral single-stranded RNA (ssRNA) is recognized by TLR7/8 initiating anti-HIV immune response by inducing type I IFN. However, as a well-adapted human pathogen HIV must be able to avoid – at least in part – these cell sensing mechanisms in order to evade host innate immunity.

Sterile alpha motif (SAM) and histidine/aspartic acid (HD) domain-containing protein 1 (SAMHD1), an analogue of the murine IFN-y-induced gene Mg11 [136], was identified as a HIV-1 restriction factor that blocks early-stage virus replication in DCs and other myeloid cells [137, 138]. It acts by depleting the intracellular pool of deoxynucleoside triphosphates (dNTP), thus impairing HIV-1 reverse transcription and productive infection [139-141]. The expected lower replication in DCs may enable HIV-1 to avoid intracellular viral sensor that would otherwise trigger IFN-mediated antiviral immunity [142, 143]. It seems that while SAMHD1 effectively renders DCs less permissive to HIV-1 infection, it is somewhat paradoxically responsible for the HIV-1 evasion of immune sensing and subsequent poor priming of adaptive immunity.

HIV-2 brings in a new and interesting element: Vpx (an accessory protein encoded by *vpx* gene, present in SIVsm/SIVmac and HIV-2), that is believed to have originated by duplication of the common *vpr* gene present in primate lentiviruses [144], possibly to compensate for a theorised low HIV-2 RT affinity for dNTPs [145, 146]. This accessory protein antagonizes the effect of SAMHD1 by targeting it for proteasomal degradation using the host cell E3 ubiquitin ligase complex, in which Vpx interacts with the DCAF1 subunit of the CUL4A/DDB1 ubiquitin ligase to degrade SAMHD1 via the proteasome [137, 139, 147, 148]. The degradation of SAMHD1 renders HIV-2-infected DCs much more permissive to productive infection and viral replication, allowing faster accumulation of full length viral DNA [148]. This results in a widely positive DC-specific effect in the innate immune sensing of HIV-2 infection [143, 146, 148, 149] and it

may be related to the lower viral load and slower progression to AIDS that is characteristic of HIV-2 infection (reviewed in [150]). The immunologically positive effects of Vpx was also demonstrated in monocyte-derived DCs (MMDCs) infected with HIV-1 where an increased type I IFN production and up-regulation of CD86 was only observed in the presence of Vpx [146]. Hence, by avoiding productive infection of MDDCs through preservation of SAMHD1 function, HIV-1 may also control viral antigen presentation, resulting in qualitatively or quantitatively minor CD8+ and CD4+ responses [146, 149, 151]. Furthermore, individuals with low SAMHD1 activity or silenced SAMHD1, present an enhanced immune response to HIV-1 infection, as previously hypothesised [139, 143] [139, 143] and demonstrated [146].

4.5. MxB

The myxovirus resistance (Mx) genes were discovered in the 1960s when it was observed that wild mice were resistant to influenza viruses, whereas inbred mice were susceptible [152]. This trait was later mapped to a locus on mouse chromosome 16 [153-156]. Mx family proteins are found in almost all vertebrates, demonstrating their evolutionary importance for host organisms [157]. Humans Mx gene resides on chromossome 21 [158] and encodes two proteins, called MxA and MxB, that belong to the family of dynamin-like large GTPases. The MxA protein has been recognized as a potent cell restriction factor with antiviral activity against pathogenic DNA and RNA viruses [159].

The X-ray crystal structure of human MxA showed that this protein can be divided into a globular GTPase head, a largely C-terminal α-helical stalk domain and a series of α-helices found in sequences adjacent to these domains which fold in the protein tertiary structure to form the bundle signaling element (BSE) [160]. On the basis of sequence homology and computer modeling the predicted structure of MxB is almost superimposable with that of MxA, having 63% amino acid sequence identity.

In contrast to human MxA protein that inhibits a variety of viruses [161], MxB was initially described as lacking antiviral activity against influenza or vesicular stomatitis virus [162]. Instead, MxB was solely related to cellular functions, such as regulating nuclear import and cell-cycle progression [163, 164].

This view was challenged in 2011, when Schoggings and collaborators addressed an overexpression screening to test the antiviral activity of more than 380 human interferon stimulated gene (ISGs) products against a panel of viruses, where they first uncovered an antiviral activity of human MxB against HIV-1 [165].

More recently, three additional studies [166-168] showed that MxB overexpression potently reduces the permissiveness of the cells in a single-cycle HV-1 infection assay. They also demonstrate that silencing MxB expression reduced the inhibitory potency of the interferon-α demonstrating its importance in the interferon-mediated response against the early steps of HIV-1 infection.

The next step was to understand which specific post-entry event of the HIV replication cycle was affected by MxB expression. Recent studies agreed that MxB expression potently inhibited HIV-1 infection after reverse transcription but before integration [166-168]. So MxB might be

interfering with one or more of the following processes: 1) HIV-1 uncoating; 2) nuclear import of the HIV-1 PIC; or 3) nuclear maturation of the PIC.

Fricke and colleagues [169] suggested a model in which MxB binds to the HIV-1 core in the cytoplasm of the cell and prevents the uncoating process of HIV-1 through stabilization of incoming viral capsides. In addition, they demonstrated that MxB requires capsid binding and oligomerization for effective restriction.

More recently, Matreyek et al. [170] observed that MxB restricts HIV-1 after DNA synthesis at steps that are coincident with PIC nuclear import and integration.

HIV-1 RNA is reverse transcribed into double stranded linear DNA and carries a fraction of the viron CA protein [171, 172]. HIV-1 CA protein is known to play a central role in mediating physical interactions with several host proteins involved in the post-entry step of infection. Some identified residues of CA involved in binding to cyclophilin A (CypA), TRIM5α, TNP03, CPSF6, NUP153 and NUP358/RanBP2 are also critical for the sensitivity of HIV-1 to the antiviral action of MxB. Results obtained by Liu and colleagues indicate that both silencing of CypA expression or disruption of the CA-CypA interaction by addition of cyclosporine A abrogated the antiviral activity of MxB, thus CypA binding to the HIV-1 CA appears to be required for MXB restriction. Furthermore, results obtained by diverse groups indicate that CA mutations counteracted MxB restriction [165-168, 170].

The viral integrase (IN) protein processes the long terminal repeat (LTR) ends of the viral DNA to yield the integration-competent PIC, which subsequently transports the viral DNA into the nucleus for IN-mediated integration [173]. Matreyek and collaborators [170] found evidence for an additional block in the formation of 2-LTR circular viral DNA (that are only present in the nucleus, and thus have been utilized as a marker of nuclear entry of viral DNA [174]). In contrast, results obtained by Liu and collaborators [167] showed that MxB reduces the levels of integrated HIV-1 DNA, though it does not affect the amount of 2-LTR circles. They concluded that MxB impairs the integration step and spares the nuclear entry of viral DNA.

Apparently, MxB antiviral activity is independent of its GTPase active site residues or stalk domain Loop4 (both previously shown to be necessary for MxA function) that confer functional oligomerization to related dynamin family proteins [166, 168]. There are two locations in MxB that exhibit the greatest sequence dissimilarity with MxA. The first one is Loop4 that is not critical for MxB antiviral activity but is important for the MxA inhibition of Influenza A and Thogotovirus infection [170, 175]. The other part of MxB with greatest dissimilarity to MxA is the N-terminal region. The specific particular functions conferred by this region are particularly important for MxB activity and consequent HIV-1 restriction [170].

In a global perspective, the post-entry step of HIV-1 replication cycle appears to be quite vulnerable to the actions of IFN-inducible restriction factors: TRIM5α, APOBEC3 proteins, SAMHD1 and, more recently, MxB use distinct mechanisms to prevent integration of this pathogenic virus in host genome. Certainly it will continue to be of interest to the scientific community the study of restriction factors of viral infection by antiviral host factors due to its impact in many areas. These findings raises hope as a potential clinical and epidemiological relevant approach which could be exploited to control HIV infections and AIDS.

4.6. Cholesterol-25-hydroxylase

Recently, a new antiviral IFN-induced protein (cholesterol 25-hydroxilase; CH25H) was identified as being able to block the fusion between viral envelope and target cell membrane. It exhibits a broadly antiviral activity against several enveloped virus including HIV, Ebola virus (Zaire strain), vesicular stomatitis virus, herpes simplex virus I, Rift Valley fever virus, Nipah virus, Influenza A (H1N1) virus and varicella zoster virus [176, 177]. It also revealed antiviral effect against poliovirus [178], a non-enveloped virus. The IFN-induced cholesterol-25-hydroxylase (*Ch25h*) gene encodes an endoplasmic-reticulum-associated enzyme (CH25H) that mediates the oxidation of cholesterol, by the addition of an extra hydroxyl group at position 25, converting it to 25-hydroxycholesterol (25HC). 25HC belongs to a large class of endogenous cholesterol derivatives named oxysterols. In addition to their involvement in basic metabolic processes, e.g. bile acids production in the liver [179], oxysterols also play a key role in several signaling pathways that influence the activation of macrophages, T-cells and B-cells, and thus the regulation of inflammatory response [177, 180-188].

Although several antiviral mechanisms have been suggested for CH25H and 25HC, they seem to inhibited HIV-1 replication by blocking the virus-cell fusion step [176]. One possible mechanism underlying this effect is the induction of cellular membrane changes affecting the topology and permissiveness for fusion of host cell membrane. There is extensive evidence that the lipid composition of target cell membrane influences HIV-1 fusion and entry. In fact, though the fusion event is triggered by HIV envelope glycoproteins, lipids also play a key role in virus-cell membrane fusion by themselves, directly affecting the viral receptor accessibility and distribution in lipid rafts domains of the plasma membrane, or the membrane fluidity and curvature [189]. The modifications in cellular membrane architecture induced by 25HC (considerably more hydrophilic than cholesterol [190]) would be of outstanding importance in the complex protein-lipid interplay required for successful virus-cell fusion events [176].

5. Conclusion

The pathogenesis of HIV infection is a highly complex network of interconnected processes. It likely borrows much of its complexity from the co-evolution with several mammalian species that HIV and predecessors lentiviruses have enjoyed over an unknown, but rather long period of time. During the complex interplay between HIV and host cell, different intrinsic cell factors are involved that mitigate or restrict HIV replication and spread as shown in Figure 3. Some of these host restrictions factors that have been identified inhibit early steps of replication cycle. In fact, the post-entry step of HIV-1 replication cycle appears to be quite vulnerable to the actions of IFN-inducible restriction factors: TRIM5α, APOBEC3 proteins, SAMHD1 and, more recently, MxB and cholesterol 25-hydroxylase, all of them use distinct mechanisms to prevent integration of viral DNA into host genome. The best characterized of these are the TRIM5α and the APOBEC3 proteins. APOBEC3 interacts with the nascent DNA during reverse transcription while TRIM5α interacts with incoming viral capsids resulting in premature disassembly. SAMHD1 protein acts prior to integration, by depleting the intracellular pool of deoxynucleoside triphosphates (dNTP), therefore impairing HIV-1 reverse transcription and accumulation of HIV double stranded DNA. Another restriction factor, Tetherin (BST- 2/

CD317), acts in late steps of viral replication cycle, by preventing viruses from leaving the cell during budding and release of viral particles. The recently described factors MxB and cholesterol 25-hydroxylase seem to inhibit the nuclear import/integration of viral DNA and the viral fusion events, respectively. Remarkably, despite this array of restriction factors, HIV had created viral proteins to subdue these restrictions emphasizing how well adapted this virus is to human host.

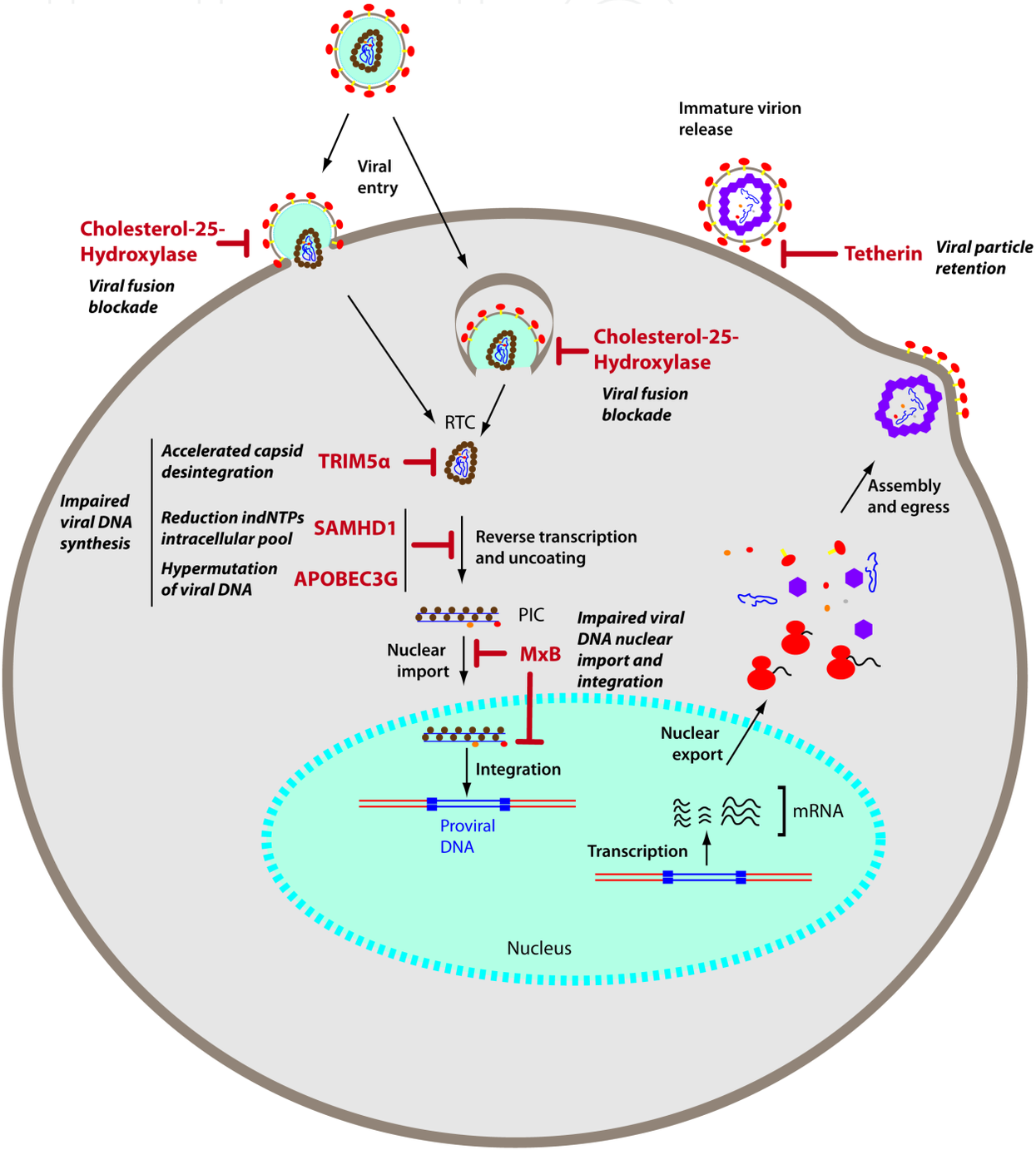

Figure 3. Schematic representation of a simplified replication cycle of HIV and the different steps that are blocked by cellular restriction factors. The cholesterol-25-hydroxylase blocks viral fusion with target cell membrane; TRIM5α, SAMHD1 and APOBEC3G impair viral DNA synthesis either by accelerating capsid disintegration, reducing dNTPs

intracellular pool or by introducing mutations in nascent chain of viral DNA; MxB impairs the nuclear import and/or the integration step; and finally, Tetherin induces virion retention at the host-cell membrane.

Finally, the identification of cellular restriction factors, such as those referred in this chapter, and the disclosure of the mechanisms by which they impede viral replication, also enabled the identification of new promising targets for therapeutic intervention. In fact, it is increasingly clear that the most successful treatment and/or prevention strategies will likely be derived from the modulation of human cell functions rather than acting directly upon viral mechanisms.

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