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REVIEW

Human Immunodeficiency Virus, Restriction Factors, and Interferon

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Recent discoveries have revealed previously unappreciated complexity with which retroviruses interact with their hosts. In particular, we have become aware that many mammals, including humans, are equipped with genes encoding so-called "restriction factors," that provide considerable resistance to retroviral infection. Such antiretroviral genes are sometimes constitutively expressed, and sometimes interferon-induced. Thus they can be viewed as comprising an intrinsic immune system that provides a pre-mobilized defense against retroviral infection or, alternatively, as a specialized extension of conventional innate immunity. Antiretroviral restriction factors have evolved at an unusually rapid pace, particularly in primates, and some startling examples of evolutionary change are present in genes encoding restriction factors. Our understanding of the mechanisms by which restriction factors interfere with retroviral replication, and how their effects are avoided by certain retroviruses, is accruing, but far from complete. Such knowledge could allow for novel forms of therapeutic intervention in pathogenic retroviral infections, as well as the development of animal models of human disease.

Introduction

Recent discoveries have revealed a previously unappreciated complexity with which HIV-1 and related retroviruses interact with their hosts. In particular, we have become aware that many mammals, including humans, are equipped with genes encoding so-called "restriction factors," that provide considerable resistance to infection by HIV-1 and other retroviruses. Because antiretroviral genes are sometimes constitutively expressed, they can provide an intrinsic pre-mobilized system of defense against retroviral infection (Bieniasz 2004; Wolf and Goff 2008). In addition, in some cell types and tissues, the expression of antiretroviral genes can be up-regulated by type I interferons, suggesting they form part of the inducible innate immune system. The importance of restriction factors in the replication and pathogenesis of retroviruses is underscored by the mechanisms that some have evolved in order to evade the antiviral activity of these proteins. The array of restriction factors that are known to be active against HIV-1 have evolved at an unusually rapid pace, particularly in primates, and some startling examples of evolutionary change are present in genes encoding them. Our understanding of the mechanisms by which restriction factors interfere with retroviral replication, and how their effects are avoided by HIV-1 in human cells, is accruing, but far from complete. Such knowledge could allow for novel forms of therapeutic intervention in HIV/AIDS, as well as the development of animal models of the disease. Here, we briefly review current progress in studies of antiretroviral genes that can inhibit HIV-1, emphasizing recent advances, questions that are yet to be resolved, and their relationship to the wider innate immune system.

The Concept of Retroviral "Restriction" and Historical Perspectives

Until the last decade, the species-specific and tissue tropism of retroviruses was thought to depend largely on whether or not a given cell type provided factors and conditions that are required for optimal replication completion of the viral life cycle (reviewed in Goff 2007). For example, a failure to replicate in a given cell type could often be ascribed to failed viral entry due to the absence of a specific cell surface receptor, or species-specific differences in receptor molecules that render them unable to support infection. Alternatively, once inside the cell, a retrovirus might encounter conditions, such as low concentrations of deoxyribonucleotides, which are not conducive for reverse transcription of the viral genome. In some cases, mitosis is required for entry into the nucleus, and the viral genome cannot traverse the nuclear membrane in nondividing cell types. At the level of

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gene expression, retroviral replication might then be halted because the correct transcriptional machinery is not in place to mediate synthesis of retroviral mRNAs. Finally, essential cellular factors required for the building and release of new viral particles again might be expressed in a tissue-specific manner or vary in species-specific ways. Investigations of all aspects of restricted retroviral tropism have resulted in the identification of a range of cellular factors that are required for the replication of retroviruses. Indeed, throughout the quarter century of HIV-1 research, the notion that the presence or absence of required factors governs HIV-1 tropism has been particularly informative in unraveling HIV-1–host cell interactions. However, more recent studies have indicated that the lack of expression essential factors did not explain at least some facets of HIV-1 tropism.

The concept that there might be innate and/or intrinsic cellular inhibitors of retroviral replication originated with studies showing that it was possible to isolate inbred mouse strains that were resistant to leukemia induced by specific variants of Friend murine leukemia virus (MLV). These studies demonstrated that there were several "Friend virus susceptibility" (Fv) loci that could give rise to inherited "immunity" to retrovirus-induced disease (Lilly and Pincus 1973). Crucially, at least 2 of these loci, Fv1 and Fv4, were dominant and could inhibit MLV replication in cell culture. While Fv4 encodes an endogenous MLV-like virus whose envelope protein directly interferes with exogenous viral entry (Ikeda and others 1985), Fv1 was more interesting in that was shown to encode a cellular protein with homology to an endogenous retroviral structural protein, Gag (Best and others 1996). Fv1 blocks the replication of sensitive MLV isolates by targeting incoming viral capsids (DesGroseillers and Jolicoeur 1983), inhibiting a step after reverse transcription, but prior to provirus integration. However, its precise mechanism of action is yet to be determined.

For some years, Fv1 remained the sole identified example of an antiretroviral restriction factor. However, beginning in the late 1990s, evidence that specific restriction factors could inhibit HIV-1 replication began to accumulate. These findings were based on investigations of restricted tropism that could not be explained by the absence of necessary factors for HIV-1 replication. A key experimental tool was the use of heterokaryons formed between "permissive" cells (ie, cells where HIV-1 replication proceeded normally) and "nonpermissive" cells (where replication was restricted at a specified step). In a number of cases, the heterokaryons were nonpermissive, implying the existence of dominant factor therein that inhibited HIV-1 replication (Simon and others 1998a; Cowan and others 2002; Münk and others 2002; Varthakavi and others 2003). This type of heterokaryon experiment was used to infer the existence of capsid-specific restriction factors in monkey cells that blocked early events of HIV-1 in replication (Cowan and others 2002; Münk and others 2002), as well as restriction factors that imposed a requirement for particular HIV-1 accessory genes (Madani and Kabat 1998; Simon and others 1998a; Varthakavi and others 2003). Specifically, all lentiviruses, including HIV-1, encode accessory genes (*Vif, Vpr/Vpx*, *Vpu*, and *Nef* for primate immunodeficiency viruses) that are dispensable for virus replication in many "permissive" cultured cell lines. However, in some "nonpermissive" cell types, particularly in the primary cell targets of HIV/SIV, the absence of accessory genes can cause a marked defect in the production of infectious virion particles. In general, HIV-1 and SIVs lacking one or more of these accessory proteins are attenuated *in vivo* (Kestler and others 1991; Hirsch and others 1998). Heterokaryon experiments were instrumental in demonstrating that the HIV-1 Vif and Vpu genes facilitated replication by antagonizing the effects of antiviral restriction factors (Simon and others 1998a; Varthakavi and others 2003).

To date, 3 major types of antiretroviral restriction factor that are potentially capable of inhibiting HIV-1 replication have been identified (Sheehy and others 2002; Stremlau and others 2004; Neil and others 2008) (Fig. 1). Moreover, there are strong suspicions that other lentivirus accessory genes are also antagonists of restriction factors that are yet to be uncovered. Of particular interest, these restriction factors are constitutively expressed in some relevant cell types but can be induced by type I interferon in others.

The APOBEC3 Family of Cytidine Deaminases

The first host gene to be identified as an inhibitor of HIV-1 replication was found to encode a cytidine deaminase, whose expression was shown to define cells that were nonpermissive for replication of HIV-1 mutants lacking a functional Vif gene (Sheehy and others 2002). The genomes of primates contain an unusually large number of genes encoding cytidine deaminases, named after the prototype member of this family of enzymes—apolipoprotein B editing complex, catalytic subunit (APOBEC) (Harris and Liddament 2004). Subsequently, several members of the APOBEC3 family have been shown to inhibit the replication of HIV-1 and other retroviruses (Bishop and others 2004; Harris and Liddament 2004; Wiegand and others 2004; Yu and others 2004; OhAinle and others 2006), and an intense research effort has illuminated significant aspects of the mechanism by which these enzymes inhibit HIV-1 replication (Fig. 1). Specifically, APOBEC3 proteins can be incorporated into HIV-1 and other retrovirus particles, at least in part through interactions with RNA that is inevitably packaged therein (Schäfer and others 2004; Svarovskaia and others 2004; Zennou and others 2004; Wang and others 2007; Xu and others 2007), and carried by the virion to a new target cell. Thereafter, upon infection and generation of nascent minus strand retroviral DNA, APOBEC3 enzymes catalyze the deamination of deoxycytidines in a sequence context-based manner, generating minus strand DNA containing many deoxyuracil nucleotides whose replication results in plus strand G to A mutations (Harris and others 2003; Lecossier and others 2003; Mangeat and others 2003; Zhang and others 2003).

The various APOBEC3 enzymes exhibit varying degrees of antiretroviral activity, depending on which retrovirus is targeted and from which primate species the APOBEC3 protein is derived, with APOBEC3G being the most prominent and consistently active against retroviruses (Bishop and others 2004; Zennou and Bieniasz 2006; Virgen and Hatziioannou 2007). In general, APOBEC3-induced hypermutation of retroviral DNA can itself be lethal to a retrovirus through the deposition of many inactivating missense and nonsense mutations in protein-coding sequences. However, recent finding suggest that the mutator activity of APOBEC3 enzymes appears to constitute only a part of the mechanism by which antiviral activity is achieved (Newman and others 2005). From the outset, it was clear that the amount of viral DNA that accumulates during HIV-1 infection is reduced when incoming virions carry APOBEC3G, or its close

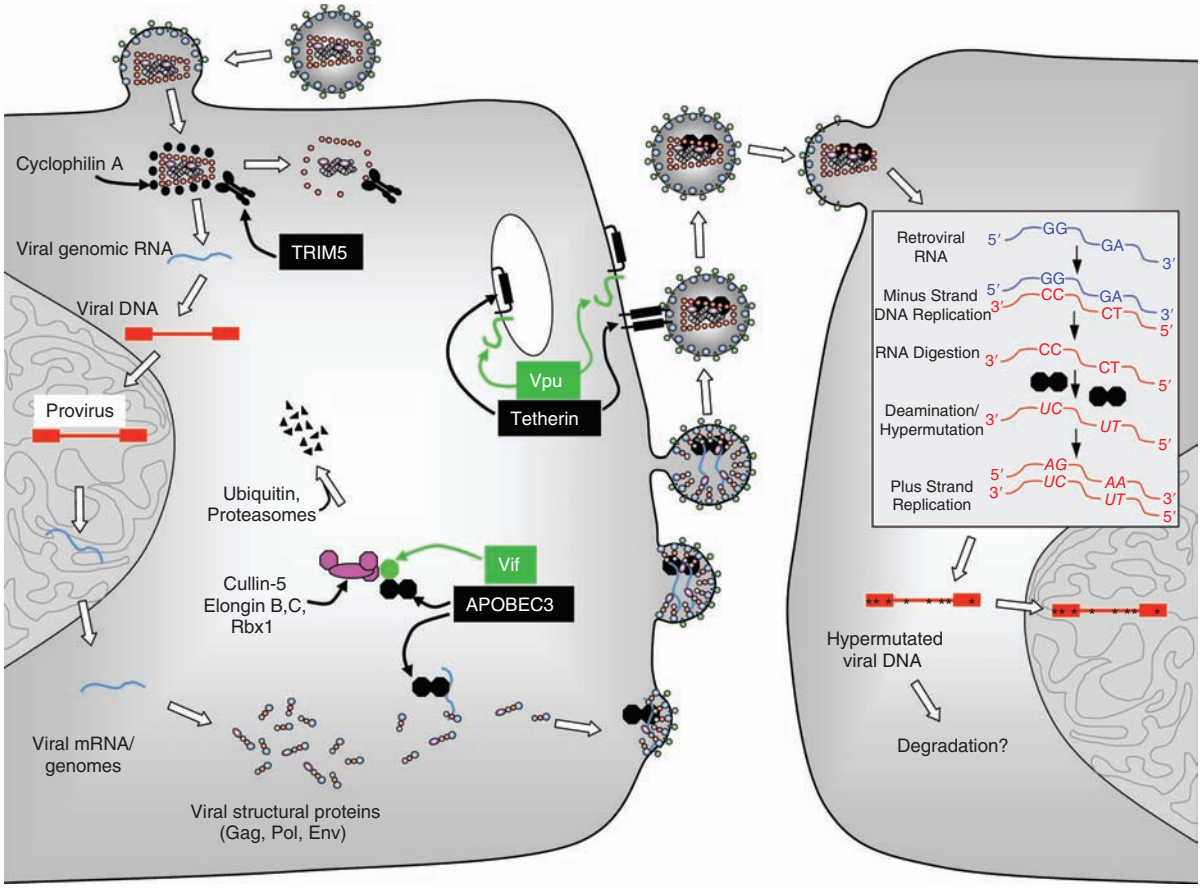

FIG. 1. Major host restriction factors capable of inhibiting HIV-1 replication, and their viral antagonists. TRIM5 recognizes incoming HIV-1 capsids and inactivates them; accelerated capsid disassembly accompanies the inactivating lesion. Cyclophilin A also binds to incoming capsids and can affect recognition by TRIM5. APOBEC3 proteins are cytidine deaminases, can be incorporated into assembling HIV-1 particles, and catalyze the deamination of nascent minus strand DNA during the subsequent round of infection. The HIV-1 Vif protein binds to APOBEC3 proteins, and also to a Cullin5-based ubiquitin ligase complex. This results in APOBEC3 protein ubiquitination and degradation in proteasomes. Tetherin is a cell surface protein that causes entrapment of nascent virions on the infected cell surface. Vpu antagonizes tetherin by sequestering tetherin from virions and by reducing the levels of tetherin on the cell surface.

relative APOBEC3F, and while this was reasonably postulated to be due to destruction of uracil-containing retroviral DNA (Schröfelbauer and others 2005), repair enzymes that are known to recognize uracil-containing DNA appear to be dispensable for the APOBEC3G antiviral activity (Kaiser and Emerman 2006). Moreover, the propensity of APOBEC3G and its close relative, APOBEC3F, to reduce viral DNA accumulation appears to be at least partly genetically separable from mutator activity, and mutants that lack cytidine deaminase activity possess residual antiretroviral activity (Newman and others 2005; Holmes and others 2007). Several studies have further suggested that APOBEC3 proteins can inhibit the replication of retroelements without causing their mutation (Bogerd and others 2006; Chen and others 2006b; Chiu and others 2006; Stenglein and Harris 2006; Hulme and others 2007), and that APOBEC3G can directly inhibit specific steps of HIV-1 reverse transcription or integration (Luo and others 2007; Mbisa and others 2007; Bishop and others 2008). However, no consensus has yet emerged as to what is dominant process by which APOBEC proteins inhibit viral or retroelement DNA accumulation, and how intimately connected is this effect cytidine deaminase activity. Nonetheless, in the case of APOBEC3G, enzymatic activity clearly increases the magnitude with which viral DNA accumulation is impaired and it is not completely clear that some of the cytidine deaminase-independent antiretroviral activities ascribed to APOBEC3 proteins occur at physiological levels of protein expression (Miyagi and others 2007; Schumacher and others 2008). Other studies have further elaborated the range of activities reported for APOBEC3G and suggest that it can function in target cells to block HIV-1 infection and that this underlies the resistance of certain cell types or cells in particular physiological states to HIV-1 infection (Chiu and others 2005; Chiu and others 2006). The molecular details of this mode of inhibition are completely unclear at present and the finding itself is controversial (Kamata and others 2009). Finally, in a fascinating re-evaluation of classical genetic resistance to Friend MLV-induced disease in mice, the recovery from Friend virus 3 (*RFv3*) gene has been identified as murine APOBEC3 (Santiago and others 2008; Takeda and others 2008). *RFv3* controls the ability of mice to produce neutralizing antibodies to F-MLV and clear plasma viremia (Hasenkrug and others 1995). The recessive allele of *RFv3* encodes a less active

APOBEC3 whose mRNA may be aberrantly spliced, and *Rfv3*-sensitive mice progress to erythroleukemia. Similarly APOBEC3-deficient mice exhibit an *Rfv3*-sensitive phenotype (Santiago and others 2008), and are also more susceptible to the betaretrovirus, mouse mammary tumor virus (MMTV) (Okeoma and others 2007). MLV has been shown to be at least partly resistant to murine APOBEC3 through exclusion from assembling virions (Doehle and others 2005), so how the antiretroviral activity of murine APOBEC3 relates to the *Rfv3* phenotype in F-MLV pathogenesis remains to be determined. However, these data suggest the possibility of linkage between APOBEC3 and downstream mobilization of adaptive immunity against a retrovirus. If this proves to be the case, then these findings clearly have wider implications for the role of these genes in HIV/AIDS.

TRIM5, a Capsid-Targeting Restriction Factor

TRIM5α was originally discovered as the gene product responsible for a series of dominant retrovirus restriction phenotypes that can be observed in human and nonhuman primate cells (Towers and others 2000; Besnier and others 2002; Cowan and others 2002; Münk and others 2002; Hatziioannou and others 2003; Owens and others 2003; Stremlau and others 2004). In particular, TRIM5α is responsible for the inability of HIV-1 to infect many old world monkey cells (Stremlau and others 2004), as well as the resistance of human and other primate cells to certain strains of MLV, and equine infectious anemia virus, a lentivirus (Hatziioannou and others 2004; Keckesova and others 2004; Perron and others 2004; Yap and others 2004). More recent studies have expanded the range of retroviruses that are potentially targeted by TRIM5 proteins to include betaretroviruses and foamy viruses (Diehl and others 2008; Yap and others 2008). Even before TRIM5α was discovered, it was clear that it represented an activity that targeted a range of incoming retroviral capsids, blocking infection before the establishment of a provirus in the target cell (Towers and others 2000; Besnier and others 2002; Cowan and others 2002; Münk and others 2002; Hatziioannou and others 2003) (Fig. 1). The activity was saturable by high amounts of challenge virus, and thus shared several characteristics with the aforementioned Fv1-induced resistance to MLV. Indeed, Fv1 and TRIM5 target overlapping determinants on the MLV capsid, although Fv1 appears to allow reverse transcription to proceed, while TRIM5α prevents retroviral DNA synthesis, in most cases.

The identification of TRIM5α as the protein responsible for the resistance of certain cells to HIV-1 (Stremlau and others 2004) enabled many detailed studies of its evolution and mechanism of action. However, because of the inherent technical difficulty in studying the particular step of the viral lifecycle targeted by TRIM5α, several aspects of how TRIM5α functions remain poorly understood. Nonetheless, we have a rudimentary understanding of the molecular details by which TRIM5 proteins block retroviral infection. Specifically, a C-terminal domain of the TRIM5α protein directly recognizes the incoming viral capsids (Sebastian and Luban 2005; Stremlau and others 2006a) and thereby governs antiretroviral specificity (Perez-Caballero and others 2005a; Stremlau and others 2005; Yap and others 2005; Perron and others 2006), while a central coiled-coil drives TRIM5α multimerization, which is essential for inhibition. An N-terminal "effector" domain markedly increases the potency with which TRIM5α inhibits infection, through unknown mechanisms (Javanbakht and others 2005; Perez-Caballero and others 2005a). The molecular events that lead to virus inactivation are not well understood, but it is apparent that an irreversible, lethal lesion in the incoming viral capsid occurs within minutes of entry of the viral capsid into the target cell cytoplasm (Perez-Caballero and others 2005b). The timing of this lesion significantly precedes the completion of viral DNA synthesis, and in most (but not all) cases, TRIM5α proteins inhibit the accumulation of retroviral DNA (Stremlau and others 2004; Ylinen and others 2005). One clear and highly suggestive observation is that TRIM5 proteins induce the premature disassembly of incoming retrovirus capsids (Stremlau and others 2006a). Curiously, however, the application of proteasome inhibitors prevents TRIM5-induced capsid disassembly and rescues TRIM5α-inhibited synthesis of viral DNA but does not reverse TRIM5α-inhibited infection (Wu and others 2006; Diaz-Griffero and others 2007). Thus, neither proteasome activity itself, inhibition of reverse transcription, nor accelerated capsid disassembly appears essential for TRIM5 to block retroviral infection. These observations leave significant mechanistic questions; unfortunately, probing the mechanism by which TRIM5α proteins work is not straightforward—biochemical and microscopic analysis of the events that follow retrovirus entry into the target cytoplasm is notoriously difficult. Nonetheless, the urge to understand how TRIM5 proteins work is providing additional impetus for the development of new biochemical and imaging assays to probe this heretofore comparatively impenetrable area of retrovirus biology (Stremlau and others 2006a; Campbell and others 2008).

Tetherin, an Inhibitor of HIV-1 Release

Recent work has identified an antiviral protein that works by a novel mechanism in that it can inhibit the release of HIV-1 particles from infected cells (Neil and others 2008; Van Damme and others 2008) (Fig. 1). This protein, termed tetherin (otherwise known as BST-2, CD317, or HM1.24) is a membrane protein, with unusual topology (Kupzig and others 2003). Specifically, it harbors a transmembrane anchor near its N-terminus, and a putative glycophosphatidyl-inositol lipid anchor at its C-terminus, which is essential for its antiviral function. Tetherin appears to induce the formation, and may be a component, of protein-based tethers that cause the retention of HIV-1 particles on infected cell surfaces (Neil and others 2006; Neil and others 2008) (Fig. 1). Interestingly, the retained particles are fully formed and mature and have independent lipid bilayers that are discontinuous with cell membranes (Neil and others 2006). Thus, tetherin seems to act after the formation of virus particles and prevents their dissemination to uninfected cells, perhaps simply by cross-linking the virion and cell membranes. Subsequently, tetherin-retained virions can be reinternalized into the infected cell and targeted to late endosomes, where they may be retained or destroyed by lysosomal enzymes (Neil and others 2006). Ordinarily, tetherin is expressed on a limited subset of cell types, but upon exposure to type I interferon, tetherin is broadly expressed (Blasius and others 2006), suggesting that it is part of a broader innate immune defense that limits the replication of, perhaps, many enveloped viruses. In fact recent data has shown that virus-like particles derived from

a wide range of retroviruses, as well as filoviruses and arenaviruses, are also similarly sensitive to tetherin (Neil and others 2007; Neil and others 2008; Jouvenet and others 2009; Kaletsky and others 2009; Sakuma and others 2009).

Antagonism of, and Adaptation to, Antiretroviral Genes by HIV-1

While the aforementioned restriction factors can impart very strong blocks at various stages of retrovirus replication, HIV-1 has evolved a number of strategies to avoid and antagonize these host defenses (Fig. 1). In the case of capsid recognition by TRIM5α proteins, it is sometimes the case that minor sequence variation in capsid proteins can ablate or confer recognition by TRIM5α proteins (Ylinen and others 2005). Additionally, however, a variety of lentivirus capsids have the ability to bind cyclophilin A (CypA), a very abundant cytoplasmic host protein. The reasons for this are not entirely clear, but in some instances it appears that CypA binding can inhibit restriction by TRIM5α proteins (Towers and others 2003; Zhang and others 2006), perhaps by coating the incoming capsid, or by isomerizing peptidy–prolyl bonds (Fig. 1). In the case of HIV-1, its capsid sequence and cyclophilin-binding activity both appear to contribute to resistance to human TRIM5α. However, in at least some instances, CypA binding by capsids appears to have the opposite effect and enhance TRIM5α recognition (Berthoux and others 2005; Keckesova and others 2006; Stremlau and others 2006b). Thus, while CypA binding by retroviral capsids can clearly modify the effect of TRIM5α proteins, whether lentiviruses evolved to acquire this interaction in response to restriction by TRIM5α is not clear at present.

Some entirely new biological activities have been uncovered as a consequence of studies of antiretroviral genes and their antagonists. Indeed, the APOBEC3 and tetherin proteins were discovered based on the ability of their antagonists (the HIV-1 Vif and Vpu proteins) to selectively enhance HIV-1 replication in the so-called "nonpermissive" cells that express them (Sheehy and others 2002; Neil and others 2008). For example, the HIV-1 Vif protein is essential for primate lentivirus replication in cells that express certain APOBEC3 proteins, including primary T cells, and functions by simultaneously binding to a Cullin5-based ubiquitin ligase complex and to APOBEC3 proteins, resulting in their polyubiquitination and degradation (Conticello and others 2003; Marin and others 2003; Sheehy and others 2003; Yu and others 2003) (Fig. 1). Similarly, tetherin was discovered based on the finding that the HIV-1 Vpu protein was required for efficient particle release from certain human cell types, and that type I interferon induced a requirement for Vpu in others (Neil and others 2007). The mechanism by which Vpu antagonizes tetherin is not well established, although it appears that Vpu sequesters tetherin from sites of HIV-1 particle assembly, thereby preventing it for encountering nascent virions (Neil and others 2008; Jouvenet and others 2009) (Fig. 1). This may be linked to the ability of Vpu to reduce the level of tetherin at the cell surface (Van Damme and others 2008) and to trigger its proteasome-dependent degradation (Goffinet and others 2009). It is likely that many other viruses encode mechanisms to antagonize tetherin (Bartee and others 2006). Indeed, the Ebola virus surface glycoprotein (GP) associates with tetherin and antagonizes its ability to inhibit virion release (Kaletsky and others 2009), and a similar activity may be conferred by the envelope glycoprotein of HIV-2, which, like most primate immunodeficiency viruses, lacks a Vpu protein.

Evolution of APOBEC3, TRIM5, and Tetherin Genes

The genomic loci harboring *APOBEC3*, *TRIM5*, and *tetherin* genes show striking evidence of positively selected evolutionary change during primate speciation (Sawyer and others 2004; Sawyer and others 2005; Song and others 2005; McNatt and others 2009). Specifically, the number of nonsynonymous nucleotide substitutions uncovered during interspecies, and in some cases of intraspecies, sequence comparisons of orthologous genes are unexpectedly high. In the case of antiviral genes, positive, or diversifying, selection could be driven by the need to inhibit infection by new viruses, or viral variants. Alternatively, it could arise as a consequence of the need for the antiviral gene to avoid antagonism by viral countermeasures. In the case of TRIM5, positively selected sequences are clearly concentrated in the 3′ exons—precisely those that encode the protein domains responsible for retroviral capsid recognition (Sawyer and others 2005; Song and others 2005). Indeed, individual residues that govern capsid recognition show evidence of positive selection. In contrast, the 5′ TRIM5 exons that are required for antiviral activity but do not appear to govern specificity show the more usual signature of negative, or purifying, selection (Song and others 2005), suggesting that they have been selected to conserve, rather than diversify, function. The distribution of positively selected sites in APOBEC3 genes varies according to which particular APOBEC3 gene is analyzed (Sawyer and others 2004; OhAinle and others 2006), while in tetherin, positively selected sites are enriched toward the 5′ end of the coding sequence that encode the N-terminal cytoplasmic tail and transmembrane segments (McNatt and others 2009). Notably, these positively selected sequence coincide with the protein domains that are known to be targeted by viral antagonists, including the HIV-1 Vpu protein.

In addition to high rates of nonsynonymous nucleotide substitution in primate APOBEC3, tetherin, and TRIM5 genes, there are other quite remarkable evolutionary signatures in these genes that suggest potent selective pressures have been applied to them. For example, so-called "balancing" selection, whereby multiple alleles are maintained in a single species, is evident in old world monkey TRIM5 genes (Newman and others 2006). Another striking phenomenon, particularly at the primate *APOBEC3* locus, is gene proliferation; mice possess a single *APOBEC3* gene, while humans have no less than 7 (Harris and Liddament 2004). Gene proliferation, albeit less dramatic, is also present at the tetherin locus of bovines, where the gene has been duplicated, with significant divergence in the duplicated copy (PDB, unpublished observation). Again, this gene duplication would likely permit a broader spectrum of viruses to be inhibited, or facilitate the avoidance of viral antagonism. Additionally, the ability of certain retroviral capsids to bind CypA likely provided the impetus for a remarkable example of convergent evolution in primate TRIM5 genes that has recently been observed. In 2 separate species, owl monkeys (a new world monkey) and macaques (an old world monkey) that are separated by 35 million years of divergence,

a retrotransposition event has placed a cyclophilin cDNA into the TRIM5 locus (Sayah and others 2004; Nisole and others 2004; Liao and others 2007; Brennan and others 2008; Newman and others 2008; Virgen and others 2008; Wilson and others 2008). While the site of CypA insertion into the locus is clearly distinct in the 2 species, both events lead to the expression of TRIM5–CypA fusion proteins in which the C-terminal portion of TRIM5α that ordinarily determines restriction specificity is replaced by CypA. This obviously changes, in a profound way, the spectrum of retroviruses that can be inhibited by *TRIM5*-encoded proteins. In macaques, a single retransposition event occurred in an ancestral macaque, and this lesion was maintained at different frequencies in the various descendent macaque species (Liao and others 2007; Brennan and others 2008; Newman and others 2008; Virgen and others 2008; Wilson and others 2008). For example, the CypA insertion in TRIM5 is present in ~10% of rhesus macaque alleles, but appears to be present in 100% of pigtailed macaque alleles. Remarkably, the retrotransposed CypA cDNA acquired a single amino acid substitution that affects the specificity which retroviral capsids are recognized, and abolishes binding to the HIV-1 capsid (Virgen and others 2008). Thus, pigtailed macaques, unlike most old world monkeys, lack a TRIM5 protein that is capable of inhibiting HIV-1 infection.

The rapid evolution and consequent wide divergence in other primate restriction factor genes also have profound biological consequences. In both APOBEC3 and tetherin proteins, diversity that results from positive selection means that the primate lentivirus Vif and Vpu proteins antagonize their respective host target proteins in a highly species-specific manner (Simon and others 1998b; Mariani and others 2003; Gaddis and others 2004; Virgen and Hatziioannou 2007; McNatt and others 2009). In particular, the Vif genes that are found in most SIVs have specifically adapted to antagonize the particular variants of APOBEC3 proteins that are encountered therein. Therefore, many SIV Vif proteins simply do not function effectively in human cells because they cannot bind to and remove human APOBEC3G, and perhaps other inhibitory human APOBEC3 proteins. Thus, the transmission of potentially pathogenic relatives of HIV-1 from primates to humans has likely been limited by restriction factor divergence. Similarly, the HIV-1 Vif protein fails to function effectively in many nonhuman primate cells, because of a failure to recognize and eliminate several monkey APOBEC3 proteins (Mariani and others 2003; Virgen and Hatziioannou 2007). Recently, it has also become clear that the HIV-1 Vpu protein, while an affective antagonist of human tetherin, is inactive against at least 2 monkey tetherin proteins (McNatt and others 2009). In this case, residues in the tetherin transmembrane domain that have evolved under positive selection appear to be responsible for sensitivity/resistance to Vpu, and it is possible that selective pressures driving the evident positive selection was by ancient SIV Vpu proteins, or similar viral antagonists.

A corollary of the blocks to zoonoses imposed by these antiretroviral proteins is that HIV-1 is not able to replicate nonhuman primate species. Consequently, an authentic animal model of HIV-1 infection is lacking and this has proven to be a significant impediment to AIDS research. Nonetheless, understanding the basis for species tropism of HIV-1 and its simian relatives has allowed the engineering of minimally modified HIV-1 strains that can replicate in macaque cells (Hatziioannou and others 2006; Kamada and others 2006). Recently it has been shown that replacing HIV-1 Vif sequences with those of SIV allows high-level replication and an persistence in pigtailed macaques, whose TRIM5 protein is, unusually, ineffective against HIV-1 (Hatziioannou and others 2009). Thus the development of an authentic animal model of HIV-1 infection appears feasible.

HIV-1, Interferon, and Restriction Factors

Recent evidence indicates that HIV-1 particles are capable of stimulating release of IFN-α from dendritic cells through engagement with Toll-like receptors, particularly recognition of viral genomic RNA by TLR7 from endocytosed virions (Beignon and others 2005). Moreover HIV-1-infected individuals often have high levels of plasma type I IFN (von Sydow and others 1991), and this is rapidly induced during the acute phase of HIV-1 infection, as early as a week after exposure (Stacey and others 2009). Coupled with the multiple and potentially cell type-specific effects of type I IFN on viral replication *in vitro* (Stetson and Medzhitov 2006), this suggests that the IFN system could potentially present a powerful barrier to HIV-1 systemic spread, and drive the virus to acquire mechanisms for its evasion. These findings, along with the current interest in the roles of retroviral restriction factors as effectors of innate antiviral immunity, have sparked renewed interest in how type I interferons (type I IFN) could modulate the replication of HIV-1. Historically, recombinant IFN-α was investigated early in the HIV epidemic as a potential therapeutic for AIDS-associated Kaposi's sarcoma (Volberding and others 1984) (now known to be caused by the human herpesvirus 8 (Chang and others 1994)), and administration in some patients was shown to reduce HIV plasma viremia (Lane and others 1988; Lane and others 1990). Additionally, various studies demonstrated that replication of HIV-1 in culture could be inhibited by IFN-α, but the nature of the block to virus replication was somewhat nebulous as it often differed between investigators using different cell types or viral strains (Poli and others 1989; Shirazi and Pitha 1992; Agy and others 1995; Korth and others 1998; Taylor and others 1998). Nonetheless, a common observation in primary cell types was that IFN-α-induced block to virus release and concomitant accumulation of cell-associated virions, particularly in macrophages and primary CD4+ T cells (Kornbluth and others 1989; Poli and others 1989; Göttlinger and others 1991; Smith and others 1991; Biswas and others 1992). We now know that this effect was due to the induction of tetherin (Neil and others 2007; Neil and others 2008), and that early studies of HIV-1 used highly passaged laboratory adapted strains that sometimes had lesions in 1 or more of the viral accessory genes, including Vpu.

Indeed, tetherin constitutes the clearest link between the antiretroviral activity of type I IFN and retroviral restriction factors. In cell types that do not normally express tetherin, type I IFN potently induces its expression. In primary HIV-1 target cells such as CD4+ T cells and macrophages, tetherin expression is up-regulated by cellular activation and maturation, but further enhanced by IFN-α (Neil and others 2008; Miyagi and others 2009). Thus, *in vitro* replication of HIV-1 strains carrying a lesion in the Vpu gene in primary human T cells is effectively inhibited by IFN-α (Neil and others 2007). Wild-type HIV-1 strains are substantially,

but not completely, resistant to inhibition by type I IFN—virus spread through the culture occurs, but is significantly delayed (Neil and others 2007). It remains to be determined whether the residual anti-HIV-1 activity of type I interferon is due to incomplete antagonism of high levels of tetherin by inadequate expression of Vpu, or other mechanisms. Notably, *in vitro* studies indicate that overexpression of tetherin can result in residual inhibition of particle release, even when the viral genome encodes Vpu (Van Damme and others 2008; McNatt and others 2009). Determining the magnitude of the tetherin antiviral effect and the effectiveness of Vpu antagonism *in vivo* is essential to understand the importance of tetherin as an antiviral factor in HIV/AIDS, and for providing rationale to target Vpu with novel therapeutics. Interestingly, examination of the tetherin promoter reveals likely binding sites for IFN-regulated transcription factors, and also a variety of single-nucleotide polymorphisms in the same area (http://www.ensembl.org/index.html). This raises the possibility that tetherin promoter polymorphisms might influence the course of in HIV infection, and perhaps other viral infections.

Expression of both APOBEC3G and TRIM5α can also be enhanced by IFN-α. APOBEC3G induction by type I IFN has been reported in T cells, macrophages, dendritic cells, and brain microvascular endothelial cells, and suggested to contribute to a block in HIV-1 replication in these cells upon IFN treatment (Chen and others 2006a; Peng and others 2006; Argyris and others 2007; Wang and others 2008). These effects appear to be primarily related to the less well-characterized block to HIV-1 infection when APOBEC3G is present in target cells in low-molecular-weight complexes (Chiu and others 2005), rather than the conventional mechanism by which APOBEC3G is thought to act. Additional, TRIM5 induction by IFN-α has been reported to enhance the ability of human cells to restrict infection by human TRIM5-sensitive MLV strains, and the ability of monkey cells to restrict infection by HIV-1 (Asaoka and others 2005; Sakuma and others 2007; Carthagena and others 2008). In each of these cases, TRIM5α was expressed, and able to inhibit HIV-1 infection in the absence of IFN-α, but IFN-α treatment increased TRIM5α mRNA levels and intensified the infection block. However, since human TRIM5α only marginally inhibits HIV-1 infection (Stremlau and others 2004), even at high expression levels, it is unclear at present whether IFN-α induction would result in sufficiently high TRIM5α protein levels to impact HIV-1 replication in human primary cells. Nonetheless, a significant fraction of TRIM family genes have been reported to be regulated by type I IFN and thus may harbor antiviral activities (Carthagena and others 2009). One recent report suggests that TRIM22, another type I IFN-induced TRIM protein, is capable of restricting the assembly and release of HIV-1 in some human cells (Barr and others 2008) and another study indicated that a number of TRIM proteins have activity against MLV or HIV-1 (Uchil and others 2008). Finally, TRIM28, a nuclear TRIM associated with transcriptional repression, has been found to be recruited to the primer-binding site of integrated MLV proviruses in embryonic stems cells (Wolf and Goff 2007) by the DNA-binding protein ZFP809 (Wolf and Goff 2009). This interaction mediates a silencing of MLV transcription, and may be an antiviral strategy to limit retrovirus replication/reactivation during development. Thus, it may be the case that antiretroviral activity is common among TRIM proteins, although their viral targets and mechanisms of action remain largely unexplored.

Little is known about whether the "classical" IFN-induced genes have any direct effects on HIV-1 replication. The ubiquitin homolog ISG15, which is essential in mice for innate immune resistance to RNA and DNA viruses (Lenschow and others 2007; Lai and others 2009), has been suggested to interfere with HIV-1 assembly. Specifically, conjugation of ISG15 to HIV-1 Gag has been reported to inhibit association with TSG101, an essential cellular factor for HIV-1 budding (Okumura and others 2006). A caveat with these findings is that they were generated by overexpression of both ISG15 as well as its cognate E2-conjugating enzyme. Moreover, inhibiting TSG101 engagement by Gag induces a highly characteristic "late-budding" block, whereby the lipid envelope of nascent particles remains continuous with the host cell membrane, a phenotype that is not typically observed when HIV-1-infected cells are treated with type I IFN (Smith and others 1991; Göttlinger and others 1993; Neil and others 2006; Neil and others 2007). Hints that other "classical" IFN-induced genes might have anti-HIV-1 activity derive from studies of other retroviruses and retroelements, For example, 2′6′ oligoadenylate synthetase and RNAseL have been shown to be able to inhibit the replication of a MLV strain (XMRV) (Dong and others 2007) that was recently found in human prostate cancer tissue (Urisman and others 2006), suggesting the possibility that they may be able to inhibit other retroviruses. Moreover, an interesting recent study identified the ER-associated Trex1 DNA 3′ exonuclease as being required for the degradation of cytoplasmic dsDNA (Stetson and others 2008). In its absence, dsDNA triggers type I IFN release, and mice and human with lesions in Trex1 develop lethal autoimmunity that is dependent on type I IFN. Trex1-deficient cells accumulate cytoplasmic DNAs derived from endogenous retroelements, and Trex1 overexpression suppresses retrotransposition (Stetson and others 2008). These findings raise the intriguing possibility that exogenous retroviral reverse transcripts might be removed by Trex1 or similar factors. However, 1 recent report indicates that the SET-1 complex, of which TREX is a component, actually facilitates HIV-1 infection by inhibiting autointegration (Yan and others 2009).

Possible Roles for HIV-1 Accessory Genes in Antagonizing Novel Restriction Factors or Attenuating the IFN Response

TRIM5, APOBEC3, and tetherin proteins are currently the most intensively studied of the restriction factors, primarily because there is clear evidence that specific adaptations have occurred in HIV-1 and its relatives to evade or antagonize these host defenses. However, overexpression or underexpression of a number of cellular genes can inhibit and enhance retrovirus replication, respectively (Goff 2007). Moreover, there are strong hints that other primate lentivirus accessory genes might have evolved activities to counteract additional, as yet unidentified, restriction factors or to attenuate the type I IFN response.

Inhibition of interferon and/or Toll-like receptor signaling through IRF, STAT, or NF-κB activation is a common mechanism by which mammalian viruses attempt to evade innate immune responses (Haller and others 2006). Interestingly, proteasomal degradation of STAT1 or 2 by the

V proteins of mammalian paramyxoviruses requires their recruitment to a Cullin4 E3–ubiquitin ligase complex via DDB1 (Barry and Früh 2006). This same complex is engaged by HIV-1 Vpr and SIVmac Vpx through their binding to DCAF1 (VprBP) (Hrecka and others 2007; Le Rouzic and others 2007; Schröfelbauer and others 2007; Tan and others 2007; Wen and others 2007). Intriguingly, Vpx, carried in virion particles, is able to suppress the resistance of human dendritic cells or macrophages to HIV-1 and SIVmac/HIV-2 infection and this property requires engagement of the ubiqutin ligase complex (Goujon and others 2007; Goujon and others 2008; Sharova and others 2008). We as yet do not know what "substrates" are targeted to the Cul4 ubiqutin ligase complex by Vpr/Vpx, but it is likely to be a cellular factor that has, or that mobilizes, an antiretroviral activity. It is also tempting to speculate that this accessory gene might modulate IFN-induced innate immunity through this mechanism, although this has not been demonstrated. Additionally, another HIV-1 accessory protein, Vpu binds the ubiquitin ligase adaptor β-TRCP, and in so doing, has been reported to inhibit degradation of phosphorylated IκB-α, preventing NF-κB liberation (Bour and others 2001). Thus, it too, could have a role in blunting the effects of IFNs on infected cells.

Antiretroviral Genes and the Treatment of Human Disease

Retrovirus restriction factors and their antagonists are intriguing in their own right, both because they function in biologically novel and unique ways, and because they illuminate how hosts and viruses have coevolved. Additionally, our understanding of some restriction factors, particularly the APOBEC3 and TRIM5 proteins, has progressed to the point that knowledge of them might be usefully applied to translational problems. One could envisage, for example that small molecules that disrupt the Vif:APOBEC3G interaction, or the putative Vpu:tetherin interaction, could be clinically useful inhibitors of HIV-1 replication. Indeed in a recent study, a compound that can block Vif-induced APOBEC3G degradation has been identified and shows antiviral activity against Vif+ HIV-1 replication in T-cell lines (Nathans and others 2008). Similarly, it might be possible to derive small molecules that promote TRIM5α–capsid interactions, or molecules that directly bind to capsid and mimic the apparent effects of TRIM5 on capsid (in)stability.

In addition, the rapid evolution and consequent wide divergence in primate restriction factor genes have impacted human disease and its investigation—on the one hand, the transmission of potentially pathogenic retroviruses from primates to humans has likely been limited by restriction factor divergence. On the other hand, the inability of HIV-1 to infect nonhuman primate species as a consequence of restriction factor activity has proved a significant impediment to AIDS research. Nonetheless, understanding the basis for species tropism of HIV-1 and its simian relatives has allowed the engineering of minimally modified HIV-1 strains that can replicate in macaque cells and, thus, an animal model of HIV-1 infection appears feasible. Thus, the discovery and characterization of natural antiretroviral factors have led to fascinating science, as well as possible translation applications.

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