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SnapShot: Antiviral Restriction Factors

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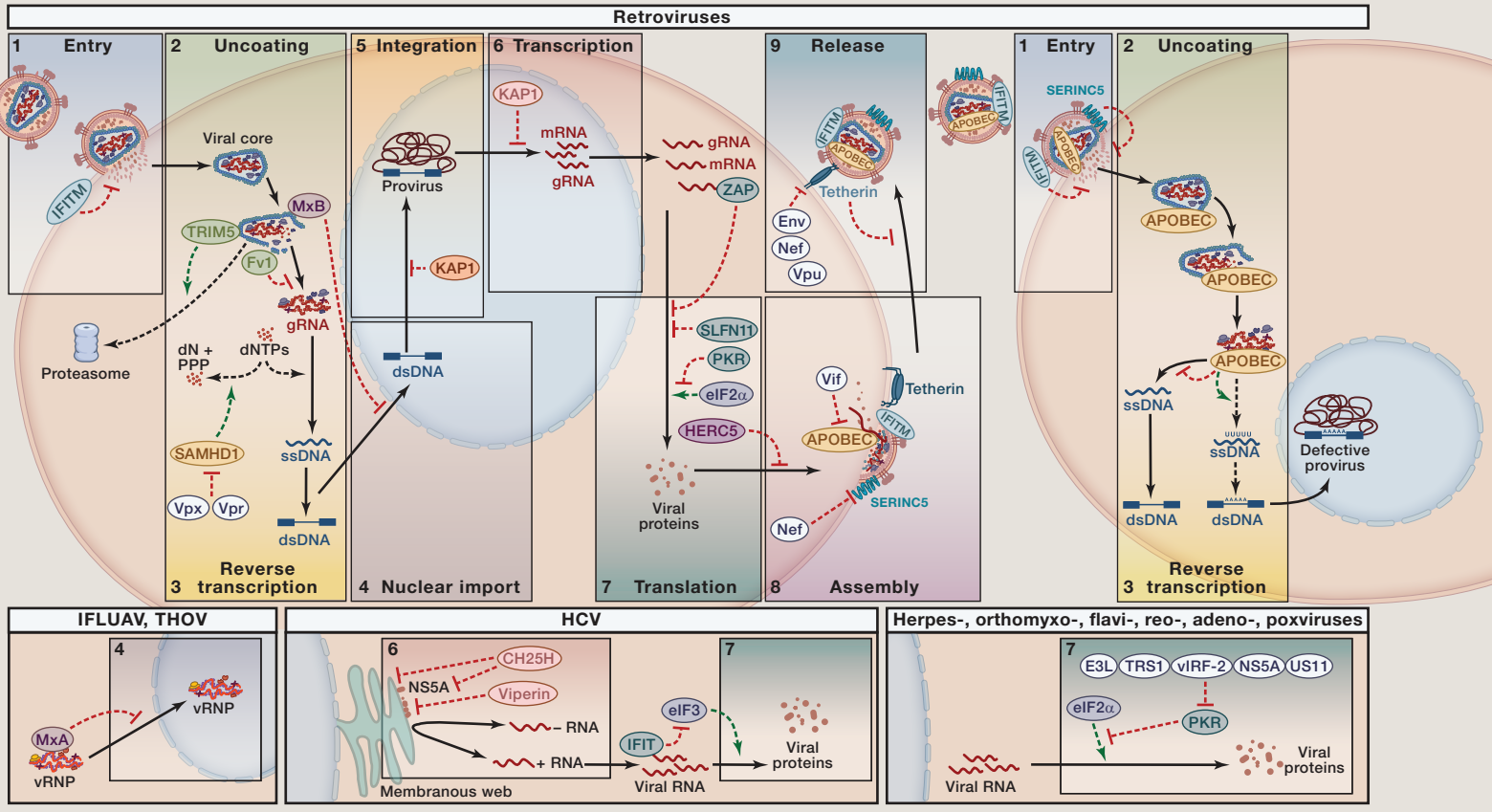

	Restriction factor	Virus(es) targeted	Mechanism(s) of restriction	Viral antagonist(s) or evasion mechanism(s)	IFN-inducible	Positive selection
1	IFITM family	Retro-, orthomyxo-, flavi-, filo-, corona-, rhabdo-, bunya-, reoviruses	Inhibits membrane fusion, modification of lipid components, or membrane fluidity	None known	Some	Some
	SERINC3, 5	Retroviruses (HIV, SIV, MLV, EIAV)	Reduces membrane fusion	Nef (HIV, SIV), Glyco-Gag (MLV), S2 (EIAV)	N	N
	CH25H	Flavi-, retro-, filo-, bunya-, rhabdo-, herpesviruses	Inhibits membrane fusion by generating 25-hydroxycholesterol	None known	Y	Unknown
2	TRIM5α, TRIM-Cyp	Retroviruses (HIV, SIV, MLV, EIAV)	Accelerates uncoating, thereby inhibiting reverse transcription	Capsid mutation	Y	Y
	Fv1	MLV	Targets the viral capsid protein and interferes with uncoating	Capsid mutation	N	Y
3	APOBEC3 family	Hepadna-, retroviruses	Induces hypermutation by deamination, inhibits reverse transcription of HIV by binding to RNA and suppressing tRNA3Lys priming	Vif (lentiviruses), Bet (spumaviruses), Gag (gammaretroviruses)	Some	Some
	SAMHD1	Retroviruses	Hydrolyzes cellular dTNP and degrades viral RNA	Vpx (HIV-2, some SIV), Vpr (some SIV)	Y	Y
4	MxA	IFLUAV, THOV	Inhibits vRNP nuclear import	Nucleoprotein mutations (pandemic IFLUAV)	Y	Y
	MxB	HIV, SIV	Prevents integration of proviral DNA by inhibiting uncoating, nuclear uptake, and/or integrity/stability of the PIC	Capsid mutation	Y	Y
5	KAP1/TRIM28	HIV-1	Induces deacetylation of HIV integrase	None known	N	N
6	KAP1/TRIM28	Herpes-, retroviruses	Silences transcription and induces latency	vPK (KSHV)	N	N
	Viperin/RSAD2	HCV, DENV	Inhibits formation of the HCV replicon complex by sequestration of hVAP-33 and interaction with NS5A, interacts with NS3 (DENV)	None known	Y	Y
	CH25H	HCV	Inhibits membranous web formation and NS5A dimerization	None known	Y	Unknown
	IFI16	HPV, HCMV, HSV1	Accumulates on the viral genome and prevents association of transcriptional activators, induces heterochromatin formation	pUL97, pUL83 (HCMV)	Y	Y
	MxA	Bunyaviruses (LACV, RVFV, BUNV)	Sequesters newly synthesized viral N protein into perinuclear complexes	None known	Y	Y
	RNaseL (+OAS1)	Picorna-, flavi-, toga-, corona-, reo-, pox-, orthomyxo-, paramyxo-, herpes-, retro-, rhabdo-, hepadna-, polyomaviruses	Degrades viral (m)RNA, RNaseL is activated by 2′-5′-linked oligoadenylates produced by OAS1	NS1 (IFLUAV), E3L, D9, D10 (VACV), σ3 (ReoV), Tat (HIV), ns2 (murine hepatitis virus), VP3 (RotaV), L* (Theiler's virus), hairpin RNA structure (poliovirus), genome adaptation (HCV)	Y	Y
	SAMHD1	Arteri-, pox-, herpesviruses	Hydrolyzes cellular dNTP and degrades viral RNA	None known	Y	Y
	APOBEC3 family	Herpes-, papillomaviruses	Induces hypermutation by deamination	None known	Some	Some
7	PKR	Herpes-, orthomyxo-, retro-, flavi-, reo-, adeno-, poxviruses	Inhibits mRNA translation by eIF2α phosphorylation	NS1 (IFLUAV), E2, NS5A (HCV), TRS1, IRS1 (HCMV), K3L, E3L (VACV), US11 (HSV1), vIRF-2, LANA2 (KSHV), NSs (RVFV), σ3, σ4 (ReoV), SM, EBER-1 (EBV), Tat (HIV), VAI RNAs (AV), C8L, K3L (Swine-poxV), Nsp3 (RotaV), γ(1)34.5 (HSV-1)	Y	Y
	SLFN11	HIV, other retroviruses	Inhibits viral protein synthesis by altering tRNA function	None known	Y	Y
	ZAP	Retro-, filo-, hepadna-, togaviruses	Recruits RNA exosome complex to degrade viral RNA	None known	Y	Y
	IFIT family	Flavi-, bunya-, rhabdo-, orthomyxo-, picorna-, coronaviruses	Inhibits cap- and IRES-dependent translation by binding to eIF3 (HCV), binding and degradation of PPP-RNA (RVFV, VSV, IFLUAV) and RNA lacking 2′-O methylation (WNV, JEV)	2′-O methylation of viral RNA (WNV, SARS-CoV, VACV), hairpin structures near the 5′ ends of viral RNA (VEEV), masking of the 5′ end by Vpg (EMCV)	Y	Y
8	HERC5 (+ISG15)	HIV, MLV, HPV, IFLUAV	Inhibits HIV and MLV assembly by ISGylation of Gag, ISGylation of IFLUAV NS1 and HPV L1 capsid reduces infectious virus yield	NS1 (?) (IFLUAV)	Y	Y
9	Tetherin/BST2/CD317	Retro-, flavi-, filo-, rhabdo-, herpes-, corona-, paramyxo-, arena-, toga-, hepadnaviruses	Prevents virus release by tethering budding progeny virions to the plasma membrane of the infected cell	Vpu (HIV-1 M/N, SIVgsn/mon/mus), Nef (most SIV, HIV-1 O), K5 (KSHV), Env (HIV-2, EBOV, MARV, SIVagm), Nsp1 (CHIKV), gM (HSV-1), HA/NA (pandemic IFLUAV), F/HN (SeV), HBs (HBV)	Y	Y

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SnapShot: Antiviral Restriction Factors

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Restriction factors are cellular proteins that inhibit viral replication and represent a first line of defense against viral pathogens. They show an enormous structural and functional diversity and target almost every step of the viral replication cycle. Although there is no unambiguous definition of restriction factors (Doyle et al., 2015), these proteins frequently share several characteristics: they are germ-line encoded, cell-intrinsic proteins that can be found in almost all cell types. While their expression is often upregulated by interferons (IFNs), many of them are constitutively expressed, allowing them to act very early during viral infection. Restriction factors frequently target conserved viral components, such as the viral genomes or membranes, and may thus be active against diverse viral families. Notably, some of them are so-called moonlighting proteins, also exhibiting biological functions outside of immunity. In some cases, restriction of viral replication may result from a cell-regulatory function rather than direct interference with the viral replication cycle. Viruses have evolved sophisticated means to evade or directly counteract many restriction factors. As a consequence of the continuous arms race with their viral antagonists, restriction factors usually evolve rapidly and show evolutionary signatures of adaptation. Sites under positive selection often directly interact with viral components, either to target them for inhibition or because they are being targeted by viral antagonists. As a consequence of virus-host adaptation, restriction factors are usually less effective against viruses in their natural hosts but represent potent barriers against cross-species transmissions. Finally, their specific interaction with viral components allows some restriction factors to act as pattern recognition receptors that do not only directly inhibit viral pathogens, but also sense them to induce antiviral immune responses.

The term “restriction factor” was established in the early 1970s, when researchers discovered that expression of Fv1 protects mice against infection by an otherwise lethal dose of MLV (Lilly, 1970). Later, it became evident that primate lentiviruses, such as HIV-1, are subject to similar restrictions. A functional screen for suppressors of HIV-1 identified rhesus TRIM5α as a potent inhibitor and determinant of retroviral species specificity (Stremlau et al., 2004). Similar to Fv1, TRIM5α and the related TRIM-CypA protein target incoming retroviral capsids and block viral replication by preventing viral cDNA synthesis. Other well-characterized retroviral restriction factors include APOBEC3G, Tetherin, and SAMHD1. APOBEC3G is a cytidine deaminase that is packaged into viral particles and inhibits viral cDNA synthesis by affecting the processivity of reverse transcription and by causing inactivating G-to-A hypermutations in the proviral genome (Sheehy et al., 2002). Tetherin inhibits the release of budding progeny virions because one of its two membrane anchors is inserted into the viral envelope while the other remains in the cell membrane (Van Damme et al., 2008; Neil et al., 2008). SAMHD1 suppresses reverse transcription in non-dividing cells by depleting dNTPs, which are required for effective cDNA synthesis, and perhaps also by degrading viral RNA (Hrecka et al., 2011; Laguette et al., 2011). With the exception of TRIM5α, that is evaded by viral capsid mutations, these restriction factors are all counteracted by accessory proteins of HIV and related lentiviruses: APOBEC3 proteins by Vif, Tetherin by Vpu of pandemic HIV-1 group M as well as Nef of many other primate lentiviruses, and SAMHD1 by HIV-2 and SIV Vpx or Vpr proteins. Very recently, SERINC5 and SERINC3 have been identified as the enigmatic factors that impair the infectivity of HIV and SIV particles and are antagonized by the viral protein Nef (Rosa et al., 2015; Usami et al., 2015).

Cellular proteins inhibiting HIV-1 have received enormous research interest, and a variety of additional antiviral factors, such as IFITM proteins, CH25H, KAP1/TRIM28, 90K, MOV10, MxB, SLFN11, and ZAP have been described. The discovery of all of these factors has relevance far beyond HIV/AIDS and other retroviruses because many of them have broad antiviral activity. For example, Tetherin suppresses the release of a large variety of enveloped viruses, including filo-, rhabdo-, arena-, and herpesviruses. Similarly, IFITMs and CH25H may impair virion infectivity of diverse virus families by altering the lipid composition of the viral membrane. Another striking example of a broadly active antiviral protein is PKR. This kinase inhibits viral mRNA translation by inhibiting the initiation factor eIF2α.

The definition of a “real” restriction factor is intensively debated. Viruses are interacting with and hijacking hundreds of cellular proteins to ensure efficient viral replication. Thus, overexpression or knockdown of many cellular factors may result in the identification of proteins with putative antiviral effects. Moreover, only a minority of the antiviral factors described to date show all features reported to be characteristic for a restriction factor. In fact, antiviral proteins without any (known) viral antagonist or evasion mechanism (e.g., IFITMs and SLFN11) have been proposed to be called “resistance factors” (Doyle et al., 2015). Here, we more broadly apply the term “restriction factor” to intrinsic cellular factors known to display antiviral activity. We apologize to both the purists who apply criteria that are more stringent and to all of the scientists who discovered interesting antiviral factors that we did not mention. We are only just beginning to understand the enormous diversity of antiviral factors and the highly sophisticated ways exploited by viruses to antagonize or evade them. No matter which definition of a restriction factor we apply, there will certainly be discoveries of novel antiviral proteins that will not satisfy the criteria.

ABBREVIATIONS

Antiviral factors: IFITM, interferon-induced transmembrane protein; SERINC, serine incorporator; CH25H, cholesterol 25-hydroxylase; TRIM, tripartite motif-containing protein; Fv1, Friend virus susceptibility-1; APOBEC3, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3; SAMHD1, SAM domain and HD domain-containing protein 1; MxA, myxovirus resistance gene A; MxB, myxovirus resistance gene B; KAP1, KRAB-associated protein 1; RSAD2, radical S-adenosyl methionine domain-containing 2; IFI16, interferon-inducible protein 16; OAS1, 2’-5’-oligoadenylate synthetase 1; PKR, (ds)RNA-dependent protein kinase R; SLFN11, Schlafen family member 11; ZAP, zinc-finger antiviral protein; IFIT, interferon-induced protein with tetratricopeptide repeats; HERC5, HECT and RLD domain-containing E3 ubiquitin protein ligase 5; ISG15, interferon-stimulated gene 15; BST2, bone marrow stromal cell antigen 2.

Viruses: HIV, human immunodeficiency virus; SIV, simian immunodeficiency virus; MLV, murine leukemia virus; EIAV, equine infectious anemia virus; IFLUAV, influenza A virus; THOV, Thogoto virus; HCV, hepatitis C virus; DENV, Dengue virus; HPV, human papilloma virus; HCMV, human cytomegalovirus; HSV1, herpes simplex virus 1; LACV, La Crosse encephalitis virus; RVFV, Rift Valley fever virus; BUNV, bunyamweravirus; VSV, vesicular stomatitis virus; WNV, West Nile virus; JEV, Japanese encephalitis virus; KSHV, Kaposi’s sarcoma-associated herpesvirus; VACV, vaccinia virus; reoV, reovirus; EBV, Epstein-Barr virus; RotaV, rotavirus; AV, adenovirus; VEEV, Venezuelan equine encephalitis virus; SARS-CoV, severe acute respiratory syndrome corona virus; EMCV, encephalomyocarditis virus; MARV, Marburg virus; CHIKV, Chikungunya virus; SeV, Sendai virus; HBV, hepatitis B virus; EBOV, Ebola virus.

Viral proteins: Nef, negative factor; NS5A, nonstructural protein 5A; Vif, viral infectivity factor; Vpr, viral protein R; Vpu, viral protein unknown; Vpx, viral protein X; Env, envelope; vIRF-2, viral IRF2-like protein; US11, tegument protein unique short 11.

Other: eIF2α, eukaryotic translation initiation factor 2α; eIF3, eukaryotic translation initiation factor 3.

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