

Accessory Regulatory Proteins of HIV-1 and Host Restriction Factors Interactions

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ABSTRACT

Primate immunodeficiency viruses, including HIV-1, The presence of accessory genes are characteristic of them, such as vif, vpr, vpx, vpu, and nef. The current knowledge indicates that none of this lentiviral accessory proteins has enzymatic activity. These proteins interact with cellular ligands to either act as adaptation of molecules to redirect the normal function of host factors for virus-specific purposes or to inhibit a normal host function by mediating degradation or causing intracellular sequestration of the factors involved. The intrinsic antiviral factors that restrict viral replication in host cells are countered by accessory proteins the HIV-1 and other lentiviruses had acquired along their evolution.

Abbreviations: HIV-1: Human Immunodeficiency Virus Type 1; SIV: Simian Immunodeficiency Virus; IFN: Interferon; GPI: Glycophosphatidylinositol; MHC-1: Major Histocompatibility Complex Class 1; CRLs: Cullin-Ring Ligases; Vpr: Viral Protein r; VprBP: Vpr Binding Protein

Mini Review

Accessory Regulatory Proteins

When the human immunodeficiency virus type 1 was cloned and sequenced for first time, the researchers were surprised to find that this virus contained several additional open reading frames. In addition to the prototypical retroviral gag, pol, and env genes; Collectively, they were termed accessory genes due to a lack of understanding of their biological functions. Viruses need to counteract intrinsic antiviral factors that restrict viral replication in host cells and for this purpose HIV and SIV might have acquired accessory proteins along their evolution. Virus protein U or Vpu is a lentiviral viroporin of 81 aminoacid, that is specific of HIV-1. This accessory protein is a membrane phosphoprotein, oligomeric with diversified biological functions. Vpu accessory protein is implicated in CD4 degradation, involving the ubiquitin proteasome pathway as well as in the release of virions from host cells. Viral infectivity factor or Vif is a highly conserved 23 kDa phosphoprotein, Vif is binded to the restriction factor APOBEG3AG which is cellular cytidine deaminases that provides immunity against HIV and promotes its degradation.

Vif is outstanding for the infectivity of HIV-1 virions that depends on the cell type. Vif is necessary to the synthesis of infectious virions in macrophages, lymphocytes, and dendritic cells expressing hA3G. Negative factor or Nef, is a membrane associated phosphoprotein with the N-terminal myristoylated. Nef is involved in many functions during the replication cycle of the VIH-1, therefore, it is believing that plays an important role in the increase virus infectivity and in cell apoptosis. Virus protein R or Vpr is a regulatory protein with nucleocytoplasmic shuttling. Vpr through the nuclear import of the preintegration complex play an important part in replication of the virus, Vpr also appears to cause its host cells to arrest their cell cycle in the G2 phase. Vpx is an HIV-2 and SIV encoded protein which functions are associated with Vpr. The HIV-1 is strictly adapted to human host.

Cellular activation has been considered a requirement for HIV infection of CD4 T cells, as HIV fails to infect resting CD4 T cells from peripheral blood. Infection is aborted either during reverse transcription [1]. Like other primate retroviruses, the human immunodeficiency virus type 1 (HIV-1) is characterized by the

presence of accessory genes, for example: vif, vpr, vpx, vpu, and nef. Current knowledge indicates that none of the primate lentiviral accessory proteins has enzymatic activity. Extensive studies on the underlying mechanism have revealed that Vif is one of viral accessory proteins, is critical for the HIV-1 species tropism in addition to Gag-capsid protein. Another auxiliary protein is Vpu that also has been demonstrated that affects this HIV-1 property. The restriction factors are multitaskers and highly conserved, one of the restriction factors function is the regulation of cross-species infections. Consequently, in their natural hosts. they are less effective against viruses.

Vif (Viral Infectivity Factor) and APOBEC3G

APOBEC are a family of cellular cytidine deaminases and represent a group of proteins recently identified. APOBEC protect the cell from endogenous mobile retro elements and provide immunity against infection by retroviruses. Vif is an accessory protein of HIV-1 required for productive infectivity of T-lymphocytes, macrophages and dendritic cells expressing hA3G [2-5]. Vif plays a fundamental role in the viral replication, is a protein of 23 kD that inhibits the host cell protein APOBEC3G (hA3G), which is a host defense factor human. Vif binding to hA3G since the viral entry prevents the assembly with viral particles and also mediates by the proteosomal pathway elimination through ubiquitination and degradation. hA3G binds to the HIV-1 RNA genome and attenuates the viral replication during the post entry phase of the HIV-1 infection. An important mechanism of Vif involves its ability to bind to both Elongin B/C complex of the ubiquitination machinery and to the human host defense factor APOBEC3G (hA3G).

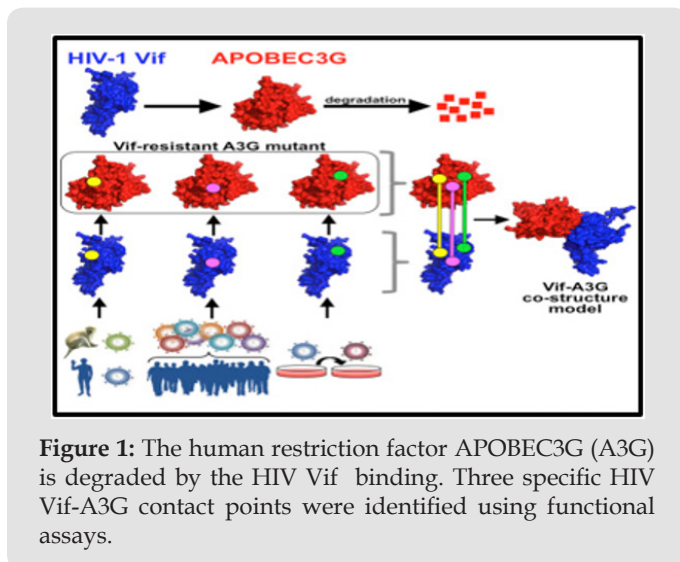


Figure 1: The human restriction factor APOBEC3G (A3G) is degraded by the HIV Vif binding. Three specific HIV Vif-A3G contact points were identified using functional assays.

Through the deamination of deoxycytidines to form deoxyuridines within single stranded DNA regions of the replicated viral genome hA3G inhibits the viral replication [6-13]. A functional Vif-A3G interface model was generated by Letko, et al. through the identification and use of specific interaction points between Vif and A3G. There are three specific HIV Vif-A3G contact points identified

in this model, the A3G binding site on Vif consists of a defined, positively charged pocket using functional assays. The Vif-A3G interface is revealed by the use of protein docking Vif-A3G anchor points (Figure 1).

Vpu (Viral Protein U) and BST2 (Tetherin/CD317)

Vpu is an accessory viral protein that has two functions, degradation of CD4 molecule in the endoplasmic reticulum and enhancement of virion release from cells. Vpu is a type IA viroporin, encoded by human immunodeficiency virus type 1 (HIV-1), also vpu is encoded by some simian immunodeficiency virus (SIV) strains. Vpu is a small protein conformed by 81 amino acids and contain a single transmembrane domain. The functionality of Vpu is well conserved in pandemic virus isolates notwithstanding the high variability of its amino acid sequence. There is a correlation direct between structure, topology and function of Vpu pointed by a functional analysis of this membrane protein. The two biological activities of Vpu protein were charted in two separable structural domains: the transmembrane N-terminus and the cytoplasmic C-terminus by early studies [14-16]. The CD4 receptor in infected cells is downregulated by the HIV-1 Negative Regulatory Factor (Nef) and Vpu proteins. While Vpu targets the newly synthesized CD4 molecules in the endoplasmic reticulum, Nef degrades pre-existing CD4 at the plasma membrane [17].

The cytoplasmic C-terminus domain of the Vpu protein regulate this activity. The enhancement induced by Vpu of the release of viral particles from infected cells was by first time mapped in the transmembrane region of Vpu, which suggest that Vpu does not interact directly with viral proteins, but rather, via cellular factors, mediates this function. On the other hand, some other studies focused on the ion channel activity of Vpu. Thus, Vpu promote budding from the plasma membrane of infected cells was suggested by the Vpu-induced movement of monovalent cations across the internal cellular membrane and the reorganization of raft structures s creating cellular conditions for that [18-22]. The identification of the interferon (IFN)- α -induced glycoprotein Bone Marrow Stromal Cell Antigen 2 (BST2) (tetherin/CD317) has allowed the development the model based on antiviral host restriction which inhibits the release of virus and is antagonized by Vpu.

BST2 is a type II transmembrane protein with two membrane anchors, both are joined by an ectodomain; the transmembrane domain near the N-terminus and a glycosylphosphatidylinositol (GPI)-linked anchor at the C terminus [23-25]. Thus, tetherin has the potential to restrict replication and spread of HIV-1 in humans. Importantly, the human ortholog of tetherin contains a deletion in its cytoplasmic domain that was already present in archaic hominins but is absent from tetherin proteins of nonhuman primates. This deletion usually confers resistance to the accessory Nef protein used by most SIVs, including the precursors of HIV-1 and HIV-2, to counteract tetherin in their respective primate hosts. Pandemic HIV-1 group M strains switched from Nef to Vpu to clear

the tetherin barrier in the human host. The Vpu proteins of group N HIV-1 strains are usually less active than group M Vpus (M-Vpus) and also has acquired some anti-tetherin activity, but they lack other functions like the ability to degrade CD4 [26-31].

Nef and SERINC3, SERINC5

Nef (Negative Regulatory Factor) is a small myristoylated protein of 27-35 kDa that is encoded by primate lentiviruses. These include Human Immunodeficiency Viruses (HIV-1 and HIV-2) and Simian Immunodeficiency Virus, is a small peripheral membrane protein expressed early during the viral replication cycle, before the viral enzymes and structural proteins including Env. Nef associates with membranes via N-terminal myristoylation. Nef, unlike HIV-1 Vpu, shows activity against the factor of restriction of SERINC5. This SERINC5, antagonism occurred in parallel with other Nef activities, like trans-Golgi network targeting of Lck, cell surface receptor downregulation, and inhibition of host cell actin dynamics. Nef is associated with membranes via N-terminal myristoylation. Simian immunodeficiency viruses (SIVs) use their Nef proteins to counteract the restriction factor tetherin. However, a deletion in human tethering prevents antagonism by the Nef proteins of SIVcpz and SIVgor, which represent the ape precursors of human immunodeficiency virus type 1 (HIV-1).

To promote virus release from infected cells, pandemic HIV-1 group M strains evolved Vpu as a tetherin antagonist, whilst the Nef protein of less widespread HIV-1 group O strains acquired the ability to target a region adjacent to this deletion. Through manipulation of the cell machinery the HIV-1 evades the host's immune response. This process involves the use of vesicular traffic to efficiently direct cell markers such as major histocompatibility complex class 1 (MHC-1) and CD4 from the plasma membrane to the endosomes, to finally degrade in the lysosome. The SERINC proteins belong a family of transmembrane proteins that are present in all eukaryotic cells. The SERINC family is comprised of five members, from SERINC1 to SERINC5, structurally characterized as having from 10 to 11 transmembrane domains. SERINC proteins participate in the biosynthesis of sphingolipids and phosphatidylserine by incorporating serine into membrane lipids SERINC3 (serine incorporator 3) and SERINC5, and in the transport of the serine amino acid across the lipid bilayer.

SERINC3/5 are recently identified as host cell inhibitors of HIV-1 particle infectivity and are counteracted by the viral pathogenesis factor Nef. SERINC5 decrease the ability of the virions to fuse with the target cells by the enlargement of the fusion pore. SERINC5 could prevent the entry of the virus prior to small pore formation by promoting structural changes in envelope glycoproteins [32]. Nef antagonize the antiviral activity of SERINC5, leading to a decrease in its incorporation in the virions, because Nef removes it from the plasma membrane and sequesters it in the endosomes for its subsequent degradation [33]. Nef induces, by using the cellular transport machinery, downregulation of SERINC3 and SERINC5

from the cell membrane, mainly using the trans-Golgi network and the endolysosomal system, in a mechanism similar to that used for CD4 downregulation [34-36].

Myristoylation requires Nef to anchor in the membrane for a posttranslational change and execute sequestration of the proteins [37,38].

Vpr (Viral Protein R) and VprBP (DCAF1)

The HIV protein, Vpr is critical for efficient viral infection of target CD4+ T cells and macrophages, it is a multifunctional accessory protein. Vpr is a 96 amino acid 14-kDa protein [39,40], Vpr is required for virus replication in non-dividing cells such as macrophages and plays an important role in the regulation of nuclear import of the HIV-1 pre-integration complex. Vpr is incorporated into virions and functions to transport the preintegration complex into the nucleus where the process of viral integration into the host genome is completed. Numerous investigations over the last 30 years have shown that Vpr mediates many processes that aid HIV-1 infection, the evasion of the immune system, and persistence in the host. Retroviruses require entry into the nucleus to replicate, hence, it is naturally restricted to those cells that undergo mitosis. Lentiviruses such as HIV-1, however, are unique among retroviruses where they are able to infect non-dividing cells [41,42].

Vpr protein shuttles between cytoplasm and nucleus once the virion enters the cell, to facilitate viral replication and, at late stages in the virus life cycle, newly synthesized Vpr is exported from the cell.

Two forms of nuclear Vpr have been observed, monomers and very large complexes, 1000× larger than a monomer. One of the outstanding activities performed by Vpr is the blockade of the cell cycle at G2 after HIV-1 infection of dividing cells [43-46]. The viral LTR promoter is more active in the phase G2 of the cell cycle. Other activities of Vpr include the transcriptional modulation of immune function and the regulation of apoptosis [47-50]. Several proteomic analyses have been undertaken in an attempt to unravel the precise mechanism of action of HIV-1 Vpr. There are changes induced by Vpr to protein modulators and mediators of signaling pathways related to glycolysis and other energy processes, involved in cell cycle, cell death and DNA repair, mitochondrial activity and redox homeostasis. Cullin-RING ligases (CRLs) comprise a large group of modular eukaryotic E3 ubiquitin ligases. DCAF1 was originally discovered as the cellular target of the HIV-1 accessory protein viral protein r (Vpr), hereafter was originally named Vpr binding protein (VprBP) [51]. The substrate receptors for CRL4 have been termed DDB1 and CUL4-associated factors (DCAFs). The number of identified and putative DCAFs is in excess of 50 members and is likely to continue growing.

Conclusion

A fundamental concept to the biology of restriction factors is that HIV-1 generally evades their potent inhibitory activities in human

cells, thereby allowing virus replication to proceed efficiently. Viruses need to counteract intrinsic antiviral factors that restrict viral replication in host cells and for this purpose lentiviruses might have acquired accessory proteins along their evolution. The understanding of the structure, function of these accessory proteins and their mechanisms of interaction with ligands in the host cell could be important for the development of new therapies for the HIV infection.

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