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Review

Biological properties of the HIV-1 Tat protein and its regulatory mechanisms on immune cells

Yang Weiling[1,2,3], Xiao Na[1,2,3], Jiang Yan[2,3,*] and Zeng Yi[3,4,*]

[1] Graduate School, Youjiang Medical University for Nationalities, No.98 Chengxiang Road, Baise 533000, Guangxi, China
[2] Basic Medical School, Youjiang Medical University for Nationalities, No.98 Chengxiang Road, Baise 533000, Guangxi, China
[3] Key Laboratory of Basic Research and Transformation of Tumor Immunity and Infectious Diseases, Youjiang Medical University for Nationalities, No.98 Chengxiang Road, Baise 533000, Guangxi, China
[4] General Practitioners School, Youjiang Medical University for Nationalities, No.98 Chengxiang Road, Baise 533000, Guangxi, China

* **Correspondence:** Email: jiangyan9hr@ymun.edu.cn, yizeng@ymun.edu.cn.

Abstract: The transactivator of transcription (Tat) protein is a transactivative transcription factor of the Human Immunodeficiency Virus Type 1 (HIV-1) that contains multiple functional domains and exhibits diverse biological activities, including the activation of viral gene expression and the regulation of host cellular pathways. In immune cells, Tat profoundly affects the function of immune cells by inducing apoptosis, modulating immune responses, promoting inflammation, and impairing antigen presentation. In this review, we provided a comprehensive overview of Tat's molecular structure, its function, and its impact on the gene transcription of hose cells. Furthermore, the multidimensional mechanisms by which immune cells T cells, B cells, macrophages, and dendritic cells are impacted by Tat were also reviewed. We state that Tat is potentially regarded as a therapeutic target, emphasizing the importance of developing targeted intervention strategies.

Keywords: HIV-1 Tat; T cell; B cell; macrophage; dendritic cell

1. Introduction

Human Immunodeficiency Virus Type 1 (HIV-1), the principal causative agent of the global Acquired Immunodeficiency Syndrome (AIDS) pandemic, presents a major challenge to human health and societal stability. As a member of the Retroviridae family, HIV-1 displays high replicative capacity and genetic variability. Through the action of reverse transcriptase, the viral RNA genome is converted into DNA, which subsequently integrates into the host genome, establishing long-term latency and persistent infection [1]. During the early stages of infection, the transactivator of transcription (Tat) protein is expressed from the integrated proviral DNA [2]. Subsequently, Tat translocates into the nucleus and binds to the viral long terminal repeat (LTR) region, enhancing viral RNA transcription and promoting viral replication [3]. The Tat protein can also be released from infected cells and enter neighboring cells, where it modulates host gene expression and alters host cell behavior [4]. Its effects on immune cells have been widely studied.

The Tat protein exhibits a dual role in immune regulation: In activating immune function, it upregulates the expression of inflammatory factors, immune stimulatory cytokine 1, and monocyte chemoattractant protein-1 (MCP-1), which may lead to the activation of the immune system. Relatively speaking, immunosuppression is more dominant in Tat-mediated immune function regulation. By inducing T cell apoptosis, antigen-driven and non-specific T cell proliferation are inhibited, the phagocytosis of apoptotic tumor cells by helper cells is interfered, IL-12 secretion is blocked, NK cell activity and Th1 cell differentiation are inhibited, and the tumor killing function of NK cells is directly inhibited. This may be related to the inhibition of granzyme A secretion. These effects together weaken the anti-tumor immune surveillance, natural immune function, and the ability to respond to foreign antigens, which may promote the immunosuppression and Th1-Th2 imbalance observed in AIDS patients, causing systemic immune dysfunction [5–8].

Given the diverse biological functions and pathogenic mechanisms of Tat, we summarize the findings on Tat-mediated regulation of immune cell function and examine its role in HIV pathogenesis and therapeutic strategies.

2. Biological properties of the HIV-1 Tat protein

2.1. The six functional domains of the Tat protein, nucleolar localization, and secretion

The Tat protein is an intrinsically unstructured protein with a molecular weight between 14 and 16 kDa, comprising 80 to 104 amino acids depending on the viral strain [9,10]. Encoded by two exons, Tat contains several functional domains, including the N-terminal, cysteine-rich, core, arginine-rich, glutamine-rich, and C-terminal domains [11]. The first five functional domains are within the first exon [12]: 1) The N-terminal region, also known as the proline-rich domain, includes the first 21 amino acids and facilitates interactions with CYCT1 while contributing to LTR transactivation in coordination with the cysteine-rich and core domains. A conserved tryptophan residue at position 11 is essential for efficient Tat secretion [13]. 2) The cysteine-rich domain spans residues 22 to 37 and contains closely spaced cysteines that form intramolecular disulfide bonds, which are critical for structural stability [14,15]. 3) The core domain, encompassing residues 38 to 48, cooperates with the cysteine-rich region to mediate cofactor binding, particularly with CREB-binding protein (CBP)/p300, histone acetyltransferases (HATs), and the transcription factor Sp1 [16,17]. 4) The arginine-rich domain, also referred to as the basic domain, spans

residues 49 to 57 and includes the conserved motif 49RKKRRQRRR57, which is essential for TAR binding as well as for Tat secretion and uptake [13,18]. 5) The domain rich in glutamine binds to the domain rich in arginine, commonly known as the alkaline region, which contains the remaining portion of the first exon from amino acids 58 to 72, contributes to nuclear localization and mediates interaction with the CCAAT/enhancer-binding protein (C/EBP) [18–20].

The basic domain (BD, N-terminal domain) of HIV-1 Tat determines its nuclear localization. BD is rich in positively charged amino acids, which can interact with importin-α to transport the Tat protein into the nucleus. Moreover, studies have shown that BD does not solely perform the nuclear localization function. For example, BD can actively transport Tat to the nucleus, and deletion of BD leads to a diffuse distribution of Tat in the cytoplasm. However, ATP depletion experiments indicate that the concentration of the complete Tat protein structure significantly decreases in the absence of ATP but remains higher than that of the control group. The nuclear concentration in the absence of BD is comparable to that of the control group. This suggests that there are other domains in the Tat structure that also contribute to nuclear transport functions. Furthermore, the accumulation of Tat in the nucleus relies not only on importin-α mediated input but also on its binding with nuclear core components (such as RNA or nucleoproteins) for nuclear retention [21]. In summary, BD is a key nuclear localization signal for the Tat protein, but its full function depends on the synergistic action of the complete structural domains of Tat and the involvement of other nuclear components.

The final domain of Tat, known as the C-terminal region, is encoded by the second exon and typically spans amino acids 73 to 101. Compared to the first exon, the second exon of Tat is less prominent in transactivation but is essential for efficient replication of macrophage-tropic HIV-1 strains and contributes to viral persistence [22–24]. Although the final domain shows partial sequence conservation, considerable variability exists among HIV-1 subtypes [24]. The C-terminal region contains an arginine-glycine-aspartate (RGD) motif, which mediates binding to integrin receptors and can initiate intracellular signaling cascades [24,25]. The structural and functional diagram of Tat is shown in Figure 1. Functional overlap among Tat domains is common, and only a limited number of residues are highly conserved [12]. This structural flexibility enables substantial sequence variation, resulting in activating and inhibitory effects on viral and host gene expression [26].

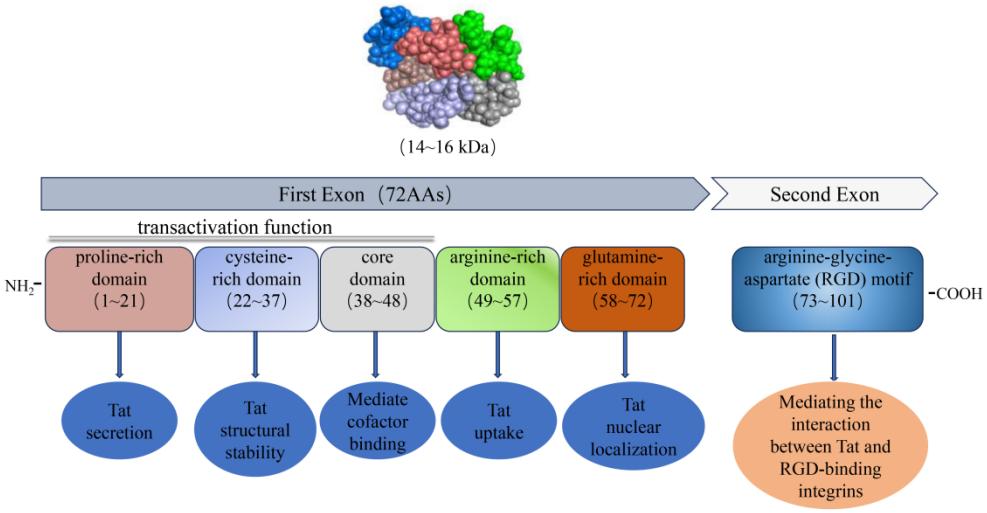

Figure 1. The structural and functional diagram of Tat.

The Tat protein is released by mechanisms other than cell death [4]. It has been reported that Tat is released from intact cells through the leaderless peptide secretion pathway. Through the basic region, the released Tat binds to the structure of heparan sulfate proteoglycans (HSPG), and Tat is stored in the extracellular matrix (ECM) [27]. Furthermore, to stabilize in the extracellular matrix, Tat is secreted and present in the form of exosomes, contributing to broaden the scope of the target cells [28]. It is widely believed that Tat has biological activities outside cells, but the secretion mechanism of the Tat protein is not fully understood.

2.2. The transactivation function of Tat

The functional domains of the Tat protein enable its participation in multiple cellular processes. The canonical role of Tat, transactivation of the HIV-1 long terminal repeat (LTR), is primarily mediated by the proline-rich, cysteine-rich, and core domains [29]. This transactivation function is essential for HIV-1 replication and markedly enhances the transcriptional efficiency of the viral genome. Tat binds to the transactivation response element (TAR), an RNA stem-loop structure encoded by the HIV-1 LTR, and subsequently recruits the host cell's positive transcription elongation factor b (P-TEFb) complex to TAR [5]. TAR is located within identical non-coding regions at the 5′ and 3′ ends of the proviral genome [30]. P-TEFb consists of two key subunits: Cyclin-dependent kinase 9 (CDK9) and cyclin T1 (CYCT1) [31]. Tat-mediated recruitment of P-TEFb to TAR leads to hyperphosphorylation of RNA polymerase II (RNAPII), thereby enhancing transcriptional elongation and promoting the accumulation of full-length viral transcripts [32]. Tat can amplify HIV-1 replication by more than 100-fold through this mechanism, significantly accelerating viral propagation and disease progression [33,34].

2.3. Regulation of host cell gene transcription by Tat

The Tat protein is a crucial regulatory protein and pathogenic factor associated with HIV-1. It plays a significant role in promoting viral replication and modulating host gene transcription through multiple mechanisms: 1) Regulating host gene promoters: Tat can enter the nucleus of host cells and function as a transcription factor [35], influencing gene transcription by precisely controlling the recruitment, pausing, and elongation of RNA polymerase II, as well as remodeling histone modifications. This leads to a comprehensive reprogramming of transcription programs in immune cells, which affects immune function, promotes viral replication, and facilitates immune evasion [36]. 2) Inhibiting miRNA function: The HIV-1 Tat protein can inhibit the function of microRNAs (miRNAs) by binding to the Dicer protein, which is essential for the production of small non-coding RNAs [37–39]. This interference disrupts the post-transcriptional regulation of host gene transcription. For instance, in astrocytes, the HIV-1 Tat protein selectively inhibits specific miRNAs, which interferes with the Wnt/β-catenin pathway, affecting normal cellular gene transcription and leading to abnormal cell function and neuroinflammation [40]. 3) Interacting with histone acetyltransferases: Following HIV-1 infection, the Tat protein interacts with host histone acetyltransferases, such as TAFII250 and Tip60, or inhibits their activity to assist in the activation of HIV-1 transcription while blocking host gene transcription [41,42], thus interfering with normal cellular behavior. 4) Regulating transcription complex assembly: The HIV-1 Tat protein activates transcription through an atypical mechanism by recruiting positive transcription elongation factor b (P-TEFb), which guides the assembly of a transcription initiation complex that includes only the TATA-Binding Protein (TBP) and lacks TBP-Associated

Factors (TAFs), thereby efficiently initiating transcription [41]. Additionally, Tat's strong "hijacking" of P-TEFb can deplete the limited P-TEFb resources within the cell, potentially inhibiting the expression of other genes that rely on P-TEFb, such as Cyclin T1-dependent genes. For instance, during the differentiation process of monocyte macrophages, Cyclin T1 is essential for the regulation of many gene expressions, and because of the consumption induced by Tat, the expression of these genes is suppressed [43,44], which may interfere with the normal physiological functions of macrophages.

In summary, the Tat protein can regulate host cell gene transcription through direct or indirect mechanisms, disrupt normal cell functions, and cause effects such as immunosuppression, inflammatory response, and neurotoxicity, playing a key role in the pathologic processes of AIDS. Therefore, in-depth research on the Tat protein as a therapeutic target for AIDS has important scientific and clinical significance.

3. Impact of the HIV-1 Tat protein on immune cells

3.1. Effects of HIV-1 Tat on T cells

According to the functional characteristics of T cells, they can be divided into two major subpopulations: CD4-expressing helper T cells (Th) and CD8-expressing cytotoxic T lymphocytes (CTL). $CD4^+$ T cells act as "commanders" in the immune system, activating and coordinating other immune cells (such as B cells and $CD8^+$ T cells) by releasing cell factors; while $CD8^+$ T cells act as "killers", directly recognizing and eliminating virus-infected cells, cancer cells, or abnormal cells, mainly by releasing mediators such as perforin and granzyme to induce target cell apoptosis. During HIV-1 infection, the virus-encoded Tat protein disrupts the synergy between $CD4^+$ T cells and $CD8^+$ T cells through intricate mechanisms, thereby promoting viral latency and immune evasion, exacerbating the process of immune depletion in the host.

3.1.1. Promoting the establishment of latent reservoirs in $CD4^+$ T cells.

HIV-1 differs from other retroviruses in that its replication does not depend on the cell cycle, meaning it does not rely on host cell proliferation [45]. Therefore, HIV-1 can infect actively dividing cells and cells in a resting state [46]. In the body, the host range of HIV-1 includes T cells, macrophages, monocytes, and B cells, among which $CD4^+$ T cells are its primary target cells, existing in resting and activated states [47]. Notably, resting $CD4^+$ T cells are the main reservoir for HIV-1 to form latent infections in the body and are the primary source of viral rebound after stopping anti-retroviral therapy (ART) [48,49]. In the process of establishing and maintaining this reservoir, the HIV-1 Tat protein is crucial and affects T cell function through various mechanisms. Specifically, the Tat protein promotes the formation of infected and latent viral reservoirs by increasing the number of resting $CD4^+$ T cells carrying HIV proviral DNA and extending their half-life [50]; after ART treatment, as latent infection cells are cleared, Tat can induce naive $CD4^+$ T cells to differentiate into memory types (memory $CD4^+$ T cells are susceptible to HIV latency) [51], creating a cell pool that is highly prone to establishing latent infections, thereby replenishing and expanding the latent viral reservoir. On the other hand, the Tat protein inhibits the activation and cytotoxicity of $CD8^+$ T cells, helping latent infected $CD4^+$ T cells evade immune clearance, providing favorable conditions for the virus to persist long-term [52].

In summary, the Tat protein promotes the survival and expansion of $CD4^+$ T cells while inhibiting

the response of $CD8^+$ T cells, thereby bidirectionally facilitating the maintenance of HIV-1 latency, which reflects its opposing immunoregulatory effects on $CD4^+$ and $CD8^+$ T cells.

3.1.2. Effects on $CD4^+$ T cells: Exhaustion, aging, and apoptosis

$CD4^+$ T cells, as the primary target cells of HIV infection, experience a reduction in number and functional exhaustion, which are core features of AIDS. The Tat protein is an "accelerator" in this process. However, its specific regulatory effects on T cells exhibit significant diversity and conditional dependence, even showing contradictory effects at different stages of infection or in different microenvironments. The regulation of $CD4^+$ T cell apoptosis by the Tat protein has a dual concentration-dependent nature: At low concentrations, it inhibits apoptosis induced by factors such as nutrient deprivation or Fas cross-linking by activating the PI3K/Akt pathway and upregulating Bcl-2 expression [53,54]; while at high concentrations, Tat, especially from rapidly progressing patient strains, induces apoptosis by upregulating FasL and activating the mitochondrial apoptosis pathway, promoting the release of cytochrome C, and strongly facilitating $CD4^+$ T cell apoptosis, with its apoptotic induction ability mainly relying on the α-helix structure rich in glutamine domains [54,55]. Additionally, Tat drives abnormal activation and differentiation of $CD4^+$ T cells: Under non-polarized conditions, it enhances the proliferation of naive cells and promotes their differentiation into memory phenotypes; after TCR activation, Tat further strengthens their activated state, promoting the secretion of cytokines such as IL-2, IFN-γ, and TNF-α, thereby driving Th1-type immune responses [56,57]. Although this Th1 response is beneficial for antiviral activity in the early stages, sustained excessive activation not only causes immune damage but also accelerates the exhaustion of the $CD4^+$ T cell pool and expands the population of memory cells susceptible to HIV infection, forming a vicious cycle of persistent viral amplification [56]. Furthermore, Tat reduces telomerase activity by inhibiting the phosphorylation and nuclear translocation of hTERT, causing $CD4^+$ T cells to lose replicative potential and age prematurely, further weakening immune regeneration capacity [58]. These multiple mechanisms collectively exacerbate the exhaustion of $CD4^+$ T cells and the collapse of the immune system.

3.1.3. Effects on $CD8^+$ T cells: Dysfunction and immune evasion

$CD8^+$ T cells are the main antiviral effector cells, and their functional exhaustion is an important reason why HIV cannot be cleared. The Tat protein directly disrupts the maintenance of $CD8^+$ T cell function and long-term survival through various mechanisms. On one hand, Tat can up-regulate transcription factors such as T-bet, Eomes, and Blimp-1 via integrin (e.g., αvβ3 and α5β1) signaling pathways under the premise of TCR activation, enhancing the ability of $CD8^+$ T cells to secrete IFN-γ, Granzyme B, and IL-2, showing increased cytotoxicity in the short term. This activation enhances the ability of $CD8^+$ T cells to secrete IFN-γ, Granzyme B, and IL-2, showing increased cytotoxicity in the short term [59]. However, this abnormal activation is a double-edged sword, which may lead to functional exhaustion in the long term, forming a phenotype of "over-activation but functionally impaired" that is highly consistent with HIV infection. In addition, Tat targets CD127 (IL-7Rα): Tat's N-terminal domain binds to the cytoplasmic region of CD127 and recruits the host protein CIS through the basic domain, mediating the ubiquitination-proteasome degradation of CD127 [60,61], thereby depriving $CD8^+$ T cells of their response capability to the key survival factor IL-7, impairing the survival and recall response functions of memory cells, significantly promoting immune evasion [60]. Tat

also induces $CD8^+$ T cells to present an incomplete differentiation state of $CD27^+CD127^-$, which maintains effector function in the short term but lacks long-term memory potential [59]. Additionally, *in vivo* experiments further show that Tat can alter the immune response dynamics of antigen-specific $CD8^+$ T cells, causing enhanced early expansion but temporary functional suppression ("stunning") and delayed responses, which not only weakens the ability to control viral infections but also exacerbates chronic immune activation [56], leading to severe dysfunction of $CD8^+$ T cells.

Due to the complex regulatory mechanisms of intracellular signal molecules, the regulatory effect of Tat protein can sometimes simultaneously impair $CD4^+$ and $CD8^+$ T cells, and its impact is not limited to a specific subtype, but leads to widespread T cell immune dysfunction. It is noteworthy that the effect of Tat on T cells is not limited to peripheral mature cells, as it also intervenes and disrupts during the thymic development stage. In transgenic mouse models, Tat expression causes thymic atrophy and T cell developmental blockade, resulting in a decrease in peripheral $CD4^+$ and $CD8^+$ T cell numbers, indicating that Tat weakens T cell output at the source [62]. Furthermore, the N-terminal peptide of Tat can inhibit its enzyme activity by interacting with dipeptidyl-peptidase IV (CD26/DPPIV), thereby suppressing T cell proliferation and antigen-specific responses [63,64], which is also a common mechanism of HIV immune dysfunction.

In summary, the Tat protein promotes the formation of core pathological features of HIV-1 infection by differentially and complementarily damaging $CD4^+$ and $CD8^+$ T cells: $CD4^+$ T cell exhaustion and persistent latent reservoirs, $CD8^+$ T cell dysfunction and failure of immune monitoring, leading to viral latency maintenance, immune exhaustion, and systemic chronic immune activation, laying the foundation for the progression of AIDS. Therefore, targeting Tat may restore the function of T cell subsets and enhance the anti-HIV immune response capability.

3.2. Impact of HIV-1 Tat on B cells

During HIV-1 infection, although T cells are the primary targets, a notably high incidence of B cell-related malignancies has been observed in individuals with AIDS. This phenomenon has led to extensive investigation into the role of the HIV-1 Tat protein in the malignant transformation of B cells. Through diverse and intricate molecular and cellular mechanisms, Tat indirectly influences B cell behavior and contributes to the pathogenesis of AIDS-associated B cell lymphomas.

Studies have demonstrated that the Tat protein activates the Akt/mTORC1 signaling pathway in B cells and suppresses transcriptional repressors such as AICDA, c-Myb, and E2F8, resulting in the aberrant activation of activation-induced cytidine deaminase (AICDA) [65,66]. After release from infected cells, the Tat protein can act on uninfected B cells, inducing oxidative stress, DNA damage, and an increased frequency of chromosomal aberrations. These effects are novel oncogenic drivers contributing to B cell lymphomas in individuals with HIV-1 infection [67]. When B cells are exposed to the Tat protein for a long time, it can cause a series of changes in B cells. Tat affects genomic instability, including chromosome translocation and structural abnormalities, leading to an increased mutation frequency in host cells. Similar results are observed even in transcriptionally inactive Tat protein mutants, indicating that the mutagenic effect of Tat on host cells largely does not depend on its transactivation activity. Tat can activate Toll-like receptor and NOD-like receptor pathways to provide abnormal proliferation and survival signals for B cells, which may be mediated by the JAK-STAT signaling pathway. Moreover, Tat can also downregulate the gene expression of cytokine-cytokine receptor signaling pathways, cell adhesion-related molecular pathways, and leukocyte transendothelial

migration-related pathways, which may be related to the low immune monitoring in B cell lymphoma patients. Furthermore, Tat can upregulate the expression of long non-coding RNAs (lncRNAs) [68], among which NEAT1 and MALAT1 have been confirmed to be involved in the malignant development of B cell tumors, and their specific mechanisms remain to be elucidated. These changes will promote the occurrence of lymphoma over time [69]. Multiple additional mechanisms support the development of B cell lymphomas. Moreover, Tat induces the expression of cytokines IL-6 and IL-10 [70], which influence the proliferation of specific B cell subsets and disrupt normal differentiation in HIV-positive individuals. For instance, Tat suppresses the proliferation of naive and memory B cells while promoting the expansion of germinal center B cells [71]. Tat also downregulates the HLA-DRB1 and HLA-DRB5 genes, reducing HLA-DR expression on B cell surfaces. This downregulation impairs NF-κB signaling and weakens EBV-specific $CD4^+$ T cell responses, facilitating immune evasion by B cells [72]. Together, these alterations contribute to the malignant transformation of B cells in the context of HIV-1 infection.

The HIV-1 Tat protein has a complex and critical role in the pathogenesis of AIDS-related B-cell lymphoma. Kaposi's sarcoma (KS) is the most common tumor associated with HIV infection and belongs to the γ-herpesvirus subfamily [73]. The KS-associated herpesvirus (KSHV) is the pathogenic factor of KSHV, characterized mainly by the endothelial-derived spindle cells of neovascularization and proliferation. Studies indicate that the HIV-1 Tat protein can enhance the infectivity of KSHV to endothelial cells, which mainly relies on the basic region within the Tat protein. The Tat protein can activate the expression of the ORF50 gene, promoting the progression of KS; this gene is an important molecular switch for the transition of KSHV from latency to lytic replication. This activation is not caused by the direct action of Tat on the ORF50 promoter but rather through the reprogramming of B cells: Tat upregulates the expression of cytokines, such as IL-6 and IL-4, further activating the JAK-STAT signaling pathway, where the IL-6/STAT3 axis exerts a negative regulatory effect, while the IL-4/STAT6 axis plays a positive promoting role. This results in the activation of the "molecular switch" ORF50 for KSHV lytic replication, thereby promoting viral proliferation and jointly driving the pathogenesis of AIDS-related B-cell lymphoma. The KSHV virus can encode a carcinogenic protein vIL-6, and a high expression of vIL-6 can induce cells to secrete IL-6 and Vascular Endothelial Growth Factor (VEGF), thereby promoting extensive neovascularization and sustaining tumor development [74]. Zhou et al. [75] found that the HIV-1 Tat protein indirectly cooperates to promote the malignant progression of tumors by activating the downstream PI3K-AKT pathway of vIL-6. Moreover, Tat can also inhibit the expression of the negative regulatory factor PTEN of PI3K and the negative regulatory factor GSK-3β of the cell cycle, further amplifying the carcinogenic activity of vIL-6 [75]. The promotion of KSHV infection, activation of lytic replication, and hijacking of key signaling pathways such as PI3K/AKT by the HIV-1 Tat protein collectively drive the key mechanisms of the occurrence and development of AIDS-related B-cell lymphoma.

In summary, the HIV-1 Tat protein contributes to the development of B cell lymphomas through diverse mechanisms, including activation of oncogenic signaling pathways, modulation of gene expression, evasion of immune surveillance, induction of oxidative stress and DNA damage, and disruption of normal B cell differentiation. Thus, multiple mechanisms indirectly regulate B-cell behavior, collectively coordinating to promote the occurrence of B cell lymphoma. These findings underscore the pivotal role of Tat in B cell malignant transformation and the pathogenesis of AIDS-related tumors, offering potential molecular targets for the development of therapeutic strategies against HIV-associated lymphomas.

3.3. Impact of HIV-1 Tat on macrophages

3.3.1. Enhancement of macrophage susceptibility to HIV-1 infection and viral dissemination

The HIV-1 Tat protein is critical in the pathogenesis of HIV-1 infection, with its multifaceted effects on macrophages attracting considerable research interest. Tat expression in macrophages significantly alters cellular protein activity, including the activation of NADPH oxidase in macrophages and microglia, resulting in elevated oxidative stress levels [76]. By binding to TAR RNA, Tat also enhances HIV-1 transcription and replication in macrophages, thereby increasing viral infectivity [77]. Research has shown that Tat increases the susceptibility of human monocytes and macrophages to M-tropic (macrophage-tropic) and T-tropic (T-lymphocyte-tropic) HIV-1 strains [78], thereby broadening the viral host range. Tat also plays a key role in regulating macrophage migration and infiltration. For instance, increased numbers of macrophages have been observed in the perivascular spaces of the mouse striatum following Tat exposure, along with enhanced recruitment of macrophages to the brain [79]. By downregulating Apelin-13 expression in mouse cortical tissues, Tat facilitates macrophage infiltration; *in vitro* studies further confirm that Tat promotes macrophage migration [80]. As macrophages function as target cells and reservoirs for HIV-1, Tat-induced enhancement of their migration and infiltration significantly contributes to viral dissemination during infection.

3.3.2. The dual role of Tat in regulating macrophage inflammatory responses

The Tat protein is involved in the inflammatory responses of macrophages. Studies have shown that Tat promotes the release of inflammatory mediators such as IL-1β, TNF-α, and IL-6 through reactive oxygen species (ROS)-dependent pathways [81]. Tat also synergizes with methamphetamine to impair the antioxidant capacity of macrophages, further enhancing the production of pro-inflammatory factors [82]. In the central nervous system, Tat activates microglia, the brain-resident macrophages, which produce pro-inflammatory cytokines, proteases, and ROS, contributing to neuronal damage [83,84]. While Tat predominantly induces inflammatory responses, anti-inflammatory effects have also been observed under certain conditions. In the RAW264.7 macrophage cell line, Tat suppresses interferon-induced inducible nitric oxide synthase (iNOS) activity [85] and mediates immunosuppression through TGF-β1 signaling [86], demonstrating a potential anti-inflammatory role. This functional duality may reflect distinct regulatory strategies employed by Tat during different phases of HIV-1 infection, including viral latency and active replication.

3.3.3. Inhibition of macrophage apoptosis and reservoir maintenance

The Tat protein regulates macrophage apoptosis through multiple mechanisms. Tat upregulates the expression of the anti-apoptotic gene Bcl-2 [87] and inhibits caspase-3 activation, thereby extending macrophage survival [88]. Tat also induces the expression of TREM-1, which confers anti-apoptotic properties by preserving mitochondrial function, enhancing anti-apoptotic protein expression, and suppressing the activation of apoptotic pathways, supporting the long-term persistence of viral reservoirs [89,90]. In addition, Tat antagonizes autophagy induced by factors such as TNF-α, further limiting macrophage cell death [81]. Last, Tat exerts cytoprotective effects in macrophages and human microglial cell lines by inhibiting PTEN, a negative regulator of the PI3K/AKT pathway [91]. This

inhibition promotes prolonged survival of macrophage reservoirs and supports sustained HIV-1 production.

The HIV-1 Tat protein functions as a central regulatory factor in HIV-1 infection, exerting complex effects on macrophages by modulating inflammation, apoptosis, migration, and immune responses. These functions are significant for viral replication, reservoir maintenance, and disease progression. The dual nature of its functions, pro-inflammatory and anti-inflammatory, pro-apoptotic and anti-apoptotic, reflects the virus's sophisticated strategies for long-term survival within the host. The specific effects of the HIV-1 Tat protein on various inflammatory factors are summarized in Table 1.

Table 1. HIV-1 Tat-mediated effects on inflammatory responses.

	Biological effect of Tat	Inflammation	References
IL-6	Activation	Pro-inflammatory	[92–94]
TGF-β1	Activation	Pro-inflammatory	[93]
TNF-α	Activation	Pro-inflammatory	[92,95–97]
IL1-β	Activation	Pro-inflammatory	[96,98]
IL-10	Activation	Anti-inflammatory	[99,100]
IL-1	Activation	Pro-inflammatory	[101]
IFN-γ	Activation	Pro-inflammatory	[102,103]
RANTES (Chemokine)	Activation	Pro-inflammatory	[92]
IL-4 receptor	Activation	Anti-inflammatory	[104]

3.4. Impact of the HIV-1 Tat protein on dendritic cells

Dendritic cells (DCs), known as the "sentinels" of the immune system, are crucial in antigen presentation and immune activation. During HIV-1 infection, the Tat protein disrupts multiple aspects of DC function, thereby weakening host immunity and facilitating viral persistence. Tat markedly upregulates the expression of PD-L1 on DCs through TNF-α- and TLR4-mediated pathways, impairing the ability of DCs to activate T cells [105]. In addition, Tat induces the expression and enzymatic activity of indoleamine 2,3-dioxygenase (IDO) in a dose-dependent manner, further suppressing the ability of monocyte-derived dendritic cells (MoDCs) to stimulate T cell proliferation [106]. These mechanisms highlight Tat as a key factor contributing to DC dysfunction during HIV-1 infection, significantly compromising their antigen-presenting capacity [107]. Tat also interferes with the host transcriptional machinery by suppressing the activity of the mannose receptor promoter, resulting in reduced surface expression of mannose receptors, molecules essential for pathogen capture by DCs [108]. This impairment limits the capacity of DCs to recognize and internalize pathogens. Additional studies have shown that Tat inhibits DC function by blocking dihydropyridine-sensitive L-type calcium channels, thereby reducing extracellular calcium influx critical for DC activation [109]. Additionally, HIV-1 infection or Tat expression induces interferon (IFN) response gene expression in immature dendritic cells without triggering cellular maturation. The resulting chemokines recruit activated T cells and macrophages, increasing their susceptibility to HIV-1 infection and enhancing viral amplification [110].

The HIV-1 Tat protein disrupts dendritic cell function through several mechanisms, including upregulation of PD-L1, induction of IDO expression, inhibition of calcium channel activity, and downregulation of mannose receptor expression. These alterations collectively impair the antigen-presenting capacity of dendritic cells, contributing to immune dysfunction and promoting conditions that support viral persistence and disease progression.

4. Conclusions

The HIV-1 Tat protein, a key viral regulatory factor, is vital in viral replication, latency, dissemination, and disruption of the host immune system. In this review, we summarize the biological properties of Tat and its broad impact on the function of immune cells, underscoring its central role in the pathogenesis of HIV-1 infection and AIDS. Through its complex domain structure and diverse mechanisms of action, Tat regulates the transcription of host genes, impacts immune cell apoptosis, modulates immune responses, and induces immune dysfunction. These effects collectively facilitate viral persistence and accelerate disease progression (shown in Figure 2).

So far, therapeutic vaccines targeting the HIV-1 Tat protein aim to suppress viral replication by triggering an immune response. This approach could reduce the dependence on antiretroviral therapy (ART). Furthermore, Tat-neutralizing antibodies are produced against the HIV-1 Tat protein and neutralize or inhibit HIV activity. Studies [111] have verified that experimental vaccines based on the Tat-BH10 and Tat-Oyi strains can induce Tat-neutralizing antibodies, leading to inhibition of HIV-1 reverse transcription. These vaccines significantly increase $CD4^+$ cell levels in HIV-infected individuals, promote the stable recovery of the immune system, and reduce viral load, thereby indicating their potential as therapeutic agents.

Despite significant advances in understanding Tat function, the specific regulatory networks and molecular mechanisms it engages in immune cells remain incompletely characterized. Thus, further research is needed to elucidate the spatiotemporal functions of Tat within the immune system and to explore its interactions with host factors. These insights will be critical for identifying new therapeutic targets and designing strategies to inhibit Tat-mediated immune dysregulation. A deeper understanding of the molecular mechanisms underlying Tat activity will not only expand our knowledge of HIV-1 pathophysiology but also provide a foundation for the development of innovative therapies aimed at controlling or eradicating HIV-1 infection.

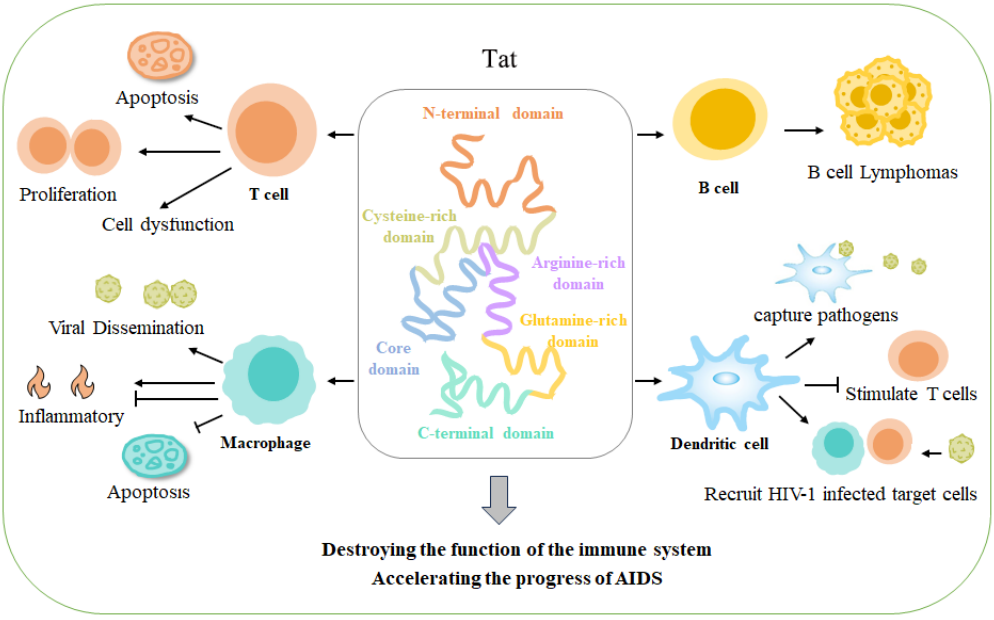

Figure 2. Biological properties of the HIV-1 Tat protein and its regulatory mechanisms on immune cells.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

All authors contributed to the study conception and design. Yang Wei-ling performed data analysis and drafted the work. Xiao Na performed the literature search. Zeng Yi had the idea for the article. Jiang Yan supported and revised the work. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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