

T Cell Transcription Factors and Their Impact on HIV Expression

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ABSTRACT: By targeting CD4⁺ effector T cells, HIV has a dramatic impact on the depletion, expansion and function of the different polarized T cell subsets. The maturation of T cell lineages is in part driven by intrinsic transcription factors that potentially influence how efficiently HIV replicates. In this review, we explore whether transcription factors that are required for polarizing T cells influence HIV replication. In particular, we examine provirus transcription as well as the establishment and maintenance of HIV latency. Furthermore, it is suggested these factors may provide novel cell-specific therapeutic strategies for targeting the HIV latent reservoir.

KEYWORDS: CD4⁺ T cells, HIV, latency, transcription

CITATION: Kaczmarek et al. T Cell Transcription Factors and Their Impact on HIV Expression. *Virology: Research and Treatment* 2013;4 41–47 doi:10.4137/VRT.S12147.

TYPE: Review

FUNDING: This work was partly supported by NIH grant AI097117.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

CD4⁺ effector T cell subsets possess diverse specialized functions. CD4⁺ T helper cells (T_H1, T_H2, T_H17) are responsible for the production of cytokines stimulating specific immune responses. Follicular B helper T cells (T_{FH}) support B cell activation, while regulatory T cells (T_{reg}) suppress immune responses elicited by CD4⁺, CD8⁺ T cells and B cells.^{1–3} During infection, antigen-presenting cells (APC) display antigenic peptides in the context of MHC II to naïve CD4⁺ T cells (T_H0), promoting their clonal expansion and polarization into effector T cells. A subset of activated CD4⁺ cells will generate memory T cells that are responsible for rapid recall of the adaptive immune response upon re-exposure. The differentiation of CD4⁺ T cells is driven in part by avidity of T cell receptor (TCR) engagement, strength of signaling, co-stimulatory signals and tissue microenvironments, including cytokine milieu and differential interactions with APC (Fig. 1).³ Additionally, CD4⁺ T cell development is controlled by a constellation of transcription factors that activate and repress batteries of genes that influence proliferation, differentiation and lineage commitment.^{1,2,4} Human immunodeficiency virus

(HIV) infection decreases the overall number of CD4⁺ T cells and results in a general imbalance of all T cell populations, facilitating the immune dysregulation associated with autoimmune deficiency syndrome (AIDS).^{5–7} In addition to directly impacting the number of CD4⁺ T cells, HIV infection leads to indirect immune exhaustion by activating neighboring or bystander cells. Although all CD4⁺ T cells are susceptible to HIV infection due to their expression of CD4 and chemokine receptors, CXCR4 and CCR5, the ability of different T cell populations to support HIV replication varies,^{5–7} possibly reflecting differential expression of T cell-specific transcription factors that regulate HIV expression. It is possible that these T cell factors, by promoting HIV transcription, influence the dissemination of virus at different stages of AIDS. Alternatively, it is possible that by repressing proviral transcription they contribute to the establishment of latently infected T cells. Latently infected cells, which are the source of HIV rebound following interruption of antiretroviral treatments, present a major challenge to curing HIV infection.^{8,9} The mechanisms that establish HIV latency remain incompletely defined and research has focused on general events that

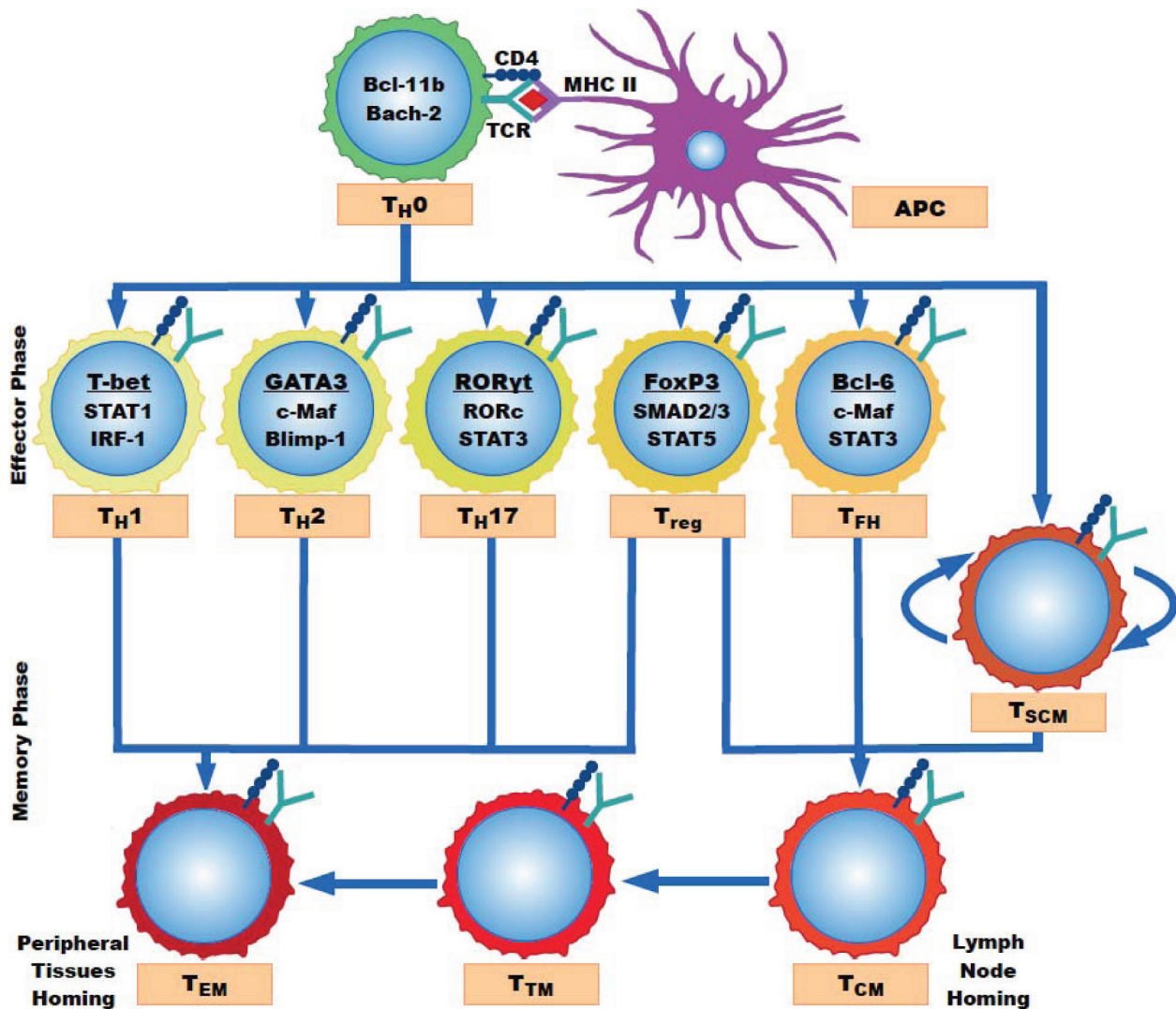


Figure 1. Model of Sequential CD4⁺ T Cell Differentiation. Upon activation by antigen presenting cell (APC), naïve T cell (T_{H0}) undergoes differentiation into effector or memory populations. The different effector populations have capacity to mature into effector memory T cells (T_{EM}). Stem cell memory T cells (T_{SCM}), follicular helper T cells (T_{FH}) and regulatory T cells (T_{reg}) mature into central memory T cells (T_{CM}), which then can become transitional memory T cells (T_{TM}) and further convert into T_{EM} .

control gene expression, including transcription initiation, elongation and epigenetic regulation of chromatin.^{8–10} Early attempts to purge HIV from the latent reservoir by targeting general biochemical pathways have had modest success; however, events regulated by T cell specific factors may provide a more cell-specific targeting strategy that would minimize potential off-target gene activation. This review highlights how key T cell restricted transcription factors impact HIV transcription in different T cell subsets.

Brief Overview of HIV Transcription

HIV transcription is regulated by multiple mechanisms and has been extensively reviewed.^{9–11} The upstream HIV-1 long terminal repeat (LTR) controls provirus transcription by functioning as a promoter/enhancer recruiting host transcription factors necessary to initiate transcription and

co-activators, including histone acetyltransferases (HATs), Lysine (K)-specific demethylase (KDM) demethylases, and Switch/Sucrose nonfermentable (Swi/Snf) complexes, that regulate the chromatin organization of integrated provirus.¹⁰ However, transcriptional repressors are also recruited to the HIV LTR, such as the SUV39 family proteins and histone deacetylases (HDACs), which respectively methylate and deacetylate histones within positioned nucleosomes favoring condensation of chromatin and making the proviral LTR less accessible for efficient transcription. Furthermore, transcription of proviruses is inhibited at the step of transcription elongation. To overcome ribonucleic acid (RNA) polymerase II (RNAP II) promoter proximal pausing, HIV encodes a transcriptional activator, Tat, which in the context of the nascent RNA, binds a 5' stem loop structure, TAR, and recruits P-TEFb, a complex that includes Cdk9 and cyclin T1, to the

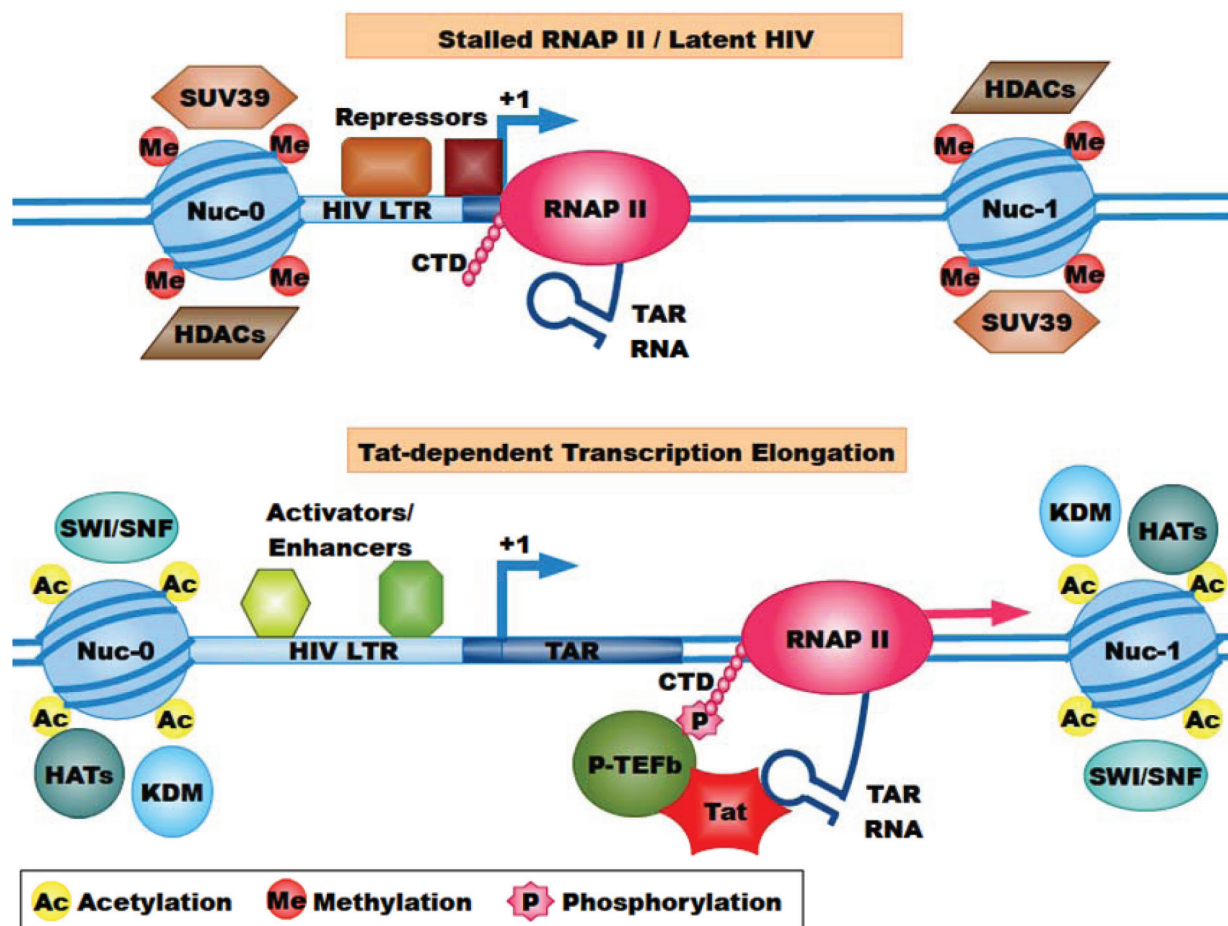


Figure 2. Model for HIV Transcriptional Regulation. During initiation of HIV transcription RNAP II is recruited to the HIV LTR and transcribes nascent TAR RNA. However, methyltransferases, HDACs, and transcriptional repressors bind to the HIV LTR resulting in paused RNAP II. Upon cell stimulation transcriptional activators and enhancers are recruited to HIV LTR, Tat binds to TAR RNA and recruits P-TEFb to activate RNAP II by phosphorylating its CTD. Histone modifying factors remodel and remove methyl groups from Nuc-0 and Nuc-1 making the chromatin more accessible to the transcriptional machinery.

LTR. P-TEFb alleviates transcriptional repression by phosphorylating components of the paused RNAP II complex including the carboxyl terminal domain (CTD) of RNAP II, facilitating productive transcription elongation (Fig. 2). Strategies targeting signals that regulate recruitment of transcription factors, chromatin remodeling complexes, or regulators of RNAP II have been devised to activate and purge HIV latent reservoirs.^{8,9,12-15}

T_H1, T_H2 and T_H17 Cells and HIV Transcription

The polarization of T_H1 versus T_H2 cells is mediated by 2 primary factors, T-bet and GATA-3, respectively, whereas ROR γ t facilitates the differentiation of T_H17 cells.^{3,16,17} T_H1 cells have been reported to be limited in their ability to support HIV replication, although there is no evidence that T-bet, the T_H1 master transcription factor, directly influences HIV transcription.¹⁸ T-bet antagonizes GATA-3 function, which is considered the key regulator of T_H2 differentiation.^{3,17,19} GATA-3 binds to several sites in the HIV LTR and induces HIV transcription.^{20,21} Therefore, T-bet potentially limits

HIV transcription by targeting GATA-3. In addition to GATA-3, c-Maf promotes T_H2 differentiation²² and, in regards to HIV transcription, binds the HIV LTR and cooperates with NF- κ B and Nuclear Factor of Activated T-cells (NFAT) to enhance HIV transcription.²³ The ability of GATA-3 and c-Maf to activate HIV transcription is consistent with findings that T_H2 cells support HIV replication.^{18,23} T_H17 cells also support robust HIV replication, although ROR γ t and RORc, factors that are abundant in T_H17 cells,¹⁸ have not been shown to directly impact HIV transcription; thus, the induction of downstream T cell signaling pathways that culminate in activation of NF- κ B, NFAT and Signal Transducer and Activators of Transcription (STAT) probably strongly influence HIV transcription in T_H17 cells.

Restricting or committing T cells towards specific functional subsets is in part regulated by the transcription factor Bcl-11b (also known as CTIP-2), which is a transcriptional repressor that is expressed in multiple T cell populations.²⁴ In the context of HIV transcription, Bcl-11b binds the HIV LTR and limits transcription.^{25,26} One mechanism for this repression



is that Bcl-11b recruits HDAC1, HDAC2, and SUV39H1 to the HIV LTR, resulting in deacetylation and methylation of the positioned nucleosome adjacent to the HIV transcriptional start site.²⁵ Furthermore, Bcl-11b facilitates binding of heterochromatin protein 1 (HP1).²⁵ Overall, these posttranslational changes and recruitment of factors promote the formation of heterochromatin at the viral promoter and transcriptional repression.²⁵ Bcl-11b is also able to repress Tat-dependent transcription by binding Tat and redirecting it to heterochromatic regions.^{26,27} However, the question as to whether this factor directly contributes to HIV latency remains unresolved.

T_{reg} Cells and HIV Transcription

There has been recent interest in characterizing the role of T_{reg} cells in HIV.^{5,6} In general, changes in T_{reg} numbers and function have been documented in patients and include higher T_{reg} frequencies in untreated AIDS patients and diminished ability of these cells to suppress immune activation in HAART-treated patients.^{5,6} Whether these changes are a direct result of HIV infection or reflect more general immune dysfunction requires further investigation. T_{reg} development is in part driven by the transcription factor FoxP3.³ The data as to whether FoxP3 directly impacts HIV transcription are conflicting. Ectopically expressed FoxP3 in primary CD4⁺ T cells inhibits activation and recruitment of transcriptional activators NF-κB, CREB and NFAT2 to the LTR.^{28,29} FoxP3 may also facilitate HIV transcription by inhibiting HDAC1.^{30,31} However, overexpression of FoxP3 in different T cell subsets may result in different transcriptional outcomes. For example, forced expression of FoxP3 polarized naïve CD4⁺ T cells towards a T_{reg} phenotype and enhanced HIV replication, but had no impact on T memory cell phenotypes or HIV transcription.³² These conflicting results may reflect intrinsic differences between T cell subsets or challenges associated with overexpressing factors, and underscore the need to further study HIV transcription in primary T_{reg} cells.

T_{FH} Cells and HIV Transcription

T_{FH} are essential for mediating T cell-dependent B cell responses. T_{FH} cells also support productive HIV infection and are reported to expand during the course of HIV infection.^{33,34} Bcl-6 is the master transcription factor for the generation of T_{FH} cells.³⁵ Bcl-6 partly functions by inhibiting the expression and function of other transcriptional regulators that determine T cell subsets including GATA-3, T-bet, ROR-γt and Blimp-1.^{35,36} In particular, Bcl6 and Blimp-1 have an antagonistic relationship.^{37,38} Blimp-1 inhibits both T cell proliferation and differentiation into T_{FH} and T_{H1} cells.³⁷ Unlike Bcl-6, Blimp-1 is highly expressed in T_{H2} cells compared to T_{H1} cells and represses T_{H1} differentiation by repressing interferon, T-bet and Bcl-6 expression.³⁹ Increased Blimp-1 levels correlate with enhanced expression of inhibitory molecules, such as PD-1, CTLA-4 and LAG3, in T cells exposed to HIV.^{40,41} In addition, Blimp-1 expression

is increased in chronic HIV patients, but is not altered in long-term non-progressors.⁴² While the role of Bcl-6 and Blimp-1 in HIV transcription is unclear, it is tempting to speculate that Bcl-6 supports HIV replication, while Blimp-1 inhibits it, and that elevated Blimp-1 in CD4⁺ T cells might contribute to the establishment and maintenance of HIV latency (Fig. 3). Interestingly, the HIV LTR contains binding sites for both Bcl-6 and Blimp-1, suggesting that these factors directly regulate HIV transcription (reference 43 and Kaczmarek and Henderson unpublished observation).⁴³

Memory Cell Populations and HIV Latency

A unique feature of the adaptive immune response is the generation of memory. For CD4⁺ T cells, two distinct memory populations have been well-characterized based on the expression of surface markers, homing capacity and function upon reactivation; T central memory (T_{CM}) and T effector memory (T_{EM}) cells.^{2,44,45} Recently, stem cell memory T cells (T_{SCM}) have been described in humans.⁴⁶ These self-renewing memory CD4⁺ cells are reported to generate T memory and effector populations. The array of factors that influence the proliferation and generation of T_{SCM}, T_{CM} and T_{EM}, including cytokines, signaling events and transcription factors, have not been fully elucidated. Critical transcription factors that regulate the generation and survival of T_{CM} include Schnurri-2, STAT3, STAT5a, TBR2, FOXO3a, Bmi1 and LKLF.⁴⁷⁻⁵³ Furthermore, Bach-2, IRF-1 and p27 (Kip1) have been suggested to suppress T_{EM} differentiation.⁵⁴⁻⁵⁶ Relevant to HIV, memory cells, especially T_{CM} and T_{SCM}, have been implicated as primary reservoirs harboring latent provirus because they are susceptible to HIV infection, are long-lived and, with their ability to self-renew, may maintain and/or renew the pool of cells harboring latent provirus (reference 57 and personal communication Buzon and Lichterfeld).⁵⁷ This homeostatic proliferation of infected T_{CM} and T_{SCM} in the absence of T cell activation and robust HIV transcription presents a major barrier to eradicating persistent HIV infection and underscores the need to characterize the tissue distribution and factors that regulate these different T cell memory subsets.⁵⁸ The predisposition for HIV to establish latency in T_{CM} may reflect the expression levels of transcription factors, T_{CM} express T-bet⁵⁹ and have lower levels of Cyclin T1 and phosphorylated CDK9, the two subunits of P-TEFb required for transcription elongation.⁶⁰ However, T_{EM} have increased expression of factors shown to activate HIV transcription including GATA-3, c-Maf and RORγt.^{61,62} It has been suggested that NFAT is critical for overcoming latency and induction of HIV transcription in different T cell subsets including T_{CM}, although recent studies have questioned the role of NFAT in the reactivation of latent HIV.⁶³⁻⁶⁶ The discrepancy of what key check points limit HIV transcription in latently infected cells may reflect heterogeneity of memory cells, difference in cell culture conditions and isolation of cell subsets. The factors that repress transcription in T memory

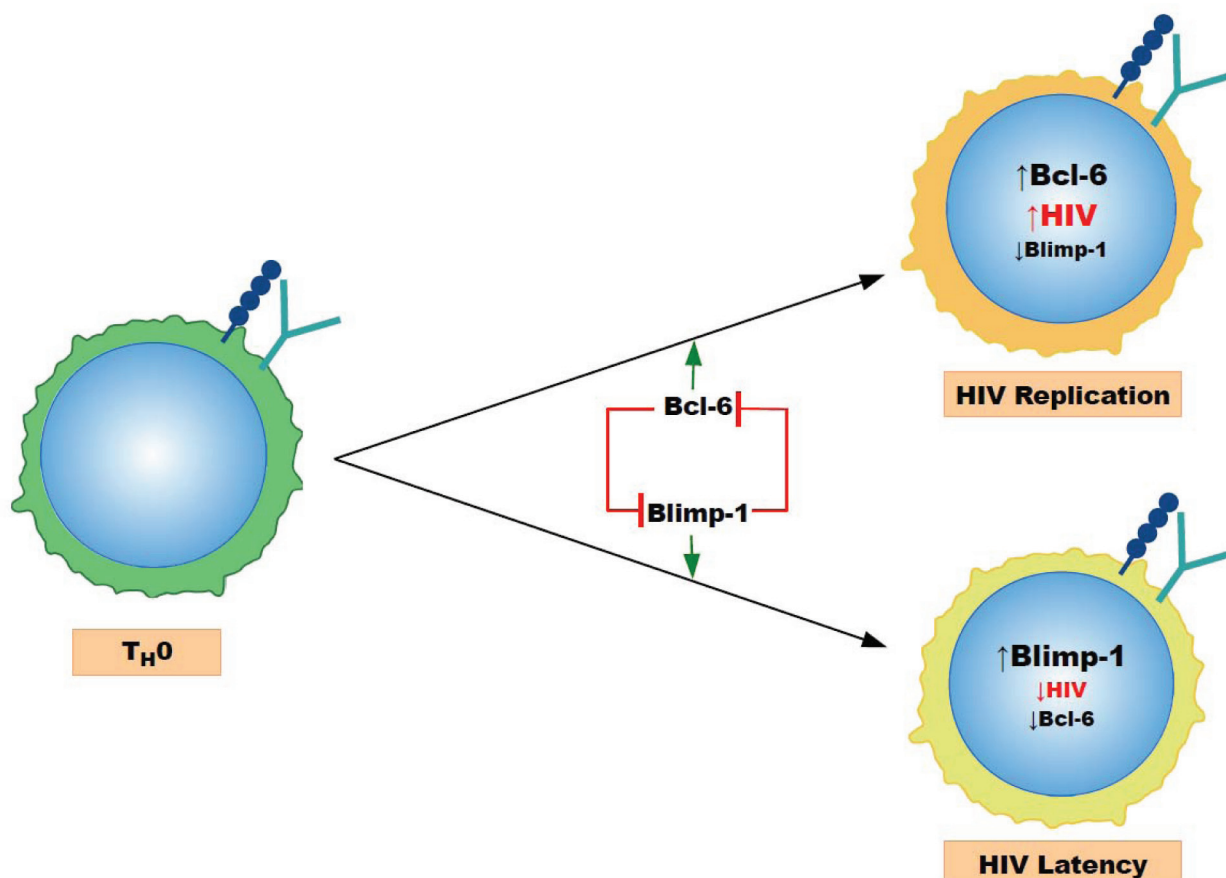


Figure 3. Model for Potential Role of Bcl-6 and Blimp-1 in HIV Transcription. Blimp-1 and Bcl-6 have potential binding sites in the HIV LTR. We hypothesize that Bcl-6 favors the high expression of HIV in T_{FH} cells, while Blimp-1, an antagonist of Bcl-6, contributes to paused RNAP II and thus to the establishment of HIV latency. See text for details.

cells have not been defined but most likely include epigenetic factors such as HDACs or methyltransferases.^{8,9}

Conclusions and Perspectives

In an effort to eradicate HIV infection, strategies to purge transcriptionally-repressed HIV provirus from latent reservoirs have been employed to complement current antiretroviral therapies.¹⁵ Recent therapeutic approaches have focused on overcoming the repressive effects of chromatin, which has been implicated as a key regulator of HIV transcription.^{8,9} For example, clinical trials have used HDAC inhibitors valproic acid^{67,68} and vorinostat,⁶⁹ which, despite modest ability to induce HIV transcription in peripheral blood of HAART patients, did not decrease the HIV reservoir. The limited success of these initial trials probably reflects the complexity of the latent reservoir in regards to the cells that are included in this compartment, as well as the multiple mechanisms that establish and maintain latency.⁸⁻¹⁰ Chromatin remodeling, recruitment of transcriptional activators and coactivators, enhanced RNAP II processivity and defective viruses have been implicated as contributing factors to HIV latency.⁸⁻¹⁰ An additional confounder is that many of the factors that

limit HIV transcription are general transcriptional regulators, which are necessary for normal gene expression. Targeting RNAP II, P-TEFb, and chromatin remodeling factors will likely be toxic, lack specificity, and have an impact on global gene expression. We suggest that T cell restricted transcription factors strongly influence HIV proviral transcription and that these factors may provide specific targets for eliminating latent HIV. For example, Blimp-1 and Bcl-11b are potential repressors of HIV transcription that are found in different T cell subsets, including those that harbor latent virus. Modulating the expression of these T cell transcriptional regulators or targeting their cofactors would be predicted to reactivate and potentially purge latent virus in specific T cell subpopulations without global T cell activation. However, further research is required to understand the mechanisms of repression of HIV transcription in different T cell subsets and to assess which T cell factors are the best candidates for the development of novel treatment strategies.

Acknowledgments

We thank Daniele Cary and Gillian Schiralli Lester, Boston University School of Medicine, for critical discussions and



constructive feedback. In addition, we thank Dr. Mathias Lichterfeld, Ragon Institute, Massachusetts General Hospital, for discussing recent unpublished work cited in this manuscript.

Author Contributions

Conceived and designed manuscript: KK, AM, AJH. Wrote first draft: KK, AM, AJH. Contributed to the writing of the manuscript: KK, AM, AJH. Agree with manuscript results and conclusions: KK, AM, AJH. Jointly developed the structure and arguments for the paper: KK, AM, AJH. Made critical revisions and approved final version: KK, AM, AJH. All authors reviewed and approved of the manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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