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The multiple functions of HIV-1 Tat: proliferation versus apoptosis

Francesca Peruzzi

Center for Neurovirology and Cancer Biology, Temple University, 1900 12th North Street, Philadelphia, Pennsylvania 19122

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1. ABSTRACT

The HIV-1 transactivating factor Tat plays critical roles in the pathogenesis of AIDS. Originally discovered as a potent activator of viral replication, Tat has now been found to be involved in the regulation of both viral and cellular gene expression. Due to its structure, Tat protein can be secreted by infected cells, and can penetrate neighboring uninfected cells, altering their function in the absence of viral replication. Indeed, increasing number of reports suggest a multifunctional effect of Tat, which depends on cell type and the degree of cellular maturation. Here, we discuss intracellular activities of Tat in HIV-infected cells, as well as in cells exposed to Tat, and focus on two contradictory aspects of Tat-mediated effects: cell proliferation and cell death.

2. INTRODUCTION

The pandemic human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) affect about 40 million people (1). Although the introduction of highly active antiretroviral therapy (HAART) greatly improved the prognosis, at least in developed countries, AIDS is the leading cause of death in Africa, and the worldwide prevalence of the disease is rising (2). The overall occurrence of HIV infection possibly reflects the complexity of the disease and a yet unclear understanding of the mechanisms by which HIV causes AIDS and AIDS-associated disorders. Nevertheless, more then twenty years of intense research in the field have uncovered many of the aspects of HIV infection. Although the structure of the viral genome is rather simple, the

molecular interactions of the virus with various host cell types are very complex. One of the viral proteins that is required for viral replication and has been associated with many of the pathologies caused by HIV infection is the trans-activating factor Tat. Soon after its discovery in 1985, Tat appeared to play key functions in controlling not only viral replication (3) but also viral and cellular transcription (4, 5). From the structural point of view, Tat gene consists of two exons that encode for two variants of the protein, which are 72 and 101 amino acids in length, respectively. While the 101 aa Tat is considered the natural full-length isoform of Tat, a shorter peptide of 86 aa is often used for *in vitro* experiments. It is thought that several passages in culture originated the 86 aa truncated variant (6). From the functional point of view, Tat has been found to bind directly to a variety of nuclear and cytoplasmic factors, therefore affecting cellular functions.

In this review, we analyze multifunctional properties of Tat, its physical and functional interactions with cellular factors in a voyage from the cytoplasmic membrane to the nucleolus. We will attempt to dissect signaling pathways involved in Tat-mediated cellular dysfunction including cell death, proliferation and dedifferentiation.

3. TAT AT THE PLASMA MEMBRANE

One remarkable property of Tat is its ability to travel between cells. The domain of Tat protein that mediates its transfer across cell membranes is the arginine-rich RKKRRQRRR region at position 49-57 (7), which is also the nuclear localization signal and the TAR (trans-activation responsive) RNA binding domain (8, 9). The uptake of Tat can occur via several means depending on the cell type (figure 1). In T cells, Tat can bind to several receptors at the plasma membrane, such as the T-cell activation molecule dipeptidyl aminopeptidase IV (DP IV), also known as CD26 (10), the chemokine receptor CXCR4 (11), cell surface lipoprotein receptors including the heparan sulfate proteoglycans (12), and the low-density lipoprotein receptor–related protein (LRP) (13). Dipeptidyl aminopeptidase IV (DP IV) is a type II membrane glycoprotein ubiquitously expressed in a variety of cell types including T lymphocytes in which it regulates growth and differentiation (14). DP IV functions by removing N-terminal dipeptides from polypeptides in which an alanine or proline is in penultimate position (15, 16). Tat contains a N-terminal XXP motif that has been shown to bind and inhibit DP IV/CD26 activity in T cells (10, 17). Specific interactions of Tat with DP IV are thought to downregulate activation and to mediate the antiproliferative effect of Tat in T cells (18, 19). Tat-mediated inhibition of DP IV-catalyzed hydrolysis affects expression of inflammatory cytokines such as IL-1, and TNF-α. In fact, high concentration of Tat had a strong suppressive effect on DNA synthesis and IL-1 beta production, while it stimulated secretion of IL-1 receptor antagonist (IL-1RA) and TNF-α in a human leukemia cell line (20).

The chemokine receptor CXCR4 is the high affinity receptor for stromal derived factor 1α (SDF1α) and the main coreceptor for HIV T-tropic strains (21). It was earlier shown that Tat enhances expression of CXCR4 receptors in resting T cells (22). Further investigation demonstrated that Tat might act as a CXCR4 antagonist; a feature that may explain the negative selection against HIV-1-CXCR4 strain observed in HIV patients (11). Of interest, CXCR4 is highly expressed in neuronal stem cells (NSC) (23), where it functions in directing the migration of these cells toward an injury site in the central nervous system (CNS) (24). The competition of Tat with SDF1α for the binding to the CXCR4 receptor on the NSC may suggest an additional component participating in the neuronal damage observed in the chronic HIV-1 infection of the brain.

The basic domain of Tat mediates its binding to heparan sulfate proteoglycans (HSPG), which results in the accumulation of Tat in the extracellular matrix (ECM) (25). In this configuration, Tat competes with the basic fibroblast growth factor (bFGF) for the binding to HSPG (26). The pool of bFGF associated with EMC of AIDS-KS cells represents a localized storage of this growth factor that is protected from proteolitic degradation (27, 28). Mobilization of bFGF by Tat enhances KS lesions (Kaposi's sarcoma) and endothelial cell growth (26). The binding of Tat to cell surface heparan sulfate proteoglycans has been additionally proposed as a mechanism for the internalization of Tat (12), as well as its biological activity (29). However, more recent data suggest that Tat peptide is internalized *via* a clathrin-dependent endocytic pathway (30), which is active also in the absence of heparan sulfate receptors (31).

Another cellular receptor that binds the viral protein Tat is the low-density lipoprotein receptor–related protein (LRP), which is particularly abundant in the brain (32). The binding of Tat to the LRP in neurons inhibits neuronal clearance of the LRP physiological substrates apoliprotein E4 (ApoE4), α2-Macroglobulin, amyloid precursor protein (APP), and amyloid β (Aβ) (13).

4. SIGNALING PATHWAYS TRIGGERED BY INTRACELLULAR TAT

4.1. Apoptotic pathways induced by Tat in T cells

HIV-1 infection induces a rapid turnover of CD4 cells (33, 34). Progressive depletion of CD4 from the immune system is thought to involve a bystander-mediated apoptosis (35). Due to its protein transduction domain (PTD), which confers the ability to travel across the cells, Tat had been earlier suspected and is now demonstrated to cause apoptosis in T cells by various means: i) The up or down regulation of cellular genes encoding cytokines (36), cell survival factors such as Bcl-2 (37-39), superoxide-dismutase (40); ii) dysregulation of the microtubule network (41-43); iii) The activation of cyclin dependent kinases (44); iv) up-regulation of TNF-related apoptosis-inducing ligand (TRAIL) in macrophages (45); and v) up-regulation of Fas ligand (46, 47).

In general, a balance of pro- and anti-apoptotic factors maintains cell survival, and several factors may disturb this balance either by up-regulating pro-apoptotic

molecule or down-regulating the expression of anti-apoptotic genes (figure 1). Indeed, expression of Tat in hematopoietic cells results in marked down-regulation of the anti-apoptotic protein Bcl2 and increased levels of the pro-apoptotic factor Bax (39). This is in contrast to an earlier study in which Zauli *et al.* showed an up-regulation of Bcl2 in Jurkat T cells and primary peripheral blood mononuclear cells (PBMCs) (37); perhaps suggesting that other factors may participate in the effects of Tat. Intracellular Tat in HeLa cells suppresses the expression of cellular manganese-containing superoxide dismutase (Mn-SOD), thus sensitizing the cells to oxygen-derived free radicals (40). The Tat-mediated suppression of manganese-containing superoxide dismutase 2 (SOD2) promoter was found to involve the increased binding activity of the transcription factor Sp3 by Tat (48).

Tat may induce apoptosis by targeting the microtubule structure. It has been shown that direct binding of Tat to αβ-tubulin alters the microtubule dynamics in T cells leading to activation of the mitochondrial apoptotic pathway (43). Enhancement of microtubule polimerization by extracellular Tat induced cytochrome c release and apoptosis in T cells (42), by a mechanism involving direct binding of Tat to the microtubule-associated protein LIS1 (41). Finally, Tat-induced apoptosis in a T cell line and in cultured peripheral mononuclear cells from uninfected donors was associated with increased activation of cyclin-dependent kinases (44).

Zhang and co-workers suggested a model in which soluble Tat increases the production of TRAIL in macrophages, which in turn can induce apoptosis in bystander T cells (45). The predominant signaling pathway elicited by an apoptotic stimulus in T cells involves the activation of death-receptors (Fas or CD95) and its ligand, Fas-L (49). Fas-dependent apoptosis in T cells can be mediated by the physical interaction of Tat with the early growth response factors 2 and 3 (Egr2, Egr3), which in turn increases the expression of Fas-L (46). In line with these data, Bartsz *et al.* showed an increased expression and activation of the apoptotic molecule caspase 8 (50). Tat may also prime T cells to apoptotic stimuli by increasing secretion of IL-2, one of the major cytokine involved in T cells growth and differentiation. Extracellular Tat increased IL-2 production in Jurkat T cells (36) by a mechanism involving the Tat-mediated enhanced activation of NF-κB and consequent activation and de-repression of a distal AP-1 site in the IL-2 promoter (51). In addition, HIV-1 infected T lymphocytes undergoing apoptosis express increased levels of the growth factor bound protein Grb3-3 (52), a signaling molecule activated by the MAPK pathway. Up-regulation of Grb3-3 appeared to be induced independently by the viral proteins Tat and Nef (52).

4.2. Apoptotic pathways induced by Tat in neuronal cells

One of the various pathologies associated with HIV-1 infection is related to the nervous system and embraces a series of dysfunctions ranging from minor cognitive/motor disorders to clear dementia (53). In an attempt to uncover the molecular mechanisms associated with HIV-1 infection of the brain, particular attention has been dedicated to the effects of extracellular and intracellular Tat on neuronal cells, including astrocytes, oligodendrocytes, microglia and neurons. The macrophages/microglia component of the neuronal cell pool is the productive source of viral particles, while HIV-infection is rarely detected and anyway not productive in oligodendrocytes, astrocytes, and neurons (54-58). Among those cell types, it is accepted that neurons suffer from an indirect injury caused by the release of toxic viral and cellular factors from HIV-1 infected and/or immune activated cells. In several instances, the activation of N-methyl-D-aspartate (NMDA)-glutamate receptor has been shown to mediate Tat-neurotoxicity (59-64). Neurotoxicity of Tat is also thought to be associated with oxidative stress (65, 66). In primary rodent cortical neurons Tat and its transcriptional substrate platelet activating factor (PAF) additionally increased ATP levels and mitochondrial membrane potential (67). Although toxicity of viral proteins like Tat and gp120 has been widely investigated and measured as an extent of neuronal death in culture, many reports emphasize the concept that cerebral injury may occur without loss of neurons. This could indicate that other molecules and cellular mechanisms *in vivo* buffer the potential toxicity of these factors showed *in vitro*. There is in fact a strong debate concerning the extent of neuronal damage caused by viral and cellular factors, mainly because of difficulties in detecting and measure concentration of those molecules in tissues. Apart from apoptosis, which can be considered as a terminal event, viral proteins including Tat alter multiple cellular functions, possibly leading to neuronal dysfunction. For instance, Tat may sensitize neuronal cells to injury by interfering with neurotrophin (68, 69) and cytokine receptor signaling pathways (70).

4.3. Tat-induced cell proliferation and dedifferentiation

Cell death is only one of the various aspects of Tat-induced toxicity. In contrast to apoptosis, Tat has been shown to enhance cell proliferation in a variety of cell types including neurons. Clinical complications associated with HIV-1 infection include two types of cancers: non-Hodgkin's lymphoma and Kaposi's sarcoma (71-73). Evidence for the participation of Tat in AIDS-associated B-cells lymphoma came from a study in which Tat was introduced into the germ line of mice. Tat-transgenic mice developed lymphoid hyperplasia in the spleen, lymph nodes, and lung (74, 75).

The tumor-like lesions known as Kaposis's sarcoma (KS) are clinical manifestations occurring frequently during HIV-1 infection and they are thought to originate from benign hyperproliferations that progress to malignancies. Although human herpes virus 8 (HHV8) is thought to be the etiological agent for KS (76), it is not sufficient to develop AIDS-KS legions. The earliest evidence to support a role for Tat in AIDS-KS came from a transgenic mouse study showing that Tat can produce KS-like lesions when it is introduced into the germ line of mice (77). Of interest is the observation that extracellular Tat has different effects depending on its concentration (reviewed in (78)). Tat promoted KS cell growth at low

concentrations (0.05 to 50 ng/ml), whereas higher concentrations of Tat (over 100 ng/ml) were not stimulatory (79, 80). The work of Ensoli further explained a synergism between bFGF and Tat protein in inducing angiogenic Kaposi's sarcoma-like lesions in mice. The synergism was due to Tat, which enhanced endothelial cell growth and type-IV collagenase expression in response to bFGF mimicking extracellular matrix proteins (81). Tat-mediated angiogenesis in KS lesions is also achieved by the cooperation between the Tat basic domain and the C-terminus RGD motif, which is known to bind to αvβ1 and αvβ3 integrins (26) (figure 1).

In addition, Tat collaborates with the HHV8 G protein-coupled receptor (vGPCR) to enhance NF-κB and nuclear factor of activated T cells (NF-AT) activities (82, 83). Pati *et al.* further showed that the enhancement of NF-AT by Tat was mediated through cumulative stimulation of the PI3-K/Akt/GSK-3 pathway by vGPCR and Tat (83). Tat-mediated activation of the PI3-K pathway enhanced the survival mechanism induced by vascular endothelial cell growth factor receptor-2 (VEGF2), insulin growth factor receptor I (IGF-IR), and interleukin-3 (IL-3) in KS cells (84). Increased levels of PI3-K phosphorylation were earlier detected in a PC12 cell model after treatment of the cultures with nanomolar concentrations of Tat (85, 86). In a similar experimental setting, intracellular expression of Tat also enhanced PI3-K activation by increasing the levels and tyrosine phosphorylation of the p120 focal adhesion kinase (p120FAK) (86). In several instances enhancement of proliferation was observed in Tat-treated or Tat-transfected PC12 cells (69, 87, 88). Milani *et al.* observed an increased proliferation rate of PC12 cells expressing Tat when cells were cultured in the absence of serum (87). In our recent study, we further investigated the tumorigenic potential of Tat in PC12 cells by using different approaches and we found that: i) Tat-expressing PC12 cells gained the ability to proliferate in serum-free media; ii) Tat induced the formation of bigger colonies in soft agar (anchorage independent conditions); and iii) Tat induced the formation of bigger tumors in nude mice when compared to the control cell lines (69). Moreover, we found that one of the mechanisms by which Tat enhanced the transformed phenotype of PC12 cells was the Tat-dependent increased level of inhibitor of differentiation 1 (Id1) (69). Enhanced expression of Id proteins is thought to correlate with cell proliferation and inhibition of cellular differentiation (89-91). Accordingly, we found that the unique activation of signal transducer and activator of transcription 5A (Stat5A) by nerve growth factor (NGF) in PC12 cells expressing Tat resulted in Id1 expression and inhibition of NGF-induced differentiation (Figure 1) (69). The presence of markers identifying undifferentiated phenotype is frequently confirmed in HIV-1 infected cells. For instance, HIV-1 infection during early macrophage differentiation resulted in sustained cyclin T1 expression, while infection at later stages of differentiation resulted in the re-expression of cyclin T1 (92). The same study further demonstrated that expression of the viral protein Nef contributed to re-induction of cyclin T1 (92). Since the proteasome/ubiquitin pathway tightly regulates cyclin T1 levels in macrophages (92) and Tat interacts with some components of the proteasome structure and blocks the proteasomal activity (93, 94) (figure 1), one may speculate that Tat may participate in the stabilization of cyclin T1.

Another example of induction of proliferation and down-regulation of cell maturity markers in Tat-bearing cells is provided by a study performed in podocytes (95). Loss of differentiation markers and enhanced proliferation of podocytes is often observed by immunohistochemical analysis in tissue samples from patients suffering of HIV-1-associated nephropathy (HIVAN). Although podocytes are refractory to HIV infection, the expression of Tat in these cells induced proliferation (95). The mechanism of Tat–induced proliferation included the increased transcription and release of basic fibroblast growth factor (bFGF) by Tat (95). In the same study, the authors found that Tat deregulated the podocyte phenotype causing down-regulation of differentiation markers such as WT-1 and synaptopodin.

5. NUCLEAR LOCALIZATION OF TAT

The basic domain of Tat, the GRKKR region, is essential for the transit and accumulation of Tat in the nucleus (96). In the nuclear compartment Tat is involved in the chromatin remodeling (reviewed in (8)) by forming a ternary complex with two histone acetyltransferases, p300 and P/CAF (97). The Tat-p300 interaction increased the histone acetyltransferase (HAT) activity of p300 on histone H4 that is associated with nucleosomal DNA (98). Interestingly, Tat was also found to be a substrate for p300 and P/CAF, which acetylate the viral protein in the TAR RNA binding domain and in the activation domain, respectively (99). PCAF-mediated acetylation enhanced Tat binding to the Tat-associated kinase, cyclin T1, whereas acetylation by p300 promoted the dissociation of Tat from TAR RNA sequence (99). Results from a recent study support a model in which HIV transcription is regulated by cycles of Tat acetylation and deacetylation (100). Deacetylation of Tat was mediated by human sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide-dependent class III protein deacetylase (100).

Another interesting property of Tat that has recently emerged from other studies is related to its ability to interfere with the DNA repair machinery. In one study Tat was found to be a potent inducer of the DNA repair protein beta- polymerase (beta-pol), which encodes a key enzyme in the DNA base-excision repair pathway (101). Tat-mediated induction of beta-pol required the binding of the Sp1 transcription factor to the beta-pol promoter (101). Although the significance of the Tat-mediated induction of beta-pol is not yet clear, it may contribute to the genomic instability in the development and growth of neoplastic B cells (101). Our recent study further demonstrated that expression of Tat protected PC12 cells from DNA double-strand breaks caused by genotoxic agents (102). The mechanism of Tat-mediated protection involved increased levels of Rad51, a key mediator of homologous recombination in cells expressing Tat (102). Tat-mediated preservation of genomic integrity during cellular division

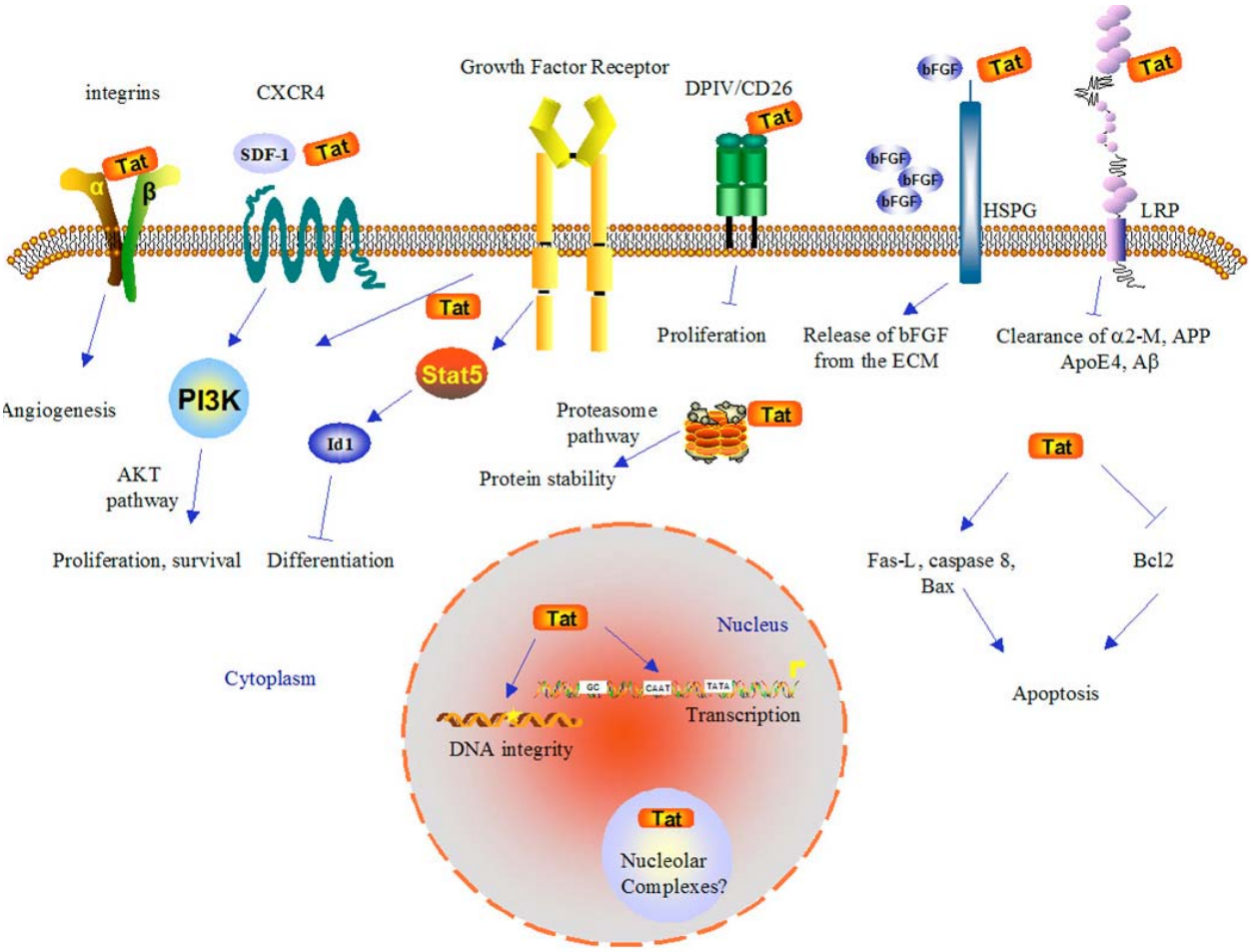

Figure 1. A model representing Tat in various subcellular compartments and the multiple effects of Tat on cellular functions. At the plasma membrane the interaction of Tat with αvβ1 and αvβ3 integrins enhances angiogenesis in KS lesions. The binding of Tat to CXCR4 enhances the PI-3K/Akt pathway involved in cell survival and proliferation. The PI-3K/Akt route may additionally be targeted by the interference of Tat with growth factor receptor signaling pathways, resulting again in enhanced proliferation. In neuronal cells, the intracellular presence of Tat may lead to the activation of a new pathway (Stat5/Id1) by NGF receptor, which results in the inhibition of cell differentiation. Internalization of Tat into the cells may occur via binding of this protein to the HSPG. By competing with bFGF for the binding to HSPG Tat mobilizes the pool of bFGF that is bound to the extracellular matrix, which may contribute to enhance KS lesions and endothelial cell growth. On the other hand, the binding of Tat to the DPIV/CD26 receptor may trigger an anti-proliferative effect. In neuronal cells, the binding of Tat to the LRP inhibits neuronal clearance of ApoE4, α2-macroglobulin (α2-M), amyloid precursor protein (APP) and amyloid β (Aβ). The interaction of Tat with the proteasome structure may regulate the expression levels of proteins involved in either proliferation or death pathways. Apoptotic pathways induced by Tat might be triggered by increased expression of pro-apoptotic molecules such as Fas-L and Bax or a down-regulation of anti-apoptotic proteins like Bcl2. Tat can in fact regulate the expression of several factors by acting on their specific promoters (represented in the nucleus). Tat-mediated dysregulation of cellular functions could involve an action of Tat on DNA genomic stability. A role of Tat in the nucleolar compartment has been finally postulated and it may involve the binding of the viral protein with nucleolar factors to form functionally active complexes.

may overcome cellular events that could be unfavorable to viral replication (102) (figure 1).

6. NUCLEOLAR LOCALIZATION OF TAT

The peptide (GRKKRRQRRRAP) of the Tat protein, which contains two short basic regions, has a strong affinity to the nucleus and has been used to target fusion proteins to the nucleolar compartment (103). Immunogold electron microscopy performed on Jurkat cells stably transfected with Tat showed dense localization of Tat in the fibrillar and granular components of the nucleolus (104). In the nucleoli Tat co-localizes with the nuclear protein B23 (nucleophosmin) (104, 105). The interaction between Tat and B23 required an intact nucleolar localization signal (NoLS) both in Tat and in B23 proteins (105). These findings were partially confirmed by later observations showing a partial interaction between Tat

and B23 in living cells (106). Although the nucleolar function of Tat remains unclear, nucleolar trafficking of viral RNA have been proposed several times. *In situ* hybridization and electron microscopy confirmed nucleolar localization of subgenomic mRNA expressing HIV-1 p37gag, a sequence of viral genome containing the Rev responsive element (107). Even though several investigators failed to detect viral RNA in the nucleolus (108, 109), Michienzi *et al.* showed again a nucleolar trafficking for HIV-1 RNA (110). In this study, the forced accumulation of a hammerhead ribozyme that specifically cleaves HIV-1 RNA into the nucleoli of human cells suppressed HIV-1 replication. The authors further speculated that the formation of a ribonucleoprotein complex containing the HIV-1 RNA, the viral regulatory proteins Tat and Rev, as well as other cellular factors could take place in the nucleolus and participate in viral RNA processing (110) (figure 1).

7. CONCLUSIONS

HIV-1 transactivator factor Tat plays pivotal roles in transcription and replication of the viral genome. However, its specific amino acidic structure confers the unusual property of shuttling Tat not only among cells but also between subcellular compartments. Tat can interact with a wide variety of cellular proteins in plasma membrane, cytoplasm, nucleus, and even nucleolus (figure 1). Such interactions alter signal transduction pathways, which often lead to contradictory responses such as proliferation and apoptosis. Some discrepancies have emerged from several studies on the effects of Tat on apoptotic death, especially in neuronal cells, where clearly documented neurotoxicity of Tat *in vitro* does not explain only modest neuronal death detected *in vivo*. Perhaps the predicted *in vitro* toxicity of Tat is counteracted by a variety of factors that may neutralize Tat-mediated pro-apoptotic signals, causing instead metabolic distress and neuronal dysfunction. Indeed, *in vitro* studies and clinical observations support a role for Tat in modulating the expression and/or activity of cellular factors in neuronal cells, which may lead to injuries without induction of apoptotic pathways. Conversely, in other cell types, such as KS cells, Tat is able to enhance cell survival and proliferation. Among the mechanisms found to be involved in the Tat-mediated cellular effects, one may include the possibility that alteration of the same molecule or a specific signaling pathway have an opposite outcomes depending on the cell type or the stage of development. Tat-mediated enhanced expression of Id1 for instance may result in enhanced proliferation but only in cells that are permissive to proliferation, while being deleterious in cells in which a cell-cycle re-entry is not supported.

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Abbreviations: Aβ, amyloid β; α2-M, α2-macroglobulin; ApoE4, apoliprotein E4; APP, amyloid precursor protein; bFGF, basic fibroblast growth factor; bax, Bcl2-associated X protein; Bcl2, B-cell CLL/lymphoma 2; DPIV, dipeptidyl aminopeptidase IV; ECM, extracellular matrix; Id1, inhibitor of DNA binding 1; Fas-L, Fas ligand; PI3-K, phosphoinositide 3-kinase; SDF1α, stromal-derived factor 1α; Stat5, signal transducer and activator of transcription 5; Tat, trans-activating factor; HSPG, heparan sulfate proteoglycans; LRP, lipoprotein receptor-related protein.

Key Words: AIDS, Immune system, Immune deficiency, Infectioin, Virus, HIV-1, Tat, Signaling Pathways, Review

Send correspondence to: Dr Francesca Peruzzi, Center for Neurovirology and Cancer Biology, Temple University, 1900 12th North Street, Philadelphia, Pennsylvania 19122, Tel. 215-204-3612. Fax 215-204-0679, E-mail: fperuzzi@temple.edu

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