

The HIV-1 Rev response element

An RNA scaffold that directs the cooperative assembly of a homo-oligomeric ribonucleoprotein complex

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The HIV-1 Rev response element (RRE) is a ~350 nucleotide, highly structured, cis-acting RNA element essential for viral replication. It is located in the *env* coding region of the viral genome and is extremely well conserved across different HIV-1 isolates. It is present on all partially spliced and unspliced viral mRNA transcripts, and serves as an RNA framework onto which multiple molecules of the viral protein Rev assemble. The Rev-RRE oligomeric complex mediates the export of these messages from the nucleus to the cytoplasm, where they are translated to produce essential viral proteins and/or packaged as genomes for new virions.

The RRE serves as a specific RNA scaffold that coordinates the assembly of a unique homo-oligomeric ribonucleoprotein (RNP) complex to mediate the nuclear export of essential, intron-containing, viral messages.

The small size of the HIV-1 genome necessitates the use of multiple reading frames and alternative splicing to encode all its viral proteins. Transcription from an integrated HIV-1 provirus generates a single 9 kilobase (kb) pre-mRNA containing multiple splice sites. In the early phase of the viral life cycle, this pre-mRNA is completely spliced to RRE-free, 2 kb messages that are exported to the cytoplasm via standard mRNA nuclear export pathways (Fig. 1A). One of these messages encodes the Rev protein, which can translocate to the nucleus.

The late phase of the viral life cycle is characterized by the expression of viral proteins from RRE-containing unspliced (9 kb) and partially spliced (4 kb) messages. Normally, these intron-containing RNAs are retained in the nucleus for splicing/degradation. Nuclear export of such RNAs is achieved by a specific, cooperative assembly of multiple Rev molecules on the RRE, followed by recruitment of the host Crm1/Ran-GTP nuclear export machinery via Rev's nuclear export sequence (NES). In the cytoplasm, these messages are translated to produce the remaining viral proteins or packaged as genomes for newly budding virions (Fig. 1A) (for a detailed review, see ref. 52).

Genome Location and Sequence Conservation of the RRE

The RRE was initially identified as a cis-acting element in the *env* region (nucleotides 7709–8063 of the HXB2 reference strain) of the HIV-1 genome (Fig. 1B), required along with Rev for cytoplasmic accumulation of unspliced HIV-1 mRNAs, viral protein expression, and hence, successful viral replication.^{2–8} The minimal size of a functional RRE is ~250 nucleotides, although the entire structured region is ~350 nucleotides.⁹ The full RRE (nt 7709–8063) (Fig. 2) is extremely well conserved across subtypes of the major group M, with conservation pressure from both the RNA structure and the overlapping *env* protein reading frame.

Keywords: HIV, Rev, RRE, export, scaffold, oligomer, assembly, RNA, virus

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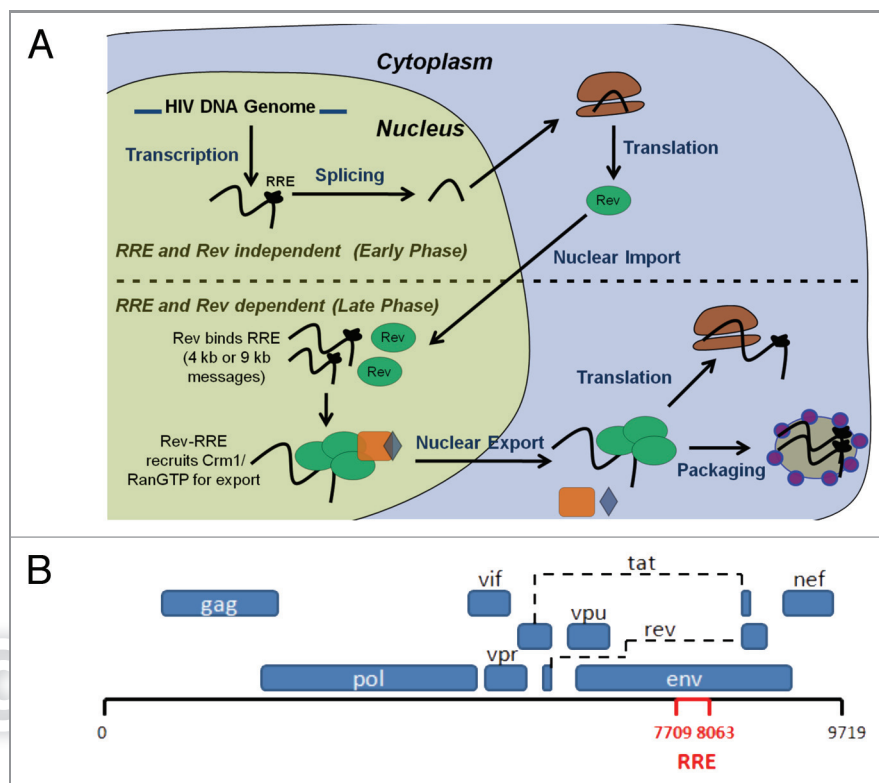


Figure 1. (A) Functional requirement of the RRE: Early in the viral life cycle, all viral transcripts are fully spliced and exported in a Rev/RRE-independent manner. A subset of these transcripts codes for Rev, which is imported into the nucleus. In the late phase, intronic, RRE-containing RNAs in the nucleus recruit Rev and cellular nuclear-export machinery to circumvent splicing and reach the cytoplasm where they are translated or packaged into new virions. (B) Genome organization of HIV-1: The RRE lies between nucleotides 7709–8063.

Secondary Structure and Rev binding

Early computational predictions of RRE secondary structure indicated a complex, highly branched structure characterized by multiple stem-loops and bulges^{5,10} (Fig. 3). Chemical and enzymatic probing studies confirmed the secondary structure^{1,9,11} and in combination with mobility shift assays, established its importance in sequence-specific Rev-binding.^{1,12–16}

Multiple molecules of Rev were shown to bind the RRE,^{1,17,18} forming a homo-oligomeric complex driven by a combination of hydrophobic Rev-Rev oligomerization interactions and Rev-RRE interactions.^{17,19}

Truncation studies and footprinting experiments established stem IIB as the high-affinity site for Rev^{18,20–22} (Fig. 3) with binding mediated by a 17-residue arginine-rich motif (ARM) in Rev.^{23,24} Structural studies indicate an RNA A-form major groove widened by purine-purine

base pairs to cradle the Rev-ARM α -helix with both base-specific contacts and electrostatic phosphate-backbone contacts cementing the interaction.²⁵

Although the Rev-stem IIB interaction is an important determinant of Rev-RRE affinity and function, oligomerization of Rev on the RRE is critical for a functional complex that can mediate nuclear export. Studies from our lab have shown that the RRE structural scaffold dictates the formation of a highly cooperative oligomeric Rev-RRE complex with a 500-fold higher affinity than the Rev-IIB interaction.²⁶ Reports from multiple groups have also demonstrated a direct correlation between cooperative Rev assembly on the RRE and export function.^{26–28}

RRE as a Scaffold for Rev Assembly and Function

Recent crystal structures of Rev dimers^{29,30} reveal a hydrophobic core that mediates

Rev-Rev interactions, with the ARMs pointing away from the core and available to contact the RNA. The structures, in combination with results from detailed biochemistry that indicate a stoichiometry of 6 Rev monomers on a \sim 250 nucleotide RRE,³¹ have led to the proposal of a “jellyfish” model for the Rev-RRE complex²⁹ (Fig. 4). Formation of the complex presumably involves nucleation of Rev assembly at stem IIB followed by sequential addition of Rev monomers,^{9,27} as supported by kinetic studies of Rev-RRE assembly.³²

Rev oligomerization and Rev-RNA interactions contribute synergistically toward formation of a high-affinity cooperative assembly that is directly correlated with its export competence. Studies with chimeric Rev and RRE (Rev fused to MS2 coat-protein and RRE stem IIB replaced with the MS2-RNA)^{33–35} and with polyvalent Rev-binding elements (e.g., stem IIB concatamers)^{36,37} have shown that although high affinity correlates with function, affinity alone is unable to recapitulate full export activity of the Rev-RRE complex.

These data suggest a model in which the RRE serves as an architectural scaffold that orchestrates the specific assembly of a Rev oligomer using a combination of affinities derived from RNA binding and oligomeric interactions. This complex in turn influences the structure, positioning, and stoichiometry of the larger Rev-RRE/Crm1/RanGTP export complex.

This model is reminiscent of other biological scaffolding strategies: scaffold proteins are central to organizing and coordinating signal transduction cascades in cells.³⁸ Integral to the functioning of macromolecular machines such as the ribosome,³⁹ spliceosome,⁴⁰ telomerase⁴¹ and signal recognition particle⁴² are scaffold RNAs that provide the structural framework to position the different components and in some cases to organize their catalytic abilities.

The RRE is an example of a unique RNA scaffold, providing the framework for assembling a homo-oligomeric complex. The protein-binding sites it presents recruit multiple Rev molecules through diverse sets of interactions with specific positional and orientation requirements. Viral evolution has thus served as a

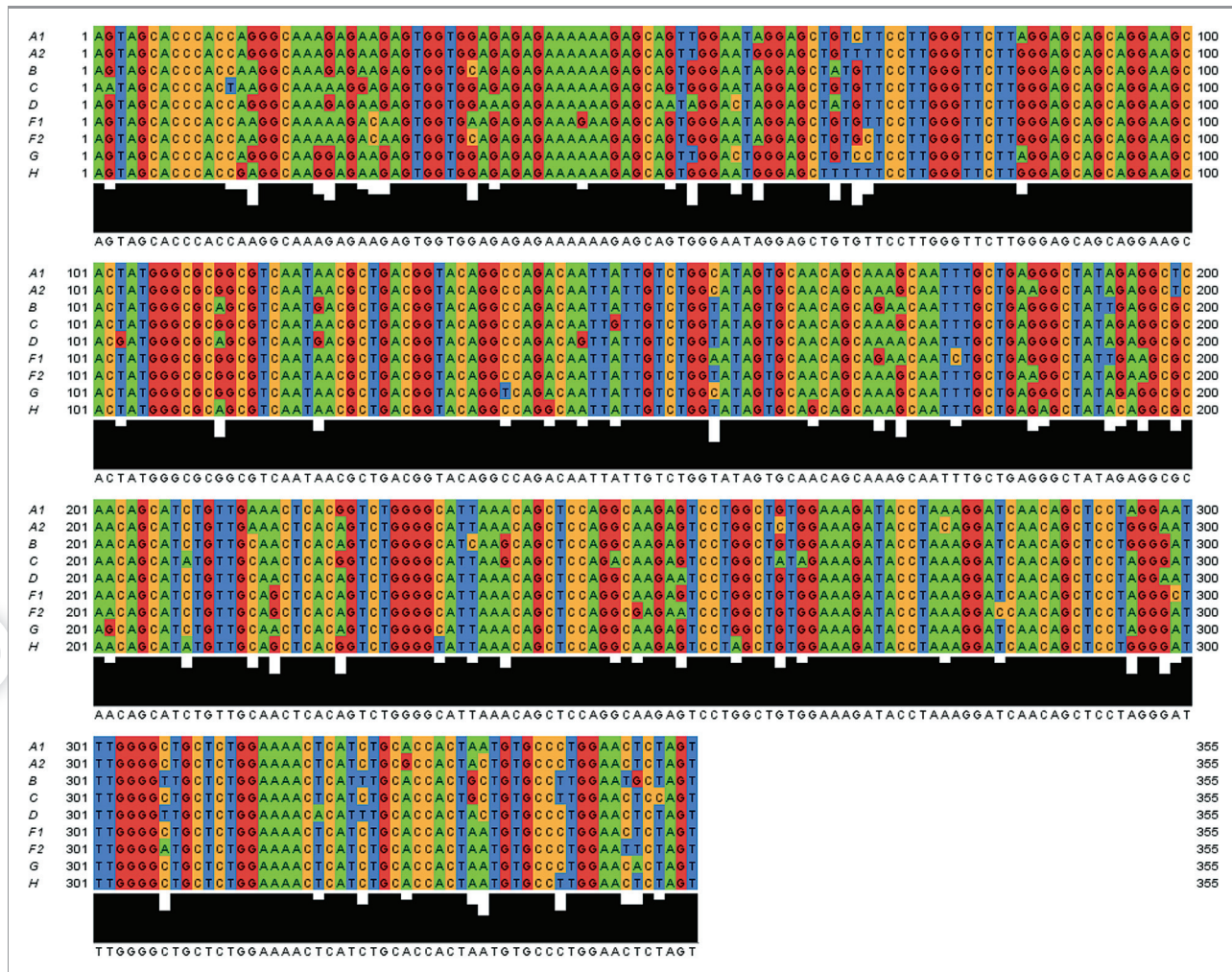


Figure 2. Sequence alignment of RREs from major HIV-1 subtypes. A sequence alignment of the consensus sequences from each of the major families of HIV-1 demonstrates the high conservation (see histogram) of the RRE. A consensus for the consensus sequences is also shown below the histogram.

selection experiment—identifying RNA-binding partners for Rev and arranging them structurally to derive maximal functional efficiency from such a complex, even under additional constraints imposed by an overlapping protein-coding reading frame. By deriving specificity from three dimensional restraints imposed by oligomer formation, the virus is able to maintain enhanced specificity of Rev for RRE over the pool of cellular RNAs without relying solely on high-affinity sequence recognition.

At least two significant observations support this model of viral evolution selection. Biochemical studies from our lab identified stem IA to be a secondary Rev-binding site²⁶ with very different structural and thermodynamic modes of Rev recognition compared with stem

IIB (Fig. 3), as might have been identified by an in vitro selection experiment. More evidence for this model comes from an intriguing study with a dominant negative Rev mutant, RevM10, that harbors a mutation in its nuclear export sequence (NES).⁴³ RevM10 assembles on the RRE like wild-type Rev but fails to trigger nuclear export of RRE-containing RNAs. Viral resistance selection experiments resulted in two silent mutations in the RRE that altered the structure of RRE in stems III/IV/V with no detectable change in binding to Rev or RevM10.⁴⁴

Related RNA Structures

All complex retroviruses face the problem of exporting unspliced and partially spliced

mRNAs and have employed the use of related RNA systems, although the scaffolding abilities of their RNAs is not well understood. Lentiviruses such as HIV-1 or SIV (simian immunodeficiency virus) use the Rev-RRE system although sequence conservation of Rev and RRE across different lentiviral species varies significantly.⁴⁵ Other complex retroviruses such as some β retroviruses, and all δ retroviruses, encode similar systems: Rem/RmRE and Rex/RxRE systems, respectively.^{46,47} Although Rev proteins from many of these viruses have been shown to oligomerize along their respective RREs, the role of these oligomeric assemblies in coordinating larger complex formation (by comparison to the Rev-RRE-Crm1/RanGTP complex of HIV-1) has not yet been elucidated.⁴⁵

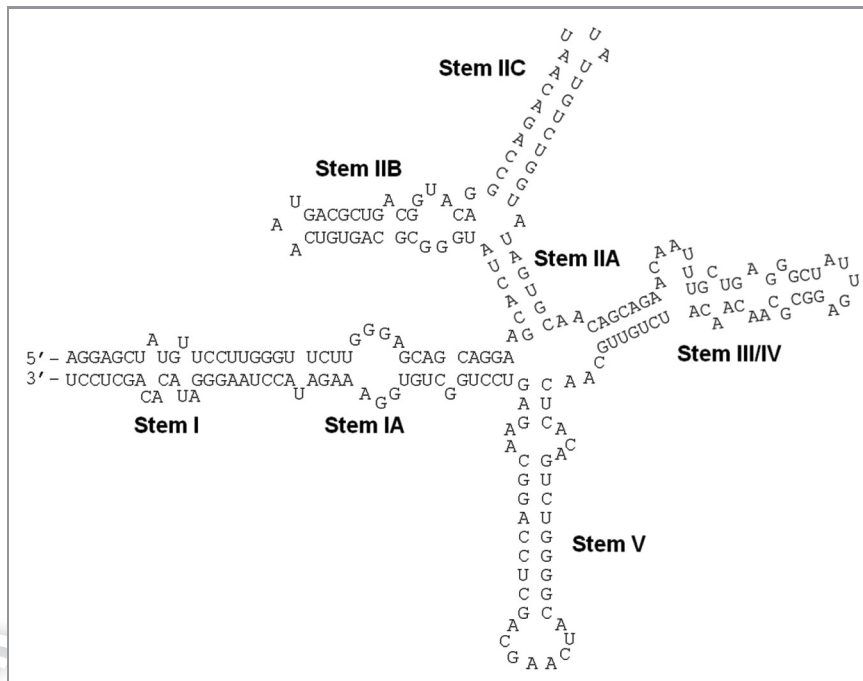


Figure 3. Predicted secondary structure of a minimal functional RRE (sequence from HXB3 strain) with the major stem loops labeled. Stem IIB is a well-characterized high-affinity site for Rev necessary but not sufficient for RRE function. Stem IA is a recently identified secondary binding site for Rev.

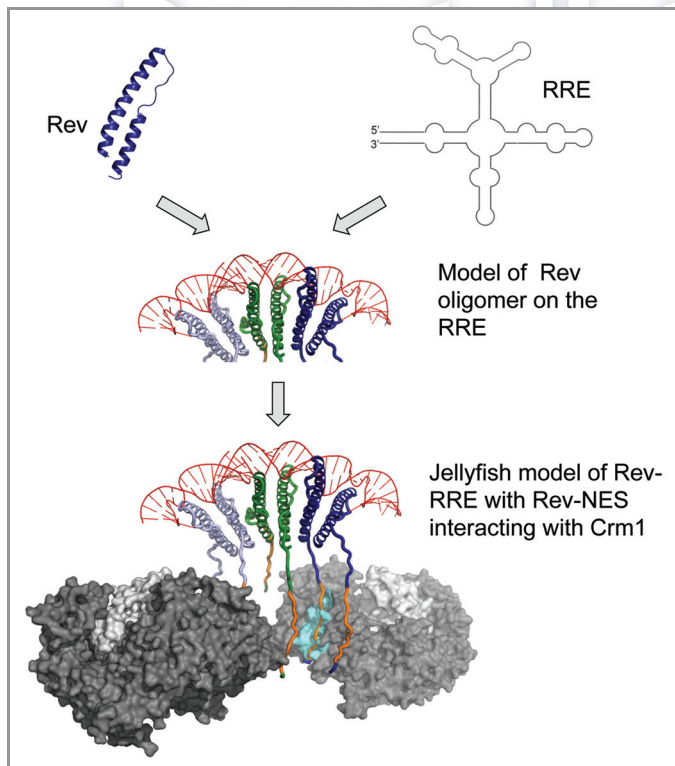


Figure 4. Schematic representation of how an export-competent Rev-RRE complex might form. Rev molecules assemble onto the RRE scaffold to form an oligomeric assembly. In the “jellyfish” model, the jellyfish head comprises Rev oligomers and RRE; the Rev-NESs form the tentacles that interact with Crm1 (shown in space-filled model) making the complex export-ready. Images of the Rev-RRE oligomer and jellyfish model have been reproduced with permission from Daugherty et al.²⁹

Many simple retroviruses, most notably Mason-Pfizer monkey virus (MPMV), do not encode a Rev-like protein, but instead have evolved a cis-acting RNA element, the constitutive transport element (CTE)⁴⁸ that directly binds to components of the host mRNA export machinery.⁴⁹ The MPMV CTE is ~220 nucleotides and consists of two identical binding sites for the Nxf1 protein.^{48,50} Although the CTE can substitute for Rev-RRE in HIV-1, export is significantly diminished in these viruses. Wild-type like export activity can be restored by engineering tandem repeats of the CTE,^{50,51} suggesting that affinity in this case is enhanced through additional sequence-specific interactions rather than through a specific structural arrangement of dissimilar but cooperative binding sites, as for the Rev-RRE complex.

Summary

The RRE is an essential viral RNA element carefully selected by many evolutionary cycles to balance specificity and adaptability. Although stem IIB serves as a high affinity anchor point, binding to the secondary binding sites on the RRE need not be driven by high affinity for the nucleotide sequence, but rather by the architecture of the entire complex. From this viewpoint, the RRE can be seen as a scaffold directing the orientation and contacts of the similarly pliable RNA binding surface of Rev. In this way, the virus is able to encode a complex and specific mechanism to achieve nuclear export without the large evolutionary penalties of maintaining the sequence of multiple high affinity binding sites.

Methods

Sequences were retrieved from the HIV sequence database (www.hiv.lanl.gov) for all isolates aligned to nucleotides 7709–8063 of the HIV-1 HXB2 sequence. Non HIV-1 sequences were removed, and sequences were realigned over the RRE using Clustal X 2.1. Analyses were performed using Consensus Maker (www.hiv.lanl.gov) and JalView.

References

- Kjems J, Brown M, Chang DD, Sharp PA. Structural analysis of the interaction between the human immunodeficiency virus Rev protein and the Rev response element. *Proc Natl Acad Sci USA* 1991; 88:683-7; PMID:1992459; <http://dx.doi.org/10.1073/pnas.88.3.683>
- Sodroski J, Goh WC, Rosen C, Dayton A, Terwilliger E, Haseltine W. A second post-transcriptional trans-activator gene required for HTLV-III replication. *Nature* 1986; 321:412-7; PMID:3012355; <http://dx.doi.org/10.1038/321412a0>
- Rosen CA, Terwilliger E, Dayton A, Sodroski JG, Haseltine WA. Intragenic cis-acting art gene-responsive sequences of the human immunodeficiency virus. *Proc Natl Acad Sci USA* 1988; 85:2071-5; PMID:2832844; <http://dx.doi.org/10.1073/pnas.85.7.2071>
- Hadzopoulou-Cladaras M, Felber BK, Cladaras C, Athanassopoulos A, Tse A, Pavlakis GN. The rev (trs/art) protein of human immunodeficiency virus type 1 affects viral mRNA and protein expression via a cis-acting sequence in the env region. *J Virol* 1989; 63:1265-74; PMID:2783738
- Malim MH, Hauber J, Le SY, Maizel JV, Cullen BR. The HIV-1 rev trans-activator acts through a structured target sequence to activate nuclear export of unspliced viral mRNA. *Nature* 1989; 338:254-7; PMID:2784194; <http://dx.doi.org/10.1038/338254a0>
- Emerman M, Vazeux R, Peden K. The rev gene product of the human immunodeficiency virus affects envelope-specific RNA localization. *Cell* 1989; 57:1155-65; PMID:2736624; [http://dx.doi.org/10.1016/0092-8674\(89\)90053-6](http://dx.doi.org/10.1016/0092-8674(89)90053-6)
- Chang DD, Sharp PA. Regulation by HIV Rev depends upon recognition of splice sites. *Cell* 1989; 59:789-95; PMID:2686839; [http://dx.doi.org/10.1016/0092-8674\(89\)90602-8](http://dx.doi.org/10.1016/0092-8674(89)90602-8)
- Hammarskjöld ML, Heimer J, Hammarskjöld B, Sangwan I, Albert L, Rekosh D. Regulation of human immunodeficiency virus env expression by the rev gene product. *J Virol* 1989; 63:1959-66; PMID:2704072
- Mann DA, Mikaelian I, Zimmel RW, Green SM, Lowe AD, Kimura T, et al. A molecular rheostat. Co-operative rev binding to stem I of the rev-response element modulates human immunodeficiency virus type-1 late gene expression. *J Mol Biol* 1994; 241:193-207; PMID:8057359; <http://dx.doi.org/10.1006/jmbi.1994.1488>
- Dayton ET, Powell DM, Dayton AI. Functional analysis of CAR, the target sequence for the Rev protein of HIV-1. *Science* 1989; 246:1625-9; PMID:2688093; <http://dx.doi.org/10.1126/science.2688093>
- Charpentier B, Stutz F, Rosbash M. A dynamic in vivo view of the HIV-1 Rev-RRE interaction. *J Mol Biol* 1997; 266:950-62; PMID:9086273; <http://dx.doi.org/10.1006/jmbi.1996.0858>
- Zapp ML, Green MR. Sequence-specific RNA binding by the HIV-1 Rev protein. *Nature* 1989; 342:714-6; PMID:2556643; <http://dx.doi.org/10.1038/342714a0>
- Daly TJ, Cook KS, Gray GS, Maione TE, Rusche JR. Specific binding of HIV-1 recombinant Rev protein to the Rev-responsive element in vitro. *Nature* 1989; 342:816-9; PMID:2481237; <http://dx.doi.org/10.1038/342816a0>
- Olsen HS, Nelbock P, Cochrane AW, Rosen CA. Secondary structure is the major determinant for interaction of HIV rev protein with RNA. *Science* 1990; 247:845-8; PMID:2406903; <http://dx.doi.org/10.1126/science.2406903>
- Cochrane AW, Chen CH, Rosen CA. Specific interaction of the human immunodeficiency virus Rev protein with a structured region in the env mRNA. *Proc Natl Acad Sci USA* 1990; 87:1198-202; PMID:2405396; <http://dx.doi.org/10.1073/pnas.87.3.1198>
- Heaphy S, Dingwall C, Ernberg I, Gait MJ, Green SM, Karn J, et al. HIV-1 regulator of virion expression (Rev) protein binds to an RNA stem-loop structure located within the Rev response element region. *Cell* 1990; 60:685-93; PMID:1689218; [http://dx.doi.org/10.1016/0092-8674\(90\)90671-Z](http://dx.doi.org/10.1016/0092-8674(90)90671-Z)
- Malim MH, Cullen BR. HIV-1 structural gene expression requires the binding of multiple Rev monomers to the viral RRE: implications for HIV-1 latency. *Cell* 1991; 65:241-8; PMID:2015625; [http://dx.doi.org/10.1016/0092-8674\(91\)90158-U](http://dx.doi.org/10.1016/0092-8674(91)90158-U)
- Cook KS, Fisk GJ, Hauber J, Usman N, Daly TJ, Rusche JR. Characterization of HIV-1 REV protein: binding stoichiometry and minimal RNA substrate. *Nucleic Acids Res* 1991; 19:1577-83; PMID:2027765; <http://dx.doi.org/10.1093/nar/19.7.1577>
- Hope TJ, McDonald D, Huang XJ, Low J, Parslow TG. Mutational analysis of the human immunodeficiency virus type 1 Rev transactivator: essential residues near the amino terminus. *J Virol* 1990; 64:5360-6; PMID:2120472
- Malim MH, Tiley LS, McCarn DF, Rusche JR, Hauber J, Cullen BR. HIV-1 structural gene expression requires binding of the Rev trans-activator to its RNA target sequence. *Cell* 1990; 60:675-83; PMID:2406030; [http://dx.doi.org/10.1016/0092-8674\(90\)90670-A](http://dx.doi.org/10.1016/0092-8674(90)90670-A)
- Huang XJ, Hope TJ, Bond BL, McDonald D, Grahk K, Parslow TG. Minimal Rev-response element for type 1 human immunodeficiency virus. *J Virol* 1991; 65:2131-4; PMID:2002556
- Heaphy S, Finch JT, Gait MJ, Karn J, Singh M. Human immunodeficiency virus type 1 regulator of virion expression, rev, forms nucleoprotein filaments after binding to a purine-rich "bubble" located within the rev-responsive region of viral mRNAs. *Proc Natl Acad Sci USA* 1991; 88:7366-70; PMID:1871141; <http://dx.doi.org/10.1073/pnas.88.16.7366>
- Kjems J, Calnan BJ, Frankel AD, Sharp PA. Specific binding of a basic peptide from HIV-1 Rev. *EMBO J* 1992; 11:1119-29; PMID:1547776
- Tan R, Chen L, Buettner JA, Hudson D, Frankel AD. RNA recognition by an isolated alpha helix. *Cell* 1993; 73:1031-40; PMID:7684657; [http://dx.doi.org/10.1016/0092-8674\(93\)90280-4](http://dx.doi.org/10.1016/0092-8674(93)90280-4)
- Battiste JL, Mao H, Rao NS, Tan R, Muhandiram DR, Kay LE, et al. Alpha helix-RNA major groove recognition in an HIV-1 rev peptide-RRE RNA complex. *Science* 1996; 273:1547-51; PMID:8703216; <http://dx.doi.org/10.1126/science.273.5281.1547>
- Daugherty MD, D'Orso I, Frankel AD. A solution to limited genomic capacity: using adaptable binding surfaces to assemble the functional HIV Rev oligomer on RNA. *Mol Cell* 2008; 31:824-34; PMID:18922466; <http://dx.doi.org/10.1016/j.molcel.2008.07.016>
- Jain C, Belasco JG. Structural model for the cooperative assembly of HIV-1 Rev multimers on the RRE as deduced from analysis of assembly-defective mutants. *Mol Cell* 2001; 7:603-14; PMID:11463385; [http://dx.doi.org/10.1016/S1097-2765\(01\)00207-6](http://dx.doi.org/10.1016/S1097-2765(01)00207-6)
- Edgcomb SP, Aschrafi A, Kompfner E, Williamson JR, Gerace L, Hennig M. Protein structure and oligomerization are important for the formation of export-competent HIV-1 Rev-RRE complexes. *Protein Sci* 2008; 17:420-30; PMID:18218716; <http://dx.doi.org/10.1110/ps.073246608>
- Daugherty MD, Liu B, Frankel AD. Structural basis for cooperative RNA binding and export complex assembly by HIV Rev. *Nat Struct Mol Biol* 2010; 17:1337-42; PMID:20953181; <http://dx.doi.org/10.1038/nsmb.1902>
- DiMattia MA, Wats NR, Stahl SJ, Rader C, Wingfield PT, Stuart DI, et al. Implications of the HIV-1 Rev dimer structure at 3.2 Å resolution for multimeric binding to the Rev response element. *Proc Natl Acad Sci USA* 2010; 107:5810-4; PMID:20231488; <http://dx.doi.org/10.1073/pnas.0914946107>
- Daugherty MD, Booth DS, Jayaraman B, Cheng Y, Frankel AD. HIV Rev response element (RRE) directs assembly of the Rev homooligomer into discrete asymmetric complexes. *Proc Natl Acad Sci USA* 2010; 107:12481-6; PMID:20616058; <http://dx.doi.org/10.1073/pnas.1007022107>
- Pond SJ, Ridgeway WK, Robertson R, Wang J, Millar DP. HIV-1 Rev protein assembles on viral RNA one molecule at a time. *Proc Natl Acad Sci USA* 2009; 106:1404-8; PMID:19164515; <http://dx.doi.org/10.1073/pnas.0807388106>
- McDonald D, Hope TJ, Parslow TG. Posttranscriptional regulation by the human immunodeficiency virus type 1 Rev and human T-cell leukemia virus type 1 Rex proteins through a heterologous RNA binding site. *J Virol* 1992; 66:7232-8; PMID:1433516
- Venkatesan S, Gerstberger SM, Park H, Holland SM, Nam Y. Human immunodeficiency virus type 1 Rev activation can be achieved without Rev-responsive element RNA if Rev is directed to the target as a Rev/MS2 fusion protein which tethers the MS2 operator RNA. *J Virol* 1992; 66:7469-80; PMID:1433526
- Nam YS, Petrovic A, Jeong KS, Venkatesan S. Exchange of the basic domain of human immunodeficiency virus type 1 Rev for a polyarginine stretch expands the RNA binding specificity, and a minimal arginine cluster is required for optimal RRE RNA binding affinity, nuclear accumulation, and trans-activation. *J Virol* 2001; 75:2957-71; PMID:11222721; <http://dx.doi.org/10.1128/JVI.75.6.2957-2971.2001>
- Kjems J, Sharp PA. The basic domain of Rev from human immunodeficiency virus type 1 specifically blocks the entry of U4/U6.U5 small nuclear ribonucleoprotein in spliceosome assembly. *J Virol* 1993; 67:4769-76; PMID:8331728
- Symensma TL, Baskerville S, Yan A, Ellington AD. Polyvalent Rev decoys act as artificial Rev-responsive elements. *J Virol* 1999; 73:4341-9; PMID:10196332
- Good MC, Zalatan JG, Lim WA. Scaffold proteins: hubs for controlling the flow of cellular information. *Science* 2011; 332:680-6; PMID:21551057; <http://dx.doi.org/10.1126/science.1198701>
- Noller HF. RNA structure: reading the ribosome. *Science* 2005; 309:1508-14; PMID:16141058; <http://dx.doi.org/10.1126/science.1111771>
- Wahl MC, Will CL, Luhrmann R. The spliceosome: design principles of a dynamic RNP machine. *Cell* 2009; 136:701-18; PMID:19239890; <http://dx.doi.org/10.1016/j.cell.2009.02.009>
- Zappulla DC, Cech TR. Yeast telomerase RNA: a flexible scaffold for protein subunits. *Proc Natl Acad Sci USA* 2004; 101:10024-9; PMID:15226497; <http://dx.doi.org/10.1073/pnas.0403641101>
- Ataide SF, Schmitz N, Shen K, Ke A, Shan SO, Doudna JA, et al. The crystal structure of the signal recognition particle in complex with its receptor. *Science* 2011; 331:881-6; PMID:21330537; <http://dx.doi.org/10.1126/science.1196473>
- Malim MH, Bohnlein S, Hauber J, Cullen BR. Functional dissection of the HIV-1 Rev trans-activator—derivation of a trans-dominant repressor of Rev function. *Cell* 1989; 58:205-14; PMID:2752419; [http://dx.doi.org/10.1016/0092-8674\(89\)90416-9](http://dx.doi.org/10.1016/0092-8674(89)90416-9)
- Legiewicz M, Badorrek CS, Turner KB, Fabris D, Hamm TE, Rekosh D, et al. Resistance to RevM10 inhibition reflects a conformational switch in the HIV-1 Rev response element. *Proc Natl Acad Sci USA* 2008; 105:14365-70; PMID:18776047; <http://dx.doi.org/10.1073/pnas.0804461105>
- Lesnik EA, Sampath R, Ecker DJ. Rev response elements (RRE) in lentiviruses: an RNAMotif algorithm-based strategy for RRE prediction. *Med Res Rev* 2002; 22:617-36; PMID:12369091; <http://dx.doi.org/10.1002/med.10027>

46. Bodem J, Schied T, Gabriel R, Rammling M, Rethwilm A. Foamy virus nuclear RNA export is distinct from that of other retroviruses. *J Virol* 2011; 85:2333-41; PMID: 21159877; <http://dx.doi.org/10.1128/JVI.01518-10>
47. Ahmed YF, Hanly SM, Malim MH, Cullen BR, Greene WC. Structure-function analyses of the HTLV-1 Rex and HIV-1 Rev RNA response elements: insights into the mechanism of Rex and Rev action. *Genes Dev* 1990; 4:1014-22; PMID:2116986; <http://dx.doi.org/10.1101/gad.4.6.1014>
48. Bray M, Prasad S, Dubay JW, Hunter E, Jeang KT, Rekosh D, et al. A small element from the Mason-Pfizer monkey virus genome makes human immunodeficiency virus type 1 expression and replication Rev-independent. *Proc Natl Acad Sci USA* 1994; 91:1256-60; PMID:8108397; <http://dx.doi.org/10.1073/pnas.91.4.1256>
49. Braun IC, Rohrbach E, Schmitt C, Izaurralde E. TAP binds to the constitutive transport element (CTE) through a novel RNA-binding motif that is sufficient to promote CTE-dependent RNA export from the nucleus. *EMBO J* 1999; 18:1953-65; PMID:10202158; <http://dx.doi.org/10.1093/emboj/18.7.1953>
50. Taberero C, Zolotukhin AS, Valentin A, Pavlakis GN, Felber BK. The posttranscriptional control element of the simian retrovirus type 1 forms an extensive RNA secondary structure necessary for its function. *J Virol* 1996; 70:5998-6011; PMID:8709222
51. Wodrich H, Schambach A, Krausslich HG. Multiple copies of the Mason-Pfizer monkey virus constitutive RNA transport element lead to enhanced HIV-1 Gag expression in a context-dependent manner. *Nucleic Acids Res* 2000; 28:901-10; PMID:10648781; <http://dx.doi.org/10.1093/nar/28.4.901>
52. Pollard VW, Malim MH. The HIV-1 Rev protein. *Annu Rev Microbiol* 1998; 52:491-532; PMID: 9891806; <http://dx.doi.org/10.1146/annurev.micro.52.1.491>

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