

HIV and Cellular Factors

Kuan-Teh Jeang

Chief, Molecular Virology Section

LMM, NIAID, National Institutes of Health, Bethesda, MD 20892-0460

INTRODUCTION

Viruses are obligatory parasites of cells. Thus it is expected that host cell factors contribute importantly to the life-cycle of viruses. In this section, we survey four types of virus-cell interactions involving HIV-1. These four areas include: 1) DNA-binding proteins that recognize target motifs in proviral LTR; 2) RNA-binding proteins that bind HIV-1 RNAs; 3) cellular factors that form protein-protein complexes with HIV-1 regulatory proteins; and 4) cellular genes which are modulated upon viral infection. With rapid increases in knowledge in the area of virus-cell interactions, we anticipate that this initial survey would be expanded extensively in future editions of the data base. Additional discussions on HIV-cell interactions are found elsewhere (Jones and Peterlin, 1994; Jeang and Gagnol, 1994; Garcia and Gaynor, 1994).

I. DNA-BINDING PROTEINS

The promoter-enhancers of the human immunodeficiency virus (HIV) are contained in the U3 of the viral long terminal repeat (LTR). HIV-1 U3 is 454 nucleotides long and has binding sites for many transcription factors. Some of these are diagrammed in Figure 1. With the exception of NF- κ B and Sp1 (Ross et al., 1991; Kim et al., 1993; Huang and Jeang, 1993; Huang et al., 1994), direct verification of the importance of the various sequences in viral contexts has not been performed.

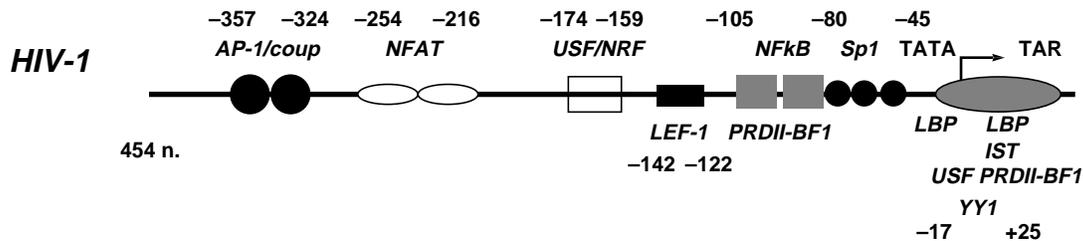


Fig. 1. Diagrammatic representation of the positions in U3 and R for some of the DNA-binding proteins that recognize the HIV-1 LTR.

Subgenomic assays in cultured cells indicate that the primary contributors to HIV-promoter activity are the NF- κ B, Sp1, and TATAA (sequences from +1 to -105; Berkhout and Jeang, 1992). Nonetheless, it is likely that other DNA-binding factors also contribute *in vivo*. Beginning directionally from the 5' end of U3, binding sites for AP-1 (a fos/jun hetero-complex; van Straaten et al., 1983; Hattori et al., 1988) and COUP (a member of the steroid/thyroid receptor superfamily; Cooney et al., 1991) are found between -324 and -357. Both COUP and AP-1 are expressed in human T-cells, and thus could compete with each other for the same proviral DNA sites during HIV-1 infection.

More proximally, between -216 and -254 are binding motifs for nuclear factor from activated T-cells (NFAT; Shaw et al., 1988). NFAT is an intermediating transducer of signals initiated at the

T-cell antigen receptor. Recent evidence suggests that NFAT binding activity is composed of three discrete polypeptides, NFATp (McCaffrey et al., 1993), Fos and Jun (Yaseen et al., 1993).

In the region between -159 and -174 is a binding consensus sequence for USF (Gregor et al., 1990). USF was characterized initially as a positive activator of adenovirus major-late-promoter transcription. In the HIV context, there is conflicting information on whether this factor has moderating (and thus be regarded as a negative regulatory factor; NRF; Lu et al., 1990) or stimulating (Maekewa et al., 1991) effects. Interestingly, USF also binds a second unrelated sequence (-5 to +11) that surrounds the HIV-1 initiator (Hu et al., 1993). USF interaction at the initiator-proximal site strongly activates expression from the TATAA-promoter (Hu et al., 1993). Of note, a factor distinct from USF, which binds the same DNA-sequence, has been cloned and characterized (TFE3; Bechmann and Kadesch, 1991).

LEF-1 is a T-cell specific transcription factor (Waterman and Jones, 1990). Once bound to its cognate site, LEF-1 bends DNA and thereby facilitates the assembly of nucleoprotein complexes at the promoter (Giese et al., 1992; reviewed in Jones and Peterlin, 1994). A high affinity LEF-1 binding site is present at -122 to -143. Two low affinity binding sites exist at -37 to -51 and +17 to +32 (Waterman and Jones, 1990).

NF-kB (Nabel and Baltimore, 1987) and Sp1 (Jones and Tjian, 1985; Jones et al., 1986) motifs are perhaps the best characterized sequence elements in the HIV-1 LTR. These sequences directly impact viral replication (Ross et al., 1991; Kim et al., 1993; Huang and Jeang, 1993; Huang et al., 1994), viral transcription (Harrich et al., 1990; Berkhout and Jeang, 1992; and references cited therein), and Tat transactivation (reviewed in Jones and Peterlin, 1994; Jeang and Gatignol, 1994). For more extensive discussions of the biochemical and functional properties of NF-kB (Ghosh et al., 1990; Kieran et al., 1990; Nolan et al., 1991; Liou et al., 1991; and references cited therein) and Sp1 (Dyan and Tjian, 1983; Briggs et al., 1986; Kadonaga et al., 1987; and references cited therein), readers should consult elsewhere.

PRDII-BF1 is a 300 kDa zinc-finger containing protein (Baldwin et al., 1990; Seeler et al., 1994). PRDII-BF1 recognizes and binds the NF-kB motif; however, it also binds a divergent sequence in R (+27 to +52; Seeler et al., 1994).

Positioned at the junction of U3 and R are sites for LBP (Yoon et al., 1994) and YY1 (Useheva and Shenk, 1994; Seto et al., 1991). While the role for LBP in HIV-1 transcription is not wholly understood (Jones et al., 1988; Kato et al., 1991), binding of YY1 to the LTR has been shown to repress HIV-1 expression and production of virions (Margolis et al., 1994). Besides LBP and YY1, a DNA-mediated activity for the induction of short transcripts (IST) has also been mapped to the same general vicinity (-5 to +26; Sheldon et al., 1993). The cDNA for the cellular factor that mediates IST-activity has not been isolated, and thus the authentic identity of this factor is unknown. HIP 116 is another newly cloned cDNA that binds to the TATA/initiator of the HIV-1 promoter (K.A. Jones, pers. communication).

II. RNA-BINDING PROTEINS

In recent years, it has become evident that RNA-binding proteins play important roles in gene regulation (see reviews, Keene and Query, 1991; Mattaj, 1993; Burd and Dreyfuss, 1994). For HIV-1, cellular proteins that bind viral regulatory RNAs have been studied in detail. In particular, at least eight host cell factors have been described to bind TAR RNA. Similarly, two RRE-binding factors have been characterized. There are also biologically compelling reasons as to why TAR- and RRE-binding proteins are meaningful contributors to the HIV-1 lifecycle.

The HIV-1 leader RNA, TAR, forms a stem-bulge-loop structure of approximately 60+ nucleotides (Muesing et al., 1987; Berkhout and Jeang, 1989). Early, it was reported that many human cellular proteins bound TAR RNA (Gatignol et al., 1989; Gaynor et al., 1989). Since then, some of these factors have been defined further. Tabulating from extant studies, eight proteins associate with either the bulge, loop, or stem of TAR RNA (see Figure 2). TAR loop-binding proteins include p68 (Marciniak et al., 1990), and TRP1/TRP185 (185 kDa; Sheline et al., 1991; Wu et al., 1991), while TRP2 (70-110 kDa; Sheline et al., 1991) binds to TAR-bulge. Proteins that complex with the

double-stranded stem of TAR RNA consist of P1/dsI (newly renamed as PKR; McCormack et al., 1992; Roy et al., 1991), SBP (140 kDa; Rounseville and Kumar, 1992), and TRBP (Gatignol et al., 1991; Gatignol et al., 1993). Finally, two human autoantigens recently have been identified as TAR RNA-binding factors. Lupus antigen Ku (Kaczmarek and Khan, 1993) binds to the loop of TAR, while La (Chang et al., 1994; Svitkin et al., 1994) recognizes U-residues within the overall context of the TAR secondary structure.

RRE-binding proteins have been studied less extensively. We know that TRBP also can bind RRE (Park et al., 1994), and that a 56 kDa factor has been described as a specific RRE-binding protein (Vaishnav et al., 1992). It is expected that other RRE-factors will emerge from future studies.

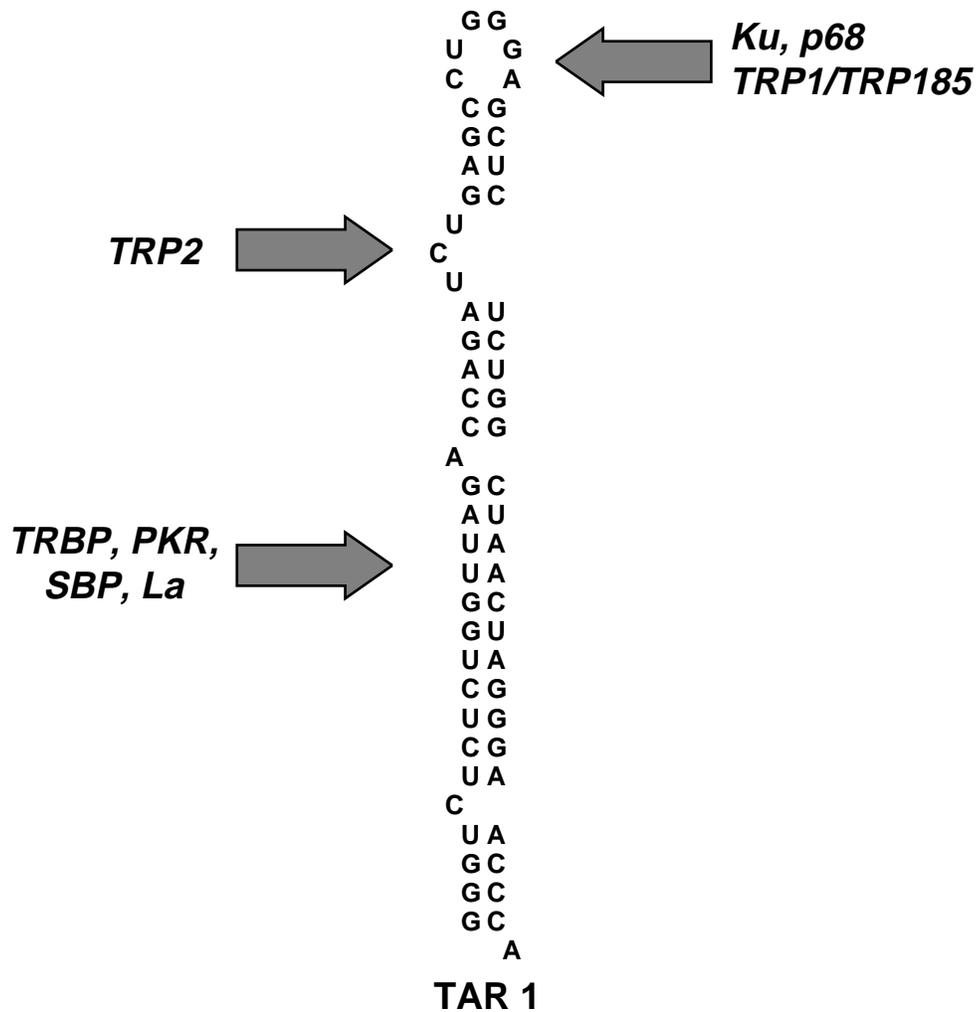


Fig. 2. Structure of the HIV-1 TAR RNA. Identities of the different proteins that bind to the loop, bulge or stem of the TAR hairpin are indicated.

III. PROTEIN-PROTEIN INTERACTIONS

Protein-protein interactions are well-documented to be important in gene regulation (see reviews, Lewin, 1990; Greenblatt, 1991). Recent studies suggest that many HIV-1 proteins complex

with host cell factors. We describe below, in a non-exhaustive fashion, some examples pertaining to Tat, Rev, Gag, and Nef.

Although Tat is best known for transcription, it has other functions (Huang et al., 1994) and has been reported to be a secretable factor that promotes the growth of Kaposi-like cells (Ensoli et al., 1990). There is evidence that Tat can be taken up actively into cells (Frankel and Pabo, 1988) through binding to a cell-surface protein (Weeks et al., 1993) implicated to be avb5 integrin (Vogel et al., 1993). Once inside cells, Tat interacts with multiple partners in activating transcription.

Two factors that bind Tat are themselves critical components of the eucaryotic polII transcription machinery. Genetic evidence supports a critical role for Sp1 in HIV-1 Tat-mediated transactivation (Harrich et al., 1989; Kamine et al., 1991; Southgate and Green, 1991; Berkhout and Jeang, 1992). Interestingly, a direct interaction between Tat and Sp1 (Jeang et al., 1993) has been documented and perhaps reflects observed virus-cell biology. In addition, there is evidence that Tat also contacts TFIID (Kashanchi et al., 1994) and that Tat-Sp1-TFIID could be a multiprotein complex (Huang et al., 1993) inside cells.

A large family of proteins related to the 26S protease from human erythrocytes (Dubiel et al., 1994) are Tat-binding polypeptides. Members of this family include TBP-1 (Nelbock et al., 1990; Ohana et al., 1993), TBP-7 (Ohana et al., 1993; Shaw and Ennis, 1993), MSS1 (Shibuya et al., 1992), and SUG1 (Swaffield et al., 1992). The exact role of this family of proteins in cellular metabolism is not wholly clear; however, the 26S protease seems to regulate the degradation of some cyclins and in this manner has been implicated in modulating the stability of oncoproteins such as c-Mos, c-Myb, c-Myc and p53 (Dubiel et al., 1994).

Two other cellular proteins, a 36 kDa protein (Desai et al., 1991) and a cellular protein kinase (Hermann and Rice, 1993), have been reported to bind Tat. The biological roles of these two factors remain to be defined.

There are at least three cellular factors that bind Rev. Rev localizes to the nucleolus, and work by Laemmli and colleagues (Fankhauser et al., 1991) has demonstrated a tight association between Rev and nucleolar B23 protein. This protein-protein complex likely directs the subcellular localization of Rev.

At the functional level Rev transactivation could be modulated by associations with cellular factors. Two additional proteins have been shown to bind Rev, translation factor eIF-5A (Ruhl et al., 1993), and a p32 protein (YL2; Luo et al., 1994) originally characterized by Krainer and colleagues (Krainer et al., 1991) as a splicing factor-SF2-associated polypeptide. YL2 was identified as a Rev-binding factor through random screening using the yeast-two-hybrid assay; however, in the same assay YL2/p32 also binds HIV-1 and HIV-2 Tat proteins (Trinh and Jeang, unpublished observation; B.R. Cullen, pers. communication).

In addition to Tat and Rev, both HIV Gag and Nef also have cellular partners. p55 and p24 Gag bind cyclophilin A and cyclophilin B proteins (Luban et al., 1993). The cyclophilins are cellular polypeptides originally characterized for their specific binding to cyclosporin A. Nef has been found to bind b-COP, a coat protein from non-clathrin-coated vesicles (R. Benarous, pers. communication). This interaction may be important in promoting the intracellular sequestration of CD4. Another group of investigators has found that Nef binds directly to the Ick-kinase in vitro (D. McPhee, pers. communication).

IV. CELLULAR GENES MODULATED BY HIV

Infection of cells by HIV most likely results in activation and repression of many cellular genes. Because of the ambient complexity of gene expression inside cells, it is logistically difficult to dissect those genes that are upregulated from those that are downregulated from those that remain unperturbed. Nevertheless, several examples of genes that respond to HIV infection are known. These include IL-2 (Westendorf et al., 1994), IL6 (Scala et al., 1994), and TGF-b (Buonaguro et al., 1994), among others. The identification of these genes has been based on classical approaches; however, we anticipate that with the advent of mRNA differential display technology (Liang and

Pardee, 1992) the exhaustive characterization of cellular genes that respond to infection by HIV should be accomplished soon.

References

REFERENCES

- [1] Baldwin, A. S. J., K. P. LeClair, H. Singh, and P. A. Sharp. 1990. A large protein containing zinc finger domains binds to related sequence elements in the enhancers of the class I major histocompatibility complex and kappa immunoglobulin genes. *Mol. Cell. Biol.* 10:1406-1414.
- [2] Beckmann, H., and T. Kadesch. 1991. The leucine zipper of TEF3 dictates helix-loop-helix dimerization specificity. *Genes Dev.* 5:1057-1066.
- [3] Benichou, S., M. Bomsel, M. Bodeus, H. Durand, M. Doute, F. Letourneur, J. Camonis, and R. Benarous. 1994. HIV-1 nef interacts with B-COP, a coat protein from non-clathrin-coated vesicles. submitted.
- [4] Berkhout, B., and K.-T. Jeang. 1989. trans Activation of human immunodeficiency virus type 1 is sequence specific for both the single-stranded bulge and loop of the trans-acting-responsive hairpin: a quantitative analysis. *J. Virol.* 63:5501-5504.
- [5] Berkhout, B., and K.-T. Jeang. 1992. Functional roles for the TATA promoter and enhancers in basal and Tat-induced expression of the Human Immunodeficiency virus type 1 long terminal repeat. *J. Virol.* 66:139-149.
- [6] Berkhout, B., R. H. Silverman, and K.-T. Jeang. 1989. Tat trans-activates the human immunodeficiency virus through a nascent RNA target. *Cell* 59:273-282.
- [7] Braddock, M., R. Powell, A. D. Blanchard, A. J. Kingsman, and S. M. Kingsman. 1993. HIV-1 TAR RNA-binding proteins control TAT activation of translation in *Xenopus* oocytes. *FASEB J.* 7:214-222.
- [8] Briggs, M. R., J. T. Kadonaga, S. P. Bell, and R. Tjian. 1986. Purification and biochemical characterization of the promoter specific transcription factor, Sp1. *Science* 234:47-52.
- [9] Buonaguro, L., F. M. Buonaguro, G. Giraldo, and B. Ensoli. 1994. The human immunodeficiency virus type 1 Tat protein transactivates tumor necrosis factor beta gene expression through a TAR-like structure. *J. Virol.* 68:2677-2682.
- [10] Burd, C. G., and G. Dreyfuss. 1994. Conserved structures and diversity of functions of RNA-binding proteins. *Science* 265:615-621.
- [11] Chang, Y., D. J. Kenan, J. Keene, A. Gatignol, and K. T. Jeang. 1994. Direct interactions between the autoantigen La and the human immunodeficiency virus (HIV-1) leader RNA. *J. Virol.* 68:7008-7020.
- [12] Cooney, A. J., S. Y. Tsai, B. W. O'Malley, and M.-J. Tsai. 1991. Chicken ovalbumin upstream promoter transcription factor binds to a negative regulatory region in the human immunodeficiency virus type 1 long terminal repeat. *J. Virol.* 65:2853-2860.
- [13] Desai, K., P. M. Lowenstein, and M. Green. 1991. Isolation of a cellular protein that binds to the human immunodeficiency virus Tat protein and can potentiate transactivation of the viral promoter. *Proc. Natl. Acad. Sci. USA* 88:8875-8879.
- [14] Du, H., A. L. Roy, and R. G. Roeder. 1993. Human transcription factor USF stimulates transcription through the initiator elements of the HIV-1 and the Ad-ML promoters. *Embo J.* 12:501-511.
- [15] Dubiel, W., K. Ferrell, and M. Rechsteiner. 1994. Tat-binding protein 7 is a subunit of the 26S protease. *Biol. Chem. Hoppe-Seyler* 375:237-240.
- [16] Dynan, W. S., and R. Tjian. 1983. Isolation of transcription factors that discriminate between different promoters recognized by RNA polymerase II. *Cell* 32:669-680.
- [17] Ensoli, B., G. Barillari, S. Z. Salahuddin, R. C. Gallo, and F. Wong-Staal. 1990. Tat protein

- of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. *Nature* 345:84-86.
- [18] Fankhauser, C., E. Izaurralde, Y. Adachi, P. Wingfield, and U. K. Laemmli. 1991. Specific complex of human immunodeficiency virus type 1 Rev and nucleolar B23 proteins: dissociation by the Rev response element. *Mol. Cell. Biol.* 11:2567-2575.
- [19] Frankel, A., and C. Pabo. 1988. Cellular uptake of the Tat protein from human immunodeficiency virus. *Cell* 55:1189-1193.
- [20] Garcia, J. A., and R. B. Gaynor. 1994. Regulatory mechanism involved in the control of HIV-1 gene expression. *AIDS* 8:S3-S17.
- [21] Garcia, J. A., D. Harrich, E. Soultanakis, F. Wu, R. Mitsuyasu, and R. B. Gaynor. 1989. Human immunodeficiency virus type 1 LTR TATA and TAR region sequences required for transcriptional regulation. *Embo J.* 8:765-778.
- [22] Garcia, J. A., F. K. Wu, R. Mitsuyasu, and R. B. Gaynor. 1987. Interactions of cellular proteins involved in the transcriptional regulation of the human immunodeficiency virus. *Embo J.* 6:3761-3770.
- [23] Gagnol, A., C. Buckler, and K.-T. Jeang. 1993. Relatedness of an RNA binding motif in HIV-1 TAR RNA-binding protein TRBP to human P1/dsI kinase and *Drosophila* Staufen. *Mol. Cell. Biol.* 13:2193-2202.
- [24] Gagnol, A., A. Buckler-White, B. Berkhout, and K.-T. Jeang. 1991. Characterization of a human TAR RNA-binding protein that activates the HIV-1 LTR. *Science* 251:1597-1600.
- [25] Gagnol, A., A. Kumar, A. Rabson, and K.-T. Jeang. 1989. Identification of cellular proteins that bind to the human immunodeficiency virus type 1 trans-activation-responsive TAR element RNA. *Proc. Natl. Acad. Sci. USA* 86:7828-7832.
- [26] Gaynor, R., E. Soultanakis, M. Kuwabara, J. Garcia, and D. S. Sigman. 1989. Specific binding of a HeLa cell nuclear protein to RNA sequences in the human immunodeficiency virus transactivating region. *Proc. Natl. Acad. Sci. U.S.A.* 86:4858-4862.
- [27] Ghosh, S., A. M. Gifford, L. R. Fiviere, P. Tempst, G. P. Nolan, and D. Baltimore. 1990. Cloning of the p50 DNA-binding subunit of NF- κ B: homology to rel and dorsal. *Cell* 62:1019-1029.
- [28] Giese, K., J. Cox, and R. Gosschedl. 1992. The HMG domain of lymphoid enhancer factor 1 bends DNA and facilitates assembly of functional nucleoprotein structures. *Cell* 69:185-195.
- [29] Goyer, C., H. S. Lee, D. Malo, and N. Sonenberg. 1992. Isolation of a yeast gene encoding a protein homologous to the human Tat-binding protein, TBP-1. *DNA Cell Biol.* 13:579-585.
- [30] Greenblatt, J. 1991. Roles of TFIID in transcriptional initiation by RNA polymerase II. *Cell* 66:1067-1070.
- [31] Gregor, P. D., M. Sawadogo, and R. G. Roeder. 1990. The adenovirus major late transcription factor USF is a member of the helix-loop-helix group of regulatory proteins and binds to DNA as a dimer. *Genes Dev.* 4:1730-1740.
- [32] Han, X. M., A. Laras, M. P. Rouseville, A. Kumar, and P. R. Shank. 1992. Human immunodeficiency virus type 1 Tat-mediated trans activation correlates with the phosphorylation state of a cellular TAR RNA stem-binding factor. *J. Virol.* 66:4065-4072.
- [33] Harrich, D., J. Garcia, F. Wu, R. Mitsuyasu, J. Gonzalez, and R. B. Gaynor. 1989. Role of Sp1-binding domains in *in vivo* transcriptional regulation of the human immunodeficiency virus type 1 long terminal repeat. *J. Virol.* 63:2585-2591.
- [34] Hattori, K., P. Angel, M. LeBeau, and M. Karin. 1988. Structure and chromosomal localization of the functional intronless human JUN protooncogene. *Proc. Natl. Acad. Sci. USA* 85:9148-9152.
- [35] Hermann, C. H., and A. P. Rice. 1993. Specific interaction of the human immunodeficiency virus Tat protein with a cellular protein kinase. *Virology* 197:601-608.
- [36] Huang, L. M., and K.-T. Jeang. 1993. Increased spacing between Sp1 and TATAA renders

- HIV-1 replication defective: Implication for Tat function. *J. Virol.* 67:6937-6944.
- [37] Huang, L. M., A. Joshi, R. Willey, J. Orenstein, and K. T. Jeang. 1994. Human immunodeficiency viruses regulated by alternative trans-activators: genetic evidence for a novel non-transcriptional function of Tat in virion infectivity. *Embo J.* 13:2886-2896.
- [38] Jeang, K.-T., R. Chun, N. H. Lin, A. Gatignol, C. G. Glabe, and H. Fan. 1993. In vitro and in vivo binding of human immunodeficiency virus type 1 Tat protein and Sp1 transcription factor. *J. Virol.* 67:6224-6233.
- [39] Jones, K., P. Luciw, and N. Duchange. 1988. Structural arrangements of transcription control domains within the 5' untranslated leader regions of HIV-1 and HIV-2 promoters. *Genes Dev.* 2:1101-1114.
- [40] Jones, K. A., J. T. Kadonaga, P. A. Luciw, and R. Tjian. 1986. Activation of the AIDS retrovirus promoter by the cellular transcription factor, Sp1. *Science* 232:755-759.
- [41] Jones, K. A., and B. M. Peterlin. 1994. Control of RNA initiation and elongation at the HIV-1 promoter. *Annu. Rev. Biochem.* 63:717-743.
- [42] Jones, K. A., and R. Tjian. 1985. Sp1 binds to promoter sequences and activates herpes simplex virus "immediate-early" gene transcription in vitro. *Nature* 317:179-182.
- [43] Kaczmarek, W., and S. A. Khan. 1993. Lupus autoantigen Ku protein binds HIV-1 TAR RNA in vitro. *Biochem. Biophys. Res. Communications* 196:935-942.
- [44] Kadonaga, J. T., K. R. Carner, F. R. Masiarz, and R. Tjian. 1987. Isolation of cDNA encoding transcription factor Sp1 and functional analysis of the DNA binding domain. *Cell* 51:1079-1090.
- [45] Kamine, J., T. Subramanian, and G. Chinnadurai. 1991. Sp1-dependent activation of a synthetic promoter by human immunodeficiency virus type I Tat protein. *Proc. Natl. Acad. Sci. USA* 88:8510-8514.
- [46] Kashanchi, F., G. Piras, M. F. Radonovich, J. F. Duvall, A. Fattaey, C.-M. Chiang, R. G. Roeder, and J. N. Brady. 1994. Direct interaction of human TFIID with the HIV-1 transactivator Tat. *Nature* 367:295-299.
- [47] Kato, H., M. Horikoshi, and R. G. Roeder. 1991. Repression of HIV-1 transcription by a cellular protein. *Science* 251:1476-1479.
- [48] Kenan, D. J., C. C. Query, and J. D. Keene. 1991. RNA recognition: towards identifying determinants of specificity. *Trends Biochem. Sci.* 16:214-220.
- [49] Kieran, M., V. Blank, F. Logeat, J. Vandekerckhove, F. Lottspeich, O. LeBail, M. B. Urban, P. Kourilsky, P. A. Baeuerle, and A. Israel. 1990. The DNA binding subunit of NF- κ B is identical to factor KBF-1 and homologous to the rel oncogene product. *Cell* 44:261-272.
- [50] Kim, J., F. Gonzalez-Scarano, S. Zeichner, and J. Alwine. 1993. Replication of type 1 human immunodeficiency viruses containing linker substitution mutations in the -201 to -130 region of the long terminal repeat. *J. Virol.* 67:1658-1662.
- [51] Krainer, A. R., A. Mayeda, D. Kozak, and G. Binns. 1991. Functional expression of cloned human splicing factor SF2: Homology to RNA-binding proteins, U1, 70k, and drosophila splicing factor. *Cell* 66:383-394.
- [52] Lee, J.-S., K. M. Galvin, and Y. Shi. 1993. Evidence for physical interaction between the zinc-finger transcription factor YY1 and Sp1. *Proc. Natl. Acad. Sci. USA* 90:6145-6149.
- [53] Lewin, B. 1990. Commitment and activation at PolII promoters: a tail of protein-protein interactions. *Cell* 61:1161-1164.
- [54] Li, C., C. Lai, D. S. Sigman, and R. Gaynor. 1991. Cloning of a cellular factor, interleukin binding factor, that binds to NFAT-like motifs in the human immunodeficiency virus long terminal repeat. *Proc. Natl. Acad. Sci. USA* 88:7739-7743.
- [55] Liang, P., and A. B. Pardee. 1992. Differential display of eukaryotic messenger RNA by means of the polymerase chain reaction. *Science* 257:967-971.
- [56] Liou, H. C., G. P. Nolan, S. Ghosh, F. Fujita, and D. Baltimore. 1992. The NF- κ B p50 precursor,

- p105 contains an internal I κ B-like inhibitor that preferentially inhibits p50. *Embo J.* 11:3003-3009.
- [57] Lu, Y., N. Touzjian, M. Stenzel, T. Dorfman, J. G. Sodroski, and W. A. Haseltine. 1990. Identification of cis-acting repressive sequences within the negative regulatory element of human immunodeficiency virus type 1. *J. Virol.* 64:5226-5229.
- [58] Luban, J., K. L. Bossolt, E. K. Franke, K. V. Ganjam, and S. P. Goff. 1993. Human immunodeficiency virus type 1 gag protein binds to cyclophilins A and B. *Cell* 73:1067-1078.
- [59] Luo, Y., H. Yu, and B. M. Peterlin. 1994. Cellular protein modulates effects of human immunodeficiency virus type 1 Rev. *J. Virol.* 68:3850-3856.
- [60] Maekewa, T., T. Sudo, M. Kurimote, and S. Ishii. 1991. USF-related transcription factor, HIV-TF1, stimulates transcription of human immunodeficiency virus-1. *Nucl. Acids. Res.* 19:4689-4694.
- [61] Marciniak, R. A., M. A. Garcia-Blanco, and P. A. Sharp. 1990. Identification and characterization of a HeLa nuclear protein that specifically binds to the trans-activation-response (TAR) element of human immunodeficiency virus. *Proc. Natl. Acad. Sci. USA* 87:3642-3646.
- [62] Margolis, D. M., M. Somasundaran, and M. R. Green. 1994. Human transcription factor YY1 represses human immunodeficiency virus type 1 transcription and virion production. *J. Virol.* 68:905-910.
- [63] Mattaj, I. W. 1993. RNA recognition: A family matter? *Cell* 73:837-840.
- [64] McCaffrey, P., C. Luo, T. Kerppola, J. Jain, T. Badalian, A. Ho Burgeon, E., W. Lane, J. Lambert, T. Curran, G. Verdine, A. Rao, and P. G. Hogan. 1993. Isoation of the cyclosporin-sensitive T cell transcription factor NFATp. *Science* 262:750-754.
- [65] McCormack, S., D. Thomis, and C. Samuel. 1992. Mechanism of interferon action: identification of a RNA-binding domain within the N-terminal region of the human RNA dependent P1/eIF-2 alpha protein kinase. *Virology* 188:47-56.
- [66] Muesing, M., D. Smith, and D. Capon. 1987. Regulation of mRNA accumulation by human immunodeficiency virus trans-activator protein. *Cell* 48:691-701.
- [67] Nabel, G., and D. Baltimore. 1987. An inducible transcription factor activates expression of human immunodeficiency virus in T cells. *Nature* 326:711-713.
- [68] Nelbrock, P., P. Dillon, A. Perkins, and C. A. Rosen. 1990. A cDNA for a protein that interacts with the human immunodeficiency virus Tat transactivator. *Science* 248:1650-1653.
- [69] Nolan, G., S. Ghosh, H. C. Liou, P. Tempst, and D. Baltimore. 1991. DNA-binding and I κ B inhibition of the cloned p65 subunit of NF- κ B, a rel-related polypeptide. *Cell* 64:961-969.
- [70] Ohana, B., P. A. Moore, S. M. Ruben, C. D. Southgate, M. R. Green, and C. A. Rosen. 1993. The type1 human immunodeficiency virus Tat binding protein is a transcriptional activator belonging to an additional family of evolutionarily conserved genes. *Proc. Natl. Acad. Sci. USA* 90:138-142.
- [71] Park, H., M. V. Davis, J. O. Langland, H. Chang, Y. Nam, J. Tartaglia, E. Paoletti, B. L. Jacobs, R. Kaufman, and S. Venkatesan. 1994. TAR RNA-binding protein is an inhibitor of the interferon-induced protein kinase PKR. *Proc. Natl. Acad. Sci. USA* 91:4713-4717.
- [72] Pfeifer, K., B. Weiler, D. Ugarkovic, M. Bachmann, H. C. Schroder, and W. E. G. Muller. 1991. Evidence for a direct interaction of Rev protein with nuclear envelope mRNA-translocation system. *Eur. J. Biochem* 199:53-64.
- [73] Ross, E., A. Buckler-White, A. B. Rabson, G. Englund, and M. A. Martin. 1991. Contribution of NF- κ B and Sp1 binding motifs to the replicative capacity of human immunodeficiency virus type 1: distinct patterns of viral growth are determined by T-cell types. *J. Virol.* 65:4350-4358.
- [74] Rounseville, M. P., and A. Kumar. 1992. Binding of a host cell nuclear protein to the stem region of human immunodeficiency virus type 1 trans-activation-responsive RNA. *J. Virol.* 66:1688-1694.

- [75] Roy, S., M. Agy, A. Horvenessian, N. Sonenberg, and M. Katze. 1991. The integrity of the stem structure of human immunodeficiency virus type 1 Tat-responsive sequence RNA is required for interaction with the interferon-induced 68,000-Mr protein kinase. *J. Virol.* 65:632-640.
- [76] Ruhl, M., M. Himmelpach, G. M. Bahu, F. Mammerschmid, B. Jaksche, H. Wolffe, H. Aschauer, G. K. Farrington, H. Probst, D. Bevec, and J. Hauber. 1993. Eukaryotic initiation factor 5A is a cellular target of the human immunodeficiency virus type 1 rev activation domain mediating trans-activation. *J. Cell Biol.* 123:1309-1320.
- [77] Scala, G., M. R. Ruocco, C. Ambrosino, M. Mallardo, V. Giordano Baldassarre, F., E. Dragonetti, I. Quinto, and S. Venuta. 1994. The expression of the interleukin 6 gene is induced by the human immunodeficiency virus 1 tat protein. *J. Exp. Med.* 179:961-971.
- [78] Seeler, J. S., C. Muchardt, A. Suessle, and R. Gaynor. 1994. Transcription factor PRDII-BF1 activates human immunodeficiency virus type 1 gene expression. *J. Virol.* 68:1002-1009.
- [79] Seto, E., Y. Shi, and T. Shenk. 1991. YY1 is an initiator sequence-binding protein that directs and activates transcription in vitro. *Nature* 354:241-245.
- [80] Shaw, D., and H. L. Ennis. 1993. Molecular cloning and developmental regulation of dictyostelium discoideum homologues of the human and yeast HIV1 tat-binding protein. *Biochem. Biophys. Res. Communications* 193:1291-1296.
- [81] Shaw, J., P. Utz, D. Durand, J. Tooole, E. Emmel, and G. R. Crabtree. 1988. Identification of a putative regulator of early T cell activation genes. *Science* 244:202-205.
- [82] Sheldon, M., R. Ratnasabapathy, and N. Hernandez. 1993. Characterization of the inducer of short transcripts, a human immunodeficiency virus type 1 transcriptional element that activates the synthesis of short transcripts. *Mol. Cell. Biol.* 13:1251-1263.
- [83] Sheline, C. T., L. H. Milocco, and K. A. Jones. 1991. Two distinct nuclear transcription factors recognize loop and bulge residues of the HIV-1 TAR RNA hairpin. *Genes Dev.* 5:2508-2520.
- [84] Shibuya, H., K. Irie, J. Ninomiya-Tsuji, M. Goebel, T. Taniguchi, and K. Matsumoto. 1992. New human gene encoding a positive modulator of HIV Tat-mediated transactivation. *Nature* 357:700-702.
- [85] Svitkin, Y. V., A. Pause, and N. Sonenberg. 1994. La autoantigen transactivates translation initiation mediated by the 5' leader sequence of the human immunodeficiency virus type 1 mRNA. *J. Virol.* 68:7001-7007.
- [86] Swaffield, J., J. Bromberg, and S. A. Johnston. 1992. Alterations in a yeast protein resembling HIV Tat-binding protein relieve requirement for an acidic activation in GAL4. *Nature* 357:698-700.
- [87] Usheva, A., and T. Shenk. 1994. TATA-binding protein-independent initiation: YY1, TFIIB, and RNA polymerase II direct basal transcription on supercoiled template DNA. *Cell* 76:1115-1121.
- [88] Vaishnav, Y. N., M. Vaishnav, and F. Wong-Staal. 1991. Identification of a nuclear factor that specifically binds to the Rev-responsive element (RRE) of human immunodeficiency virus type 1. *New Biologist* 3:142-150.
- [89] vanStraaten, F., R. Mueller, T. Curran, C. P. vanBeveren, and I. M. Verma. 1983. Complete nucleotide sequence of a human c-onc gene: deduced amino acid sequence of the human c-fos protein. *Proc. Natl. Acad. Sci. USA* 80:3183-3187.
- [90] Vogel, B., S.-J. Lee, A. Hildebrand, W. Craig, M. Pierschbacher, F. Wong-Staal, and E. Ruoslahti. 1993. A novel integrin specificity exemplified by binding of the avb5 integrin to the basic domain of the HIV tat protein and vitronectin. *J. Cell Biol.* 121:461-468.
- [91] Waterman, M. L., and K. A. Jones. 1990. Purification of TCF-1a, a T-cell-specific transcription factor that activates the T-cell receptor Ca gene enhancer in a context-dependent manner. *New Biol.* 2:621-636.
- [92] Week, B., K. Desai, P. Loewenstein, M. Klotman, P. Klotman, M. Green, and H. K. Kleinman. 1993. Identification of a novel cell attachment domain in the HIV-1 Tat protein and its 90-kDa

- cell surface binding protein. *J. Biol. Chem.* 268:5279-5284.
- [93] Westendorp, M. O., M. Li-Weber, R. W. Frank, and P. H. Krammer. 1994. Human immunodeficiency virus type 1 Tat upregulates interleukin-2 secretion in activated T cells. *J. Virol.* 68:4177-4185.
- [94] Wu, F., J. Garcia, D. Sigman, and R. Gaynor. 1991. tat regulates binding of the human immunodeficiency virus trans-activating region RNA loop-binding protein TRP-185. *Genes Dev.* 5:2128-2140.
- [95] Yaseen, N. R., B. Maizel, F. Wang, and S. Sharma. 1993. Comparative analysis of NFAT (nuclear factor of activated T cells) complex in human T and B lymphocytes. *J. Biol. Chem.* 268:14285-14293.
- [96] Yoon, J.-B., G. Li, and R. Roeder. 1994. Characterization of a family of related cellular transcription factors which can modulate human immunodeficiency virus type 1 transcription in vitro. *Mol. Cell. Biol.* 14:1776-1785.
- [97] Zimmermann, K., M. Dobrovnik, C. Ballaun, D. Bevec, J. Hauber, and E. Bohnlein. 1991. trans-Activation of the HIV-1 LTR by the HIV-1 Tat and HTLV-I Tax proteins is mediated by different cis-acting sequences. *Virology* 182:874-878.