SnapShot: HIV-1 Proteins

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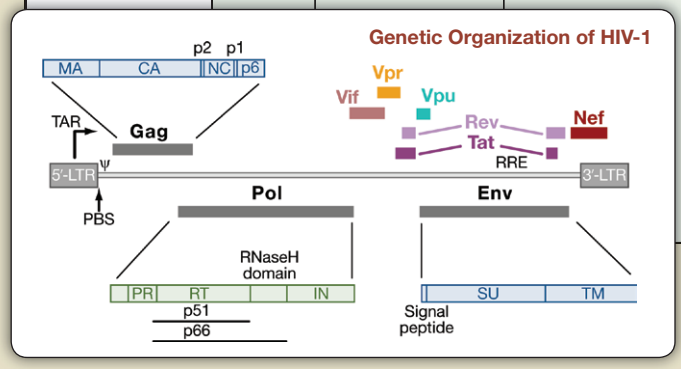
Virus Protein	# Copies/ Virion	Interactions with Other Viral Factors	Virus Protein Function	Cellular Partners	Cellular Partner Functions; Results of Interaction with Viral Proteins
Matrix, MA ($p17^{Gag}$)	~5000	Transmembrane glycoprotein (TM)	Plasma membrane targeting of Gag for virion assembly; Env incorporation; post-entry events	Phosphatidylinositol (PI) 4,5-bisphosphate [PI(4,5)P2]	Mediates Gag interaction with plasma membrane
				TIP47	Promotes Env incorporation into virions
Capsid, CA ($p24^{Gag}$)	~5000 (see Briggs et al., 2004)		Virion core structure and assembly	Cyclophilin A	Modulates sensitivity to TRIM5α; suppressed by cyclosporin A
				TRIM5α	Post-entry inhibitor of infection
Nucleocapsid, NC ($p7^{Gag}$)	~5000	RNA genome (gRNA) of virus	Virion packaging of genome RNA; RNA chaperone; virion assembly	HP68/ABCE1	Promotes virion assembly
				APOBEC3G, APOBEC3F	Packaged into virions with RNA; inhibits infection; G-to-A hypermutation
				$tRNA^{Lys3}$	Primer for reverse transcription
				7SL RNA, other cellular RNAs	Unknown
$p6^{Gag}$	~5000	Vpr	Promotes virion budding	TSG101	Recruit ESCRT machinery to promote virion budding
				ALIX	
Protease, PR	~250	Gag, Pol	Proteolytic processing of Gag and Gag-Pol polyproteins	PR may cleave many cellular proteins	
Reverse Transcriptase, RT	~250	gRNA, IN	cDNA synthesis; RNaseH domain degrades RNA	$tRNA^{Lys3}$	Primer for reverse transcription
Integrase, IN	~250	Viral cDNA, RT	Covalent insertion of virus cDNA into cellular DNA	LEDGF/p75	cDNA integration; targeting to active genes
				INI1	Virion assembly; reverse transcription/integration
				UNG2	DNA repair enzyme; enhances replication fidelity
Surface Glycoprotein, SU ($gp120^{Env}$)	4 to 35 trimers	TM	Binds cell-surface receptors; mediates virus attachment and entry	CD4	CD4 plus CCR5/CXCR4 mediate virion entry; major determinants of viral tropism
				Chemokine receptors (CCR5 and CXCR4)	
				C-type lectin receptors (DC-SIGN, Langerin)	Virion capture; viral transmission from dendritic cells to T cells
Transmembrane Glycoprotein, TM ($gp41^{Env}$)	4 to 35 trimers	SU, MA	Contains fusion peptide; mediates membrane fusion and virus entry	TIP47	Env incorporation into virions
				Clathrin sorting machinery (AP-1, AP-2)	Env downregulation from cell surface
Virion Infectivity Factor, Vif	1 to 150		Suppresses APOBEC3G/ APOBEC3F, host factors that inhibit infection	APOBEC3G, APOBEC3F	Vif recruits Cullin5-ElonginB/C-Rbx E3 ubiquitin ligase to APOBEC3G, APOBEC3F; degradation of APOBEC3G and APOBEC3F
				ElonginC, Cullin5	
Viral Protein R, Vpr	~700	p6	Moderate enhancer of post-entry infectivity; G2/M cell-cycle arrest	DCAF1/VprBP	Bridges Vpr and unknown substrates to Cullin4A-DDB1-Rbx E3 ubiquitin ligase
				nucleoporins (various)	Post-entry nuclear import
				UNG2	DNA repair enzyme; enhances replication fidelity
				CDC25C	G2 cell-cycle arrest
trans-Activator of Transcription, Tat	No	Viral RNA via *trans*-acting response (TAR) element	Potent activator of viral transcription elongation	Cyclin T1	Cyclin T with CDK9 forms p-TEFb, which promotes viral transcription
				Importin-β/Karyopherin-β1	Nuclear import receptor
Regulator of Expression of Virion Proteins, Rev	No	Intron-containing viral RNAs via Rev response element (RRE)	Induces nuclear export of intron-containing viral RNAs	CRM1/Exportin-1	Nuclear export receptor; transport of Rev and intron-containing viral RNAs to cytoplasm
				Importin-β/Karyopherin-β1	Nuclear import receptor
Viral Protein U, Vpu	No		CD4/MHC downregulation; induces virion release from host cell surface	CD4	Vpu recruits Cullin1-SCF^{TrCP} E3 ubiquitin ligase to CD4 resulting in CD4 degradation
				βTrCP	
				Tetherin/BST-2/CD317	Blocks virion release from host cell surface
Negative Factor, Nef	Yes, cleaved by PR		CD4/MHC downregulation; T-cell activation; moderate enhancer of viral infectivity; blocks apoptosis; pathogenicity determinant	CD4, CD28, MHC-I, MHC-II, TCR-CD3ζ, other cell-surface proteins	Nef connects immunologically important host surface proteins to clathrin-dependent and -independent sorting pathways to regulate trafficking, degradation, and immune recognition
				AP-1, AP-2, AP-3, β-COP, vacuolar ATPase, PACS-SRC family kinase-PI3K complex	
				Several kinases, including PAK2, LCK, ASK1	Roles in signal transduction, host cell activation, blocking apoptosis, stimulating viral replication
				Dynamin-2	Enhances virion infectivity



MA, CA, NC, p6 synthesized as the $p55^{Gag}$ polyprotein (Gag, group-specific antigen), which is cleaved by viral PR after particle assembly and during maturation to yield these four proteins and the p1 and p2 spacer peptides. PR, RT, and IN synthesized as a 160 kDa Gag-Pol polyprotein (Pol, polymerase), which is cleaved by PR to yield these three enzymes including the 51 kDa and 66 kDa subunits of the RT dimer (as well as Gag proteins).

Synthesis of the 160 kDa envelope (Env) glycoprotein precursor is followed by removal of signal peptide in the ER, extensive posttranslational modification and cleavage by a furin-like protease into SU and TM, which are further assembled into Env trimers.

TRIM5α variants in the natural host species for different HIV and SIV strains are inactive against those "cognate" viruses. For example, human TRIM5α blocks infection by SIVagm from African green monkeys but not HIV-1; African green monkey TRIM5α blocks infection by HIV-1 but not SIVagm.

APOBEC3G/F of the natural hosts of HIV and SIV strains are inhibited by the Vifs of those viruses to preserve viral infectivity. For example, human APOBEC3G is inhibited by HIV-1 Vif but not by SIVagm Vif.

Most Nefs of SIVs and HIV-2 downregulate TCR-CD3, which correlates with reduced viral pathogenicity in natural hosts; HIV-1 Nef does not downregulate human TCR-CD3.

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Table: HIV Proteins and Their Cellular Partners

Human immunodeficiency virus type-1 (HIV-1) is the etiologic agent of acquired immunodeficiency syndrome (AIDS) and the prototypic member of the lentivirus genus of retroviruses. Lentivirus infections are considered as chronic or "slow" and, when pathogenic (most notably, HIV-1 infection of humans), are associated with severe immunological and neurological dysfunction. HIV-1 has nine genes, with only the *gag*, *pol*, and *env* genes common to all replication-competent retroviruses. The *pol* gene encodes two enzymes that define the replicative strategy of the retrovirus: reverse transcriptase (RT) copies the viral RNA genome into DNA, and integrase (IN) mediates the insertion of that DNA into the genomic DNA of an infected cell to establish the provirus (and persistent infection). A third enzyme protease (PR), also derived from *pol*, is necessary for maturation of virions into an infectious form. Of the remaining six regulatory/accessory genes of HIV-1, *tat* and *rev* are essential for virus replication, whereas *vif*, *vpr*, *vpu*, and *nef* are thought to modulate immune functions in vivo (often in a species-specific fashion). Current frontline highly active antiretroviral therapy (HAART) for treating AIDS includes combinations of small-molecule inhibitors of PR and RT (nucleoside RT inhibitors, NRTIs; non-nucleoside RT inhibitors, NNRTIs). A peptide inhibitor of TM that inhibits viral entry is used in salvage therapy, and a small-molecule IN inhibitor, Raltegravir, was recently approved by the FDA. Three crucial viral enzymes are inhibited pharmacologically, but blocking remaining viral proteins and virus-host interactions is an important objective (a CCR5 coreceptor antagonist, Maraviroc, received FDA approval in 2007).

Figure: Genetic Organization of HIV-1

The ~9.7 kb provirus comprises two LTRs (long terminal repeats) flanking the internal unique sequence. The 5′ LTR is a promoter for transcription; the 3′ LTR ensures polyadenylation. Regions encoding Gag, Pol, and Env proteins (dark gray); regions encoding regulatory/accessory proteins Tat, Rev, Vif, Vpr, Vpu, and Nef (various colors); Gag, Pol, and Env precursor proteins (green/blue; origins of mature protein derivatives and sites of proteolytic cleavage are shown). PBS (primer-binding site for $tRNA^{Lys3}$) enables initiation of reverse transcription; ψ, RNA packaging sequence for virion encapsidation of viral genome RNA; Tat binds to TAR to stimulate viral transcription; Rev binds to RRE to activate nuclear export of unspliced viral RNAs.

REFERENCES

Bieniasz, P.D. (2004). Intrinsic immunity: A front-line defense against viral attack. Nat. Immunol. *5*, 1109–1115.

Brass, A.L., Dykxhoorn, D.M., Benita, Y., Yan, N., Engelman, A., Xavier, R.J., Lieberman, J. and Elledge, S.J. (2008). Identification of host proteins required for HIV infection through a functional genomic screen. Science *319*, 921–926.

Briggs, J.A., Simon, M.N., Gross, I., Kräusslich, H.G., Fuller, S.D., Vogt, V.M., and Johnson, M.C. (2004). The stoichiometry of Gag protein in HIV-1. Nat. Struct. Mol. Biol. *11*, 672–675.

Chertova, E., Chertov, O., Coren, L.V., Roser, J.D., Trubey, C.M., Bess, J.W., Jr., Sowder, R.C., Barsov, E., Hood, B.L., Fisher, R.J., et al. (2006). Proteomic and biochemical analysis of purified human immunodeficiency virus type 1 produced from infected monocyte-derived macrophages. J. Virol. *80*, 9039–9052.

Coffin, J.M., Hughes, S.H., and Varmus, H.E. (1997). Retroviruses (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press).

Goff, S.P. (2007). Host factors exploited by retroviruses. Nat. Rev. Microbiol. *5*, 253–263.

HIV-1 human protein interaction database. http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/

Holmes, R.K., Malim, M.H., and Bishop, K.N. (2007). APOBEC-mediated viral restriction: Not simply editing? Trends Biochem. Sci. *32*, 118–128.

Schindler, M., Münch, J., Kutsch, O., Li, H., Santiago, M.L., Bibollet-Ruche, F., Müller-Trutwin, M.C., Novembre, F.J., Peeters, M., et al. (2006). Nef-mediated suppression of T cell activation was lost in a lentiviral lineage that gave rise to HIV-1. Cell *125*, 1055–1067.

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