Dodging the Host Interferon-Stimulated Gene Mediated Innate Immunity by HIV-1: A Brief Update on Intrinsic Mechanisms and Counter-Mechanisms

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Host restriction factors affect different phases of a viral life cycle, contributing to innate immunity as the first line of defense against viruses, including HIV-1. These restriction factors are constitutively expressed, but triggered upon infection by interferons. Both pre-integration and post-integration events of the HIV-1 life cycle appear to play distinct roles in the induction of interferon-stimulated genes (ISGs), many of which encode antiviral restriction factors. However, HIV-1 counteracts the mechanisms mediated by these restriction factors through its encoded components. Here, we review the recent findings of pathways that lead to the induction of ISGs, and the mechanisms employed by the restriction factors such as IFITMs, APOBEC3s, MX2, and ISG15 in preventing HIV-1 replication. We also reflect on the current understanding of the counter-mechanisms employed by HIV-1 to evade innate immune responses and overcome host restriction factors. Overall, this mini-review provides recent insights into the HIV-1-host cross talk bridging the understanding between intracellular immunity and research avenues in the field of therapeutic interventions against HIV-1.

Keywords: HIV-1, restriction factors, PRR, viral counter mechanisms, ISG interferon stimulated genes, PAMP

INTRODUCTION

Human Immunodeficiency Virus-1 (HIV-1) causes Acquired Immuno Deficiency Syndrome (AIDS), one of the significant contributors to the death of adults worldwide. HIV-1 infection cycle begins with its fusion with the host cell membrane, leading to the release of the viral capsid core into the cytoplasm. The capsid core translocates to the nuclear pore complex by microtubule trafficking, from where it enters into the nucleus. In the nucleus, the capsid core undergoes uncoating, and the reverse-transcribed viral genome integrates into the host genome, forming provirus, allowing transcription and translation of viral genes (1–3). Viral proteins and RNA along with several host proteins, assemble at the plasma membrane and are released as virions. Interferons (IFNs), induced upon viral infection, are the major players in innate defense pathways against any virus. IFN signaling culminates in the transcription of interferon-stimulated genes (ISGs), many of which function as host restriction factors (RFs), which hinder almost every step of the viral life cycle. Thus, IFN signaling is the core of innate defense mechanism against viruses in general. The RFs directly interact with viral components, precluding viral replication, creating an antiviral state in the infected host cell. On the other hand, the evolutionary success of HIV-1 pathogenesis owes to its intricate strategies that block host RFs using its encoded components, such as Vpr (4), Vpu (5), Vif (6), and Nef (7). HIV-1 also targets components of IFN signaling, limiting the expression of RFs. In this mini-review, we deliberate on interferon induced innate mechanisms against HIV-1 infection, exemplified by IFITM (Interferon Induced Transmembrane) proteins, APOBEC3 (**Apo**lipoprotein **B** mRNA **E**diting enzyme **C**atalytic polypeptide like-**3**) proteins, MX2 (Myxovirus resistance-2), and ISG15 (Interferon Stimulated Gene-15) and highlight the current knowledge on the counter-mechanisms by which HIV-1 curtails the induction of innate cascade signaling as well as the restrictions posed by the RFs.

INNATE ANTIVIRAL RESPONSES AND INTRINSIC RESTRICTION OF HIV-1 INFECTION

Pattern Recognition Receptors (PRRs) in the host cell sense Pathogen-Associated Molecular Patterns (PAMPs) to drive IFN-mediated immune responses against viruses including HIV-1 (8). Several PAMPs associated with HIV-1 have been identified, which include capsid-shell, genomic RNA, reverse transcription products such as RNA-DNA hybrids, ssDNA and dsDNA, and proviral transcripts, such as, intron containing viral RNA, suggesting the occurrence of PAMPs during both early (pre-integration) and late steps (post-integration) of HIV-1 replication. These PAMPs are sensed by PRRs/sensors including Toll Like Receptors (TLRs), Retinoic acid Inducible Gene-I Like Receptors (RLRs) and DNA sensors in the HIV-1 infected cells. This section highlights the mechanisms by which host cell senses PAMPs associated with HIV-1 by using different PRRs to activate innate signaling cascade to induce ISGs and the restriction mechanisms mediated by RFs.

HIV-1 PAMPs and Associated PRRs

During its replication, HIV-1 exposes numerous PAMPs that are recognized by different PRRs present either in the endosomal compartment or cytosol of infected cells. HIV-1 RNA (both genomic RNA and newly synthesized RNA) has been reported to activate RNA-sensors and thus downstream innate signaling cascade.

It is now evident that HIV-1 genomic RNA alone can induce ISGs in peripheral blood mononuclear cells (PBMCs), and macrophages, and that this induction is mediated by cytosolic sensor RIG-I and its adaptor Mitochondrial Associated Viral Sensing protein (MAVS). The determinants of this induction have been identified to be secondary structures of genomic RNA as they were sufficient to induce innate immune responses as full-length genomic RNA (9). In addition to RIG-I, endosome associated PRRs may also act as sensors of HIV-1 genomic RNA. For example, both TLR7 and TLR8 were shown to be required to sense either HIV-1 genomic RNA or its derivatives such as U-rich oligonucleotides in the activation of innate immune signaling (10, 11). Since these studies largely used transfection-based assays to deliver HIV-1 RNA or its oligonucleotide derivatives, it was not clear whether innate immune activation requires virion associated RNA or newly transcribed RNA upon infection. Recent elegant studies conducted in dendritic cells, macrophages, microglia and CD4+T-cells showed that the transcription of viral RNA from provirus and transport of intron-containing RNA (icRNA) mediated by Chromosomal maintenance 1 (CRM1) were required for the induction of ISGs (12–14). These studies further revealed that HIV-1 encoded proteins do not play any role in inducing innate immune signaling. Though, the PRR responsible for the recognition of the newly transcribed icRNA is not yet identified, the adaptor MAVS seems to play an important role in the activation of innate immune signaling mediated by icRNA (13). In addition, abortive transcripts from provirus also seem to induce innate immune cascade. For instance, DEAD box helicase DDX3, a member of RLRs, was shown to bind to abortive viral transcripts and activate antiviral immune response *via* MAVS (15). Therefore, it is suggested that DDX3 or other unidentified RNA sensor(s) may be responsible for MAVS mediated innate immune activation through recognition of icRNA.

As mentioned earlier, the reverse transcription products may act as PAMPs to activate DNA sensors including cyclic GMP-AMP synthase (cGAS) and IFN-γ induced-16 (IFI16). cGAS is a widely studied PRR among the DNA sensors that detects reverse transcripts of HIV-1 (16–18). It was shown that cGAS binds to stem loop structures of ssDNA of HIV-1 in a sequence specific manner, which ultimately results in the activation of innate immune response (19). Although, both reverse transcription and integration of viral DNA seems to be required for the activation of cGAS, the identity of HIV-1 ligand detected by cGAS post integration is not known (17, 18). Similarly, IFI16 is shown to bind to stem loop regions of viral ssDNA and activate

the stimulator of interferon gene (STING)-IFN regulatory factor (IRF)-3/7 signaling axis in macrophages (20). Besides, IFI16 senses incomplete HIV-1 reverse transcripts accumulated in the abortively infected CD4+ T-cells and activates caspase-1 resulting in pyroptosis, suggesting the critical role of IFI16 in killing HIV-1 infected cells (21). Taken together, DNA sensors play a crucial role in the innate immune activation against HIV-1. Further, the components present in the viral inoculum *per se* (devoid of HIV-1) also induce ISGs, though not comparable to that of HIV-1 (22). These viral-associated components, primarily extracellular vesicles, seem to activate ISGs transiently, unlike HIV-1, which induces ISG persistently and predominantly. Though IRF1 was shown to be essential for the transient induction of ISGs by extracellular vesicles associated with HIV-1, PRRs for these vesicles and how HIV-1 deals with transiently expressed ISGs are yet to be identified. All the HIV-1 induced innate pathways mediated by PRRs lead to the induction of ISGs that encode antiviral factors, including RFs (23).

RFs That Block HIV-1 at Different Steps of Its Life Cycle

RFs induced by IFNs include IFITM proteins, TRIM5α (Tripartite motif-containing protein-5), APOBEC3 proteins, SAMHD1 (SAM and HD domain containing protein 1), MX2, ISG15, SERINC (serine incorporator)-3/5, Schlafen11, ERManI (endoplasmic reticulum α1,2-mannosidase-I), TSPO (Tryptophan-Rich Sensory Protein), ZAP (Zinc-finger antiviral protein), GBP5 (Guanylate binding protein-5) and BST2 (Bone marrow stromal cell antigen-2)/Tetherin (24–26) (**Table 1**). While the mode of antiviral action of several RFs such as IFITMs, MX2, Schlafen11, ZAP, ERManI, GBP5 and ISG15 is known, the associated counter mechanisms by HIV-1 are still not clear. To exemplify, we discuss one representative RF at each stage of HIV-1 infection cycle.

Entry

IFITMs mediated antiviral activity ranges from inhibition of viral entry to inhibition of viral protein synthesis, suggesting their broad spectrum of action (27, 69, 70). Specifically, IFITM2 and IFITM3 avert viral entry, while IFITM1 prevents Gag production (70). Further, the IFITMδ20 isoform also causes selective restriction of the tropic variant, X4-virus, which is abundant during the late phase of HIV-1 infection (71).

Reverse Transcription

APOBEC3 family proteins, APOBEC3C, APOBEC3D, APOBEC3F, APOBEC3G, and APOBEC3H, show potent restriction of Vif deficient HIV-1 (72–74). APOBEC3G requires both deaminase-dependent (causing mutations in viral cDNA) and independent mechanisms (attenuating reverse transcriptase activity) to exert its antiviral activity against HIV-1 (75–78). Though APOBEC3F is induced along with APOBEC3G among other ISGs, its antiviral activity does not appear to depend on deaminase catalytic activity to the extent required by APOBEC3G (79) and is packaged into virions (80).

Nuclear Entry

MX2 or MXB, another IFNα-induced ISG reduces nuclear accumulation of viral DNA in the nucleus of infected host cells without affecting the reverse transcription indicating its antiviral role at early stages of HIV-1 infection (56, 57). MX2 also prevents the uncoating of the viral capsid, leading to the abrogation of HIV-1 infection (58). HIV-1-Capsid (CA) mutations that allow alternative entry into the nucleus or abrogating MX2-Capsid interactions make the virus resistant to MX2, suggesting MX2 exerts its antiviral role through interaction with CA (56, 58).

Viral Budding and Release

ISG15 is a ubiquitin-like protein and the highest expressed ISG (81). ISG15 prevents both assembly and release of HIV-1 virions in producer cells (63, 64). Though the ISGylation (conjugation to targets) of HIV-1 viral components is not known, ISG15 blocks ubiquitination of viral Gag and host tumor susceptibility gene Tsg101 (a component of ESCRT-I), affecting virion assembly and release (63). It also disrupts the interaction between VPS4 and LIP5, which is a part of the endosomal sorting complex required for membrane budding and release of HIV-1 virions (64).

Increased expression of RFs upon HIV-1 infection ensures an effective antiviral restriction state in the infected cell; especially when HIV-1 imposes down-regulation of RFs by targeting them for degradation as one of the counter-mechanisms.

COUNTER MECHANISMS BY HIV-1 TO EVADE INTRACELLULAR INTRINSIC IMMUNITY

Like other viruses, HIV-1 utilizes its proteins, either directly or through modulation of the host machinery to dodge the restrictions imposed by the innate immune responses. These immune evasion strategies include escaping from being recognized by PRRs to degrading PRRs or their adaptors or RFs. The following section highlights the various counter mechanisms employed by HIV-1 to dodge the innate immune responses involving RFs.

Escaping Recognition by PRRs: Host-Directed HIV-1 RNA Modification

Host RNA methyltransferases help innate sensors to distinguish endogenous RNA from foreign exogenous RNA by methylating at specific sites on host RNA, including mRNA, tRNA, rRNA, and noncoding RNA. HIV-1 modifies its genomic RNA by exploiting host methyltransferase machinery to escape detection from cytosolic RNA sensors (39–42). It is now evident that the host 2-O-methyltransferase FTSJ3 is recruited with the help of TAR-RNA Binding Protein (TRBP) to HIV-1 genomic RNA. The methylation of HIV-1 RNA prevents innate immune recognition (40). 2-O methylated HIV-1 RNA is not sensed effectively by the cytosolic RNA sensors Melanoma-Differentiation-Associated Gene 5 (MDA5) and RIG-I.

TABLE 1 | The antiviral host defense mechanisms and HIV-1 counteractive measures in infected host cells.

S.No	Host factor involved	Host antiviral pathway	HIV-1 modulating factor	HIV-1 imposed counter mechanism	Other viruses	References
1	IFITM family	Inhibits fusion of virion with host membrane	Nef	Selective tropic variants resistant to IFITM	Influenza, Measles	(26–28)
2	SERINC 3/5	SERINC 3/5 incorporated into virion particles compromises their fusion with new target cells. Also, they induce differentiation of cells to myeloid lineage	Nef	Downregulation of SERINC 5	Several retroviruses (MLV, EIAV)	(28–30)
3	SAMHD1	Interferes with RT by degrading cytoplasmic dNTPs	Vpr	Degrades SAMHD1	Other retroviruses including FIV, BIV, MLV, EIAV and M-PMV;vaccinia, Herpes	(28, 31)
4	APOBEC3 family	Cytidine deamination during reverse transcription	Vif, Vpr	Degradation of APOBEC3 proteins	Retroviruses, HBV	(28, 32–38)
5	RNA-sensor RIG-I	Activation of ISGs		Modification of viral genome Degradation of RIG-I	West Nile virus, Japanese Encephalitis virus, influenza A, Sendai virus, flavivirus, coronaviruses, picornavirus, coxsackievirus B3, chikungunya virus and enterovirus 71	(39–46)
			PR			
	RNA or DNA sensor	Activation of ISGs	CA	Cloaking of viral genome		
6	DDX3	Activation of ISGs	Gp120	Inhibition of recruitment of TRAF3 to MAVS	Inhibits RT in HBV; HCV and Pox virus	(15, 47, 48)
7	TBK-1	Activation of ISGs	Vpr and Vif	Inhibition of TBK1 activation	Several DNA and RNA viruses	(49, 50)
8	IRF3	Activation of ISGs	Vif, Vpr and Vpu	Degradation and inhibition of IRF3 localization into the nucleus	Sendai virus, human herpes virus, Newcastle Disease Virus, cytomegalovirus, vaccinia	(51–55)
9	MX2	Inhibits nuclear accumulation of viral DNA	Unknown	Mutations in capsid	Myxovirus, herpes viruses,	(28, 56–58)
10	Schlafen11	This interferon-stimulated gene may block protein production from non-codon optimized transcripts by binding to tRNA. Acts at late stage of HIV infection to suppress viral protein production	CA and other factor?	Unknown	EIAV, flaviviruses, Herpes virus	(28, 59–62)
11	ZAP	The Zn fingers bind to CpG dinucleotides in viral mRNAs causing translational repression	Unknown	Unknown	Retroviruses, alphaviruses, filoviruses, and HBV	(26, 28)
12	ISG15	Blocks ubiquitination of viral Gag and Tsg101, affecting virion assembly and release	Unknown	Unknown	CMV, HTLV, influenza, Sindbis, respiratory syncytial virus, dengue and several others	(63–65)
13	ERManI/TSPO	Causes misfolding of Gp160	Vpr	Unknown	Influenza virus	(26, 66)
14	GBP5	Interferes with the activity of furin (cellular protease) causing defects in processing envelope and incorporation	Unknown	Unknown	MLV, Influenza, Zika, Measles	(28)
15	BST2/Tetherin	Virion release	Vpu, Nef	Degradation of tetherin	Retroviruses, herpes- viruses, filo-viruses, VSV and SARS coronavirus	(5, 28, 67, 68)

The table lists the host factors involved in host restriction mechanisms against HIV-1 and the counteractive measures exhibited by HIV-1. HIV-1 either hijacks host machinery or employs its encoded proteins to inhibit or degrade the first line of defenses that include antiviral/restriction factors encoded by ISGs. Other viruses that are restricted by similar host factors are also mentioned. Refer to text for details.

In HIV-1-infected dendritic cells and macrophages, the adenosine methylation (N6-methyladenosine) of HIV-1 genomic RNA correlated with resistance against IFN-mediated immune responses (39). The cellular writers, such as methyltransferase-like METTL3 and METTL14, add a methyl group to adenosine and erasers, such as fat mass and obesity-associated protein (FTO) and α-ketoglutarate dependent dioxygenase AlkB homolog-5 (ALKBH5), remove the methyl groups from mRNA. The HIV-1 produced by HEK293T cells overexpressing FTO or ALKBH5 enhanced induction of IFNs in the target cells by decreasing adenosine methylation in its genome and thus preventing the activation of IRF3 and IRF7, suggesting the importance of host-directed HIV-1 RNA modification in the immune evasion strategy (39).

Cloaking the Viral Genome

Another immune evasion strategy involves cloaking the viral genome through the interaction of HIV-1 CA with host cofactors such as CPSF6 and cyclophilin domain-containing proteins. The CA mutants, N74D and P90A that disrupt the interaction of CA with CPSF6 and cyclophilins, respectively, were unable to replicate in primary monocyte-derived macrophages, unlike wild-type CA (44). This inability to replicate is consistent with increased expression of IFNs and ISGs in the cells infected with HIV-1 CA mutants (N74 and P90A), suggesting that the evading strategy involves interaction between HIV-1 CA and its cofactor(s).

Degradation/Obstruction of Host Factors Associated With Antiviral Pathways

Transcription Factor That Controls Multiple IFN-Inducing Pathways (IRFs)

HIV-1 promotes the degradation of IRF3 as do several other viruses as it is a central transcription factor in the IFN signaling pathway. However, there are contrasting evidence of its mechanism of inhibition of IRF3, promoting efficient viral replication in the target cells, including CD4+T- and myeloid cells. While HIV-1 accessory proteins, Vpr and Vif, degrade IRF3 *via* proteasome pathway (52), HIV-1 Vpu interacts and promotes IRF3 degradation through endolysosome (53). Another study in 293T and Jurkat cell lines argued that Vpu does not colocalize with IRF3 and does not require endolysosome for IRF3 degradation; instead, it involves the activation of caspase-8 to cleave IRF3 (54). The latter study also suggested that Vpr and Vif also mediate caspase-8 dependent IRF3 cleavage. Contrary to that, Manganaro et al. identified that Vpu rather acted as an inhibitor of NFκB, which also results in the activation of ISGs but did not induce degradation of IRF3 and that Vpu played no role in the regulation of IRF3 mediated pathway (82). Recently, Khan et al. demonstrated that HIV-1 Vpr inhibits cGAMP activated IRF3 translocation to the nucleus and promoted the replication of HIV-1 in myeloid cells. They further showed that Vpr localized to the nuclear pore complex, prevented the interaction of karyopherins with IRF3 and NFκB, which is required for their transport into the nucleus. Subsequently, this immune inhibitory mechanism by Vpr was shown to be dependent on the cofactor DCAF1, a substrate receptor of Cullin-4 RING E3-Ubiquitin ligase (CRL4) (55). While most transcription factors are degraded by HIV proteins, Vpu stabilises host ISGs such as p53 that leads the host cell towards apoptosis in the late stage of infection (83).

PRR Levels and Their Activity

To further weaken the innate intracellular immunity, HIV-1 also targets PRRs and their adaptors. HIV-1 escapes detection by RIG-I by promoting its degradation in a HIV-1 protease (PR)-dependent manner in monocyte-derived macrophages (43). Surprisingly, protease activity of PR *perse* was not involved in the degradation of this RNA sensor, but the presence of PR was required for the relocalization of RIG-I from cytosol to lysosomes, wherein RIG-I undergoes degradation (43). Further, HIV-1 targets Tank Binding Kinase-1 (TBK1), an adaptor of the IFN signaling pathway. While the ubiquitination of TBK1 was not affected, the phosphorylation of TBK1 required for signal cascade activation was prevented. Accessory proteins, Vpr and Vif have been shown to prevent TBK1 activity and thus downstream signaling (50). Further investigation is required to address how these viral proteins inhibit the autophosphorylation of TBK1.

Restriction Factors (RFs)

HIV-1 uses its accessory proteins such as Vif, Vpr, Vpu, and Nef to overcome the restriction imposed by host RFs (**Table 1**). HIV-1 Vif-mediated counter mechanism against APOBEC3G has been the subject of study for the last two decades. It was shown that Vif prevents the antiviral activity of APOBEC3G by promoting its degradation *via* 26s proteasome (32). In addition, later studies suggested that Vif also reduces the levels of APOBEC3G by inhibiting translation of mRNA encoding this protein and transcription of the gene, APOBEC3G, probably by competing with host transcription cofactor CBFβ, which otherwise binds and activates this gene (33, 34). Vif also affects the incorporation and deaminase activity of APOBEC3G, suggesting the multiple ways by which it interferes with RF activities (35–37). In addition, Vpr promotes the degradation of APOBEC3G with the help of its binding protein, VprBP, suggesting a common antiviral pathway affected by two HIV-1 proteins (38). Initial reports regarding the antagonism between HIV-1 Vpu and RF tetherin showed that Vpu binds and promotes internalization of membrane-associated tetherin through their transmembrane interactions, which leads to beta transducing repeat-containing protein (TrCP2) dependent degradation (5). Furthermore, Vpu, through its cytoplasmic domain, is also suggested to displace tetherin from the sites of viral assembly leading to counteracting tetherin-mediated antiviral effect (67). The anti-tetherin role of Vpu has also been associated with IFN resistance by HIV-1 (68).

Serine Incorporator protein 5 (SERINC5) is another potent RF, but not induced by IFN that gets packaged into virions in producer cells and prevents viral fusion with the target cell (29, 30, 84). HIV-1 Nef counteracts this inhibition by promoting SERINC5 trafficking into the endosomal compartment for degradation, thus reducing intracellular SERINC5 in producer cells (29, 30).

DISCUSSION

A summary of the various intrinsic mechanisms of host antiviral defense and the counter-mechanisms by HIV is presented through a comprehensive schematic representation (**Figure 1**). The interplay between the host innate intrinsic mechanisms and its counter mechanisms by HIV-1 influences the outcome of HIV-1 infection. RFs play a crucial role in inhibiting the critical steps of HIV-1 replication and thus viral production as part of innate intrinsic mechanism. These RFs are induced along with other antiviral factors during HIV-1 infection upon interaction
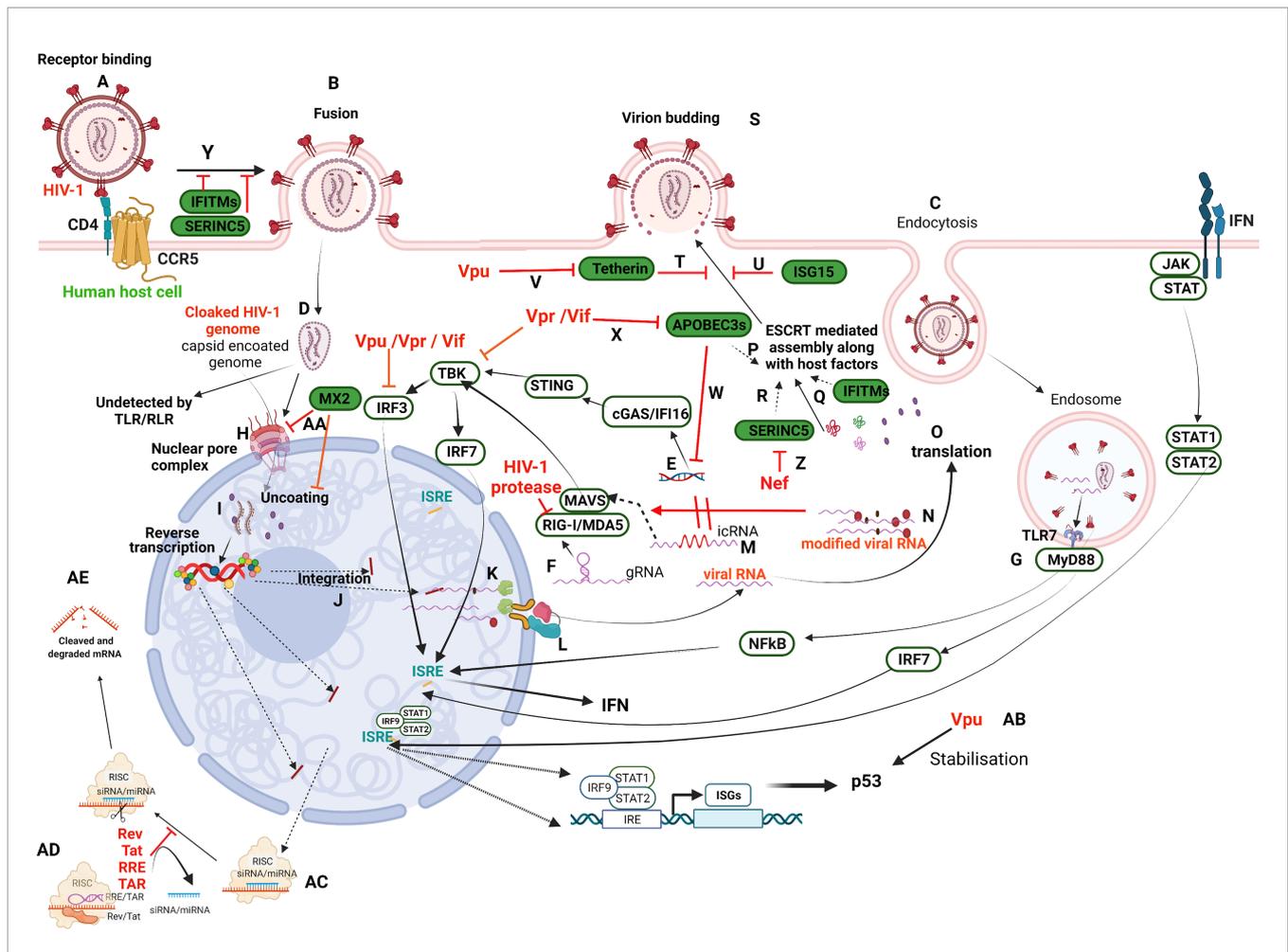
FIGURE 1 | Schematic illustration of HIV-1 infection in a target human host cell and the interception of host restriction pathways by various HIV-1 proteins. HIV-1 infects CD4+ host cells using either of the co-receptors, CCR5 or CXCR4 (here CCR5) **(A)** to fuse with the plasma membrane **(B)** or undergoes receptor-mediated endocytosis **(C)** and various other modes (not in the scope of the present review). Irrespective of the mode of entry, the viral capsid-coated core is released into the cytoplasm **(D)**. Any viral nucleic acids, probably by leakage/disassembly of capsid core, would trigger the pattern recognition receptors present either in the cytosol, such as IFI16 and cGAS **(E)** that recognize viral DNA, or RLRs (RIG-I/MDA5) that recognize viral RNA **(F)**, as well as in endosomes such as TLRs (TLR7) that recognize viral RNA **(G)**. However, the cloaked (coated by capsid) genome escapes recognition by these receptors and enters the nucleus through the nuclear pore complex (NPC) **(H)**. The new school of thought concerning early events of the HIV-1 life cycle is that reverse transcription and uncoating occur in the nucleus **(I)** against the classical theory of these events in the cytoplasm. Once integrated **(J)**, the viral transcripts are made from pro-viral DNA with some incompletely/partially spliced and some completely spliced **(K)**. All the viral transcripts are exported from the nucleus with the hijacked host RNA transport machinery **(L)**. The incompletely spliced intron-containing RNA transcripts (icRNA) are recognized by PRRs in cytosol **(M)** that activate either IRF3 or IRF7 through MAVS. However, the IRF3 activation is inhibited by viral proteins, Vpu/Vpr/Vif. The viral RNA is modified by exploiting the host RNA methyltransferase machinery **(N)** to evade RLR recognition (RIG-I and MDA5). Besides, RIG-I is also targeted by HIV-1 protease. The viral transcripts are translated to produce regulatory proteins (Rev, Tat), accessory proteins (Vpr, Vif, Vpu, Nef) and structural and enzymatic polyproteins (Gag, Pol, Env) **(O)**. The viral proteins and its genome are assembled into budding virions along with host factors that include RFs (APOBEC3s, **(P)**; IFITMs, **(Q)**; SERINC5, **(R)** using host machinery, ESCRT. Viral budding occurs from the host plasma membrane **(S)**, which is targeted by Tetherin **(T)** and ISG15 **(U)**. The viral protein Vpu targets Tetherin **(V)**. APOBEC3s inhibit reverse transcription of viral RNA **(W)** and are targeted by Vif/Vpr **(X)**. IFITM and SERINC5 incorporated into virion inhibit receptor binding and thus fusion **(Y)**. SERINC5 is degraded by Nef **(Z)**. The host factor MX2 inhibits the nuclear import of DNA and uncoating steps in the viral life cycle **(AA)**. Vpu stabilises host ISGs such as p53 that leads to apoptosis of the infected cell **(AB)**. RRE/TAR and Rev/Tat bind to TRBP in the miRNA loaded RISC complex **(AC)** to displace siRNA/miRNA from RISC complex resulting in suppression of RNAi **(AD)** that otherwise leads to activation of RISC signalling and cleavage of transcripts **(AE)**. Refer to text for details. This representative figure reflects several possible pathways and is not intended to reflect the changes in a single cell. Created with BioRender.com

of PAMPs with host PRRs. Despite the antiviral state created by these mechanisms, HIV-1 counteracts and survives inside the infected cell. To this end, HIV-1 directly targets host RFs for degradation (85) or interferes with innate immune signaling cascade that otherwise induces RFs through Vpr, Vif, Vpu, and Nef or host machinery (**Figure 1**). Furthermore, it is still not

clear how HIV-1 evades the restrictions posed by several RFs including MX2 and ISG15. Besides, HIV-1 hijacks host factors that enhance viral productivity, such as Staufen-2 (86), ZNF134 (87); CPSF6 (88–90) Nup153 (91); KIF5B and Nup358 (92). Although certain RFs such as SAMHD1, tetherin, and cholesterol-25-hydroxylase are shown to dampen the innate

immune responses, it is not clear whether HIV-1 regulates these RFs for its replication (31, 93, 94). Additionally, it is debated that whether host RNA interference (RNAi) contributes to immune responses against HIV-1. Nevertheless, several miRNAs are differentially regulated in HIV-1 elite controllers as compared to typical progressor patients, suggesting that HIV-1 interferes with host RNAi (95). HIV-1 manipulates host RNAi mechanisms through its RNA elements such as RRE (Rev Response Element) and TAR (Trans Activation Response) as well as Rev and Tat proteins. It was demonstrated that both RRE RNA and TAR elements compete with siRNA to bind to TAR-RNA Binding Protein (TRBP), which is an essential component of the RNA Induced Silencing Complex (RISC), displacing siRNA from TRBP and thus suppressing RNAi (96). On the other hand, the ability of HIV-1 Tat and Rev to suppress host RNAi was traced to the linear Arginine rich motif (ARM) that can bind to RISC loading complex component, TRBP, which otherwise binds to the target mRNA (97). Further studies are required to decipher whether RNAi suppressor activity by HIV-1 contributes to the downmodulation of innate immune responses. Although siRNA is emerging as a powerful therapeutic tool for several viral diseases, in case of HIV, the situation is more complex as it creates a selection pressure for generation of mutants that are resistant to siRNA silencing, apart from its natural tendency to suppress RNAi mechanisms.

An important observation is that not all human cells that allow HIV-1 infection permit viral replication. While host cells such as T-cells and macrophages are a haven for HIV-1 propagation, some non-immune cells such as astrocytes tend to restrict their propagation, allowing the establishment of latency in these reservoir cells. It is possible that cell specific RFs or their level of expression might contribute to the establishment of latency, a major obstacle in the treatment of HIV-1 infected patients. Thus, the studies which reveal the molecular events underlying the restriction mechanisms and factors involved therein, will help in designing strategies to eradicate latency and thus infection in patients.

AUTHOR CONTRIBUTIONS

KC and SB conceptualized the manuscript. KC, KM, and SB wrote the paper. KM made the figure. KC, KM, and SB critically analyzed all the information provided. All authors contributed to the article and approved the submitted version.

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