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CD4$^+$ T Cell Subsets and Pathways to HIV Latency

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Abstract

Latent infection of CD4$^+$ T cells is the main barrier to eradicating HIV-1 infection from infected patients. The cellular and molecular mechanisms involved in the establishment and maintenance of latent infection are directly linked to the transcriptional program of the different CD4$^+$ T cell subsets targeted by the virus. In this review, we provide an overview of how T cell activation, T cell differentiation into functional subsets, and the mode of initial viral infection influence HIV proviral transcription and entry into latency.

Keywords: HIV latency, HIV transcription, CD4 T cell differentiation

Introduction

HIV-1 is intricately linked to the biology of its preferred target host cell type, CD4$^+$ T cells. This is particularly evident when considering the transcription of the HIV provirus and the combinatorial requirement for general cellular transcriptional machinery, chromatin regulators, and cell lineage-specific factors. The presence and absence of specific factors or repressive transcriptional mechanisms in different T cell subsets may promote the repression of proviral transcription thus establishing, maintaining, and biasing latent HIV-1 infection in different T cell subsets. HIV may encounter different cellular transcriptional conditions during initial entry and integration into a host cell or the transcriptional conditions can change after HIV has already integrated into the host DNA. Whether a host cell possesses a favorable or unfavorable transcriptional environment is directly dependent on T cell activation, cell cycle progression, maturation, differentiation status, and signals generated at the time of initial infection.

T cell maturation is driven in large part by the strength of signal through the T cell receptor (TCR)–major histocompatibility complex (MHC)–peptide interactions with antigen-presenting cells (APCs). However, it is also strongly influenced by other environmental cues in the tissue microenvironment, including cytokines, chemokines, and interactions with neighboring non-APCs. There have been several reviews that have focused on the general biochemical mechanism of transcriptional regulation, such as chromatin remodeling and RNAP II (RNA polymerase II complex) pausing that limit HIV transcription.[1–3] In this review, we will focus on how intrinsic cell lineage-specific factors that are initiated by T cell maturation and the mode of infection may influence HIV replication and the establishment of latency.

Overview of T cell Activation and Maturation

Canonical antigen presentation to CD4$^+$ T cells involves the direct cell–cell interaction between APCs and naive CD4$^+$ T cells.[4] APCs present MHC-II loaded with peptide to the TCR, whereas costimulatory molecules on naive T cells interact with their ligands on the surface of APCs. The macromolecular complex generated upon cell–cell interaction is known as the immunological synapse.[5,6] Establishment of APC–T cell immunological synapses triggers cascades of positive and negative signaling that include nonreceptor tyrosine kinases, phosphorylation of downstream adaptor proteins, the assembly of multimolecular complexes that include lipid kinases, lipases, guanine nucleotide exchange factors, and small G-proteins, which culminate in increased intracellular calcium, activation of ERK/MAPK pathways, and induction of cellular transcription factors.[7–9]

T cell signals converge to remodel cortical actin and redistribute surface receptors and membrane domains of activated T cells.[7–9] These signals control the immune response in part by influencing the generation and maintenance of T effector populations, memory cells, and tolerized T cells. They also polarize T cell responses, which in turn drive the activity and function of other immune cells, including but not limited to macrophages, dendritic cells (DCs), B cells, other CD4$^+$ and CD8$^+$ T cells.

The specific effector functions of stimulated T cells will largely depend on the strength of the signaling cascade. Binding avidity of the MHC-II/peptide complex to the TCR, the duration of this interaction, and engagement of costimulatory receptors and cytokines are the primary determinants of signaling strength.[7] For example, differentiation of naive T cells to T_h1 or T_h2 effector functions can be

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modulated by stronger or weaker TCR signals, respectively.[10–12] Strong signaling can also bias naive T cells toward effector subsets that have a relatively short half-life, whereas weaker signaling in response to self antigen can drive cells into anergy to establish immunological tolerance.[10,13–16]

Upon resolution of the T cell response, most effector cells will turnover with relatively short half-lives, whereas a small subset will survive as memory cells (Fig. 1). Upon reencountering antigens, memory cells will respond more vigorously, thus forming the basis for immunological memory. Several subsets of memory cells have been recognized, including stem cell memory cells (T_{SCM}), central memory cells (T_{CM}), effector memory cells (T_{EM}), and terminally differentiated memory cells (T_{EMRA} or T_{TE}).[17] T_{SCM} are a recently identified self-renewing subpopulation of memory cells that give rise to effector T cells and other memory cell populations.[18–21] T_{CM} have long half-lives and represent the primary cellular compartment responsible for long-lasting immunological memory.[22,23] T_{EM} cells home directly to inflamed tissues and are characterized by rapid response to antigen.[22,23] T_{EMRA} have low proliferative and functional capacity and express some markers of senescence.[17] Homeostatic proliferation of these memory populations may require low-level signaling through the TCR and/or cytokines, including IL-7 and IL-15.[24]

In the absence of professional APCs, T cells can be partially activated through alternative mechanisms. T cells have been shown to be activated by nonprofessional APCs, such as endothelial cells,[25–27] stromal cells,[28] and even activated $CD4^+$ T cells.[29–32] These atypical APCs express MHC-II but lack costimulatory molecules, such as CD28, which drives partial activation and biasing T cells toward an anergic or inactive state.[33] T cell anergy is characterized by a significant reduction in cell proliferation and diminished release of cytokines upon subsequent antigen presentation. A similar inert T cell phenotype results from overstimulation or persistent signaling of T cells, as often occurs during chronic inflammatory diseases, including HIV infection and cancer. These exhausted T cells are defined by their loss of immune effector potential and proliferation.[34] Both T cell anergy and T cell exhaustion have their own transcriptional profiles and are thought to be important mechanisms for controlling overactive immune responses and antigenic tolerance.[15,35–37]

In considering the generation of T cells into different functional subsets it is important to recognize that T cell maturation is a regulated process that involves differential T cell specific gene expression patterns.[38,39] Effector and memory subsets as well as exhausted and anergic cells express distinct batteries of genes that maintain their phenotypes and function. Gene expression in these T cell subsets are actively maintained by combinatorial activities between cell-specific transcription factors, more general coactivator and corepressor complexes and chromatin remodeling factors. During HIV entry into different T subsets, the virus will encounter different transcriptional profiles and different intrinsic cellular factors, which will either support proviral transcription or drive proviral repression and latency.

T Cell Activation and Intrinsic Cellular Factors Regulate HIV Replication

HIV-1 can infect target cells through the dissemination of cell-free particles or through direct cell–cell contact.[40,41] Similar to antigen presentation, efficient cell–cell contact-mediated transfer of HIV correlates with the redistribution of surface receptors, lipid rafts, reorganization of cortical actin, and the delivery of signals across a synaptic junction.[42–46] Because of the physical and functional similarities to the immunological synapse, these structures have been termed infectious synapses (dendritic cell–T cell junctions) or virological synapses (T cell–T cell junctions).[47–50] Whether the quality of signals emanating from this synapse support or alter HIV productive infection and the establishment of latency has not been fully investigated; although, HIV co-opts T cell activation to ensure efficient infection and replication.

For example, reports, including those from our laboratory,[51–56] have demonstrated that tyrosine kinases, Lck,[55,57,58] Fyn,[59] ZAP-70,[60,61] ITK,[53,54,62] lipid kinases PI3K[52,63–65] and PI4P5 kinase,[66] and MAP kinase pathways[67] regulate HIV entry, reverse transcription, proviral transcription, virus assembly, and release. We and others have also shown that signals emanating from CD28 positively and negatively

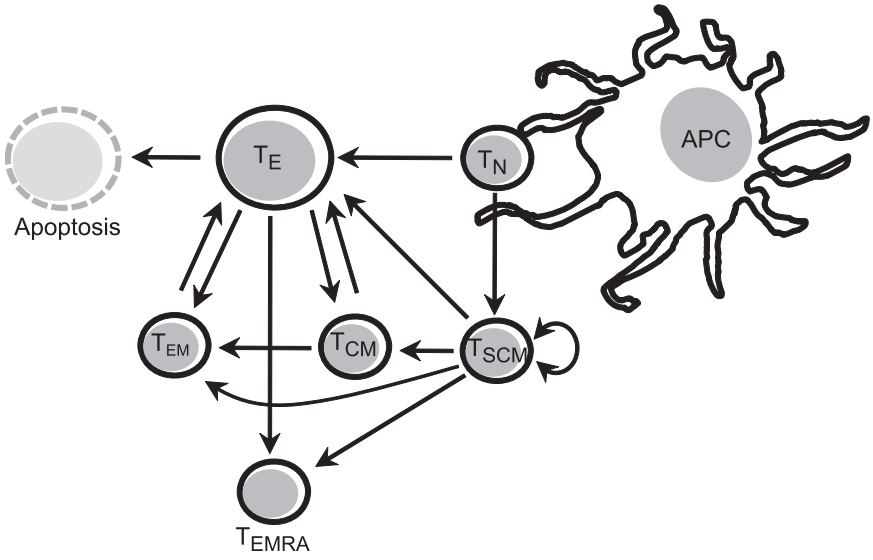

FIG. 1. Overview of T cell differentiation. Upon antigen presentation, T_N are activated and differentiate in effector cells (T_E). The specific effector functions that these cells will undertake largely depend on the stimulus and the cytokine milieu during antigen presentation. A fraction of T_E cells will undergo apoptosis after resolution of the immune response while another fraction will return to a resting state to become memory cells (T_{EM}, T_{CM}, and T_{EMRA}). T_{CM} can differentiate into T_{EM} or T_E depending on the stimulus, whereas T_{EM} can typically only differentiate into T_E during subsequent stimulus. Some T_N differentiate into T_{SCM} after antigen presentation. These cells have self-renewal potential and can also differentiate into other memory subsets.

regulate HIV transcription.[51,52,65,68,69] Weaker signals, such as those that induce homeostatic proliferation of T cells, seem sufficient for cell division but not for stimulating HIV production. This is the basis for the expansion of latently infected cell clones in some HIV-infected individuals.[70–76]

In addition, the quality, duration, and magnitude of TCR and CD28-associated signals set a threshold for completing reverse transcription and productive HIV infection.[65] For example, T cell activation has been shown to enhance the efficiency of reverse transcription since it is associated with low expression of the restriction factor SAMHD1 and increased availability of nucleotides.[77–79] T cell activation will also influence integration site selection by reorganizing general chromatin organization and localization of transcriptionally active open chromatin to the nuclear periphery near nucleoporin structures.[80–83] That antigen receptor-driven T cell activation influences HIV infection is supported by observations showing that superantigens increase susceptibility of $CD4^+$ T cells to HIV infection[84] and that *in vitro* and *in vivo* T cells specific for tetanus toxoid, *Candida albicans*,[85] adenovirus,[86] HSV-2,[86] TB,[87] and HIV[88–90] are preferentially infected.

Once integrated, the provirus will be transcribed by the host transcriptional machinery. Efficient proviral transcription involves the binding of essential host transcription factors, such as NF-κB, AP-1, NFAT, and Sp1, and processive RNAP II.[1–3] Repression of provirus transcription represents the primary mechanism of HIV latent infection. Insufficient signaling at the time of HIV infection may bias cells toward a latent infection. For example, efforts to establish primary models of latency suggest that minimal or partial activation either by polarizing cells toward a central memory phenotype,[91] treating with chemokines,[92, 93] or infecting resting $CD4^+$ T cells directly without additional stimulus[94,95] biases *in vitro* infections toward latency.

Similarly, interactions with immature DCs[96,97] or non-APCs, such as endothelial cells,[98] and neighboring T cells may impact the establishment of latency. Ectopic cell–cell interactions or cytokine release alters the expression of intrinsic factors that control T cell maturation and potentially drive expression and repression of HIV transcription and latency in different T cell subsets through cell-specific transcriptional programs (Table 1). For example, effector memory T cells have increased expression of the transcription factors GATA-3 and c-Maf; these two factors are also essential for T_h2 effector cell maturation.[99–102] Both GATA-3 and c-Maf have been demonstrated to bind the LTR to co-operate with NF-κB and NFAT to facilitate transcription in T_h2 and activated T_{EM}.[103–106]

An example of transcriptional repression by transcription factors in quiescent T cells is the Bcl6-Blimp-1 axis. These transcription factors are directly involved in the differentiation of effector T follicular helper cells (T_{FH}) and T memory subsets.[107–111] High Bcl6 expression and low Blimp-1 expression support T_{FH} differentiation, whereas, elevated Blimp-1 expression is observed in quiescent memory T cell subsets. Both of these factors have been shown to directly and indirectly regulate HIV replication. Bcl6 was recently

Table 1. Cell Lineage Specific Intrinsic Factors and Their Effect on HIV Transcription and Latency

Cell type	*Repressive transcription factor*	*Activating transcription factor*	*References*
Naïve Cells			
T_N	ND[a]		
Effector Cells			
T_h1	ND[a]		
T_h2		GATA-3 cMaf	1. Pereira LA, *et al.*[103] 2. Galio L, *et al.*[104] 3. Yang Z, *et al.*[105] 4. Zhang M, *et al.*[106]
T_h17	RUNX1 PRC2 EHMT2		1. Cleret-Buhot A, *et al.*[153] 2. Klase Z, *et al.*[154] 3. Nguyen K, *et al.*[155]
T_{reg}	FOXP3	FOXP3	1. Grant C, *et al.*[156] 2. Selliah N, *et al.*[157] 3. Holmes D, *et al.*[158] 4. Holmes D, *et al.*[159] 5. Oswald-Richter K, *et al.*[160]
T_{FH}	Bcl-6	Bcl-6	1. Baron BW, e*t al.*[161] 2. Amet T, *et al.*[112]
Memory Cells			
T_{EM}	Blimp-1, PRC2, EHMT2, G9a, SMYD2	GATA-3 cMaf	1. Kaczmarek Michaels K, *et al.*[113] 2. Nguyen K, *et al.*[155] 3. Boehm D, *et al.*[162]
T_{CM}	Blimp-1, PRC2, EHMT2, G9a, SMYD2		
T_{SCM}	Blimp-1, PRC2, EHMT2, G9a, SMYD2		
T_{EMRA}	Blimp-1, PRC2, EHMT2, G9a, SMYD2		

[a]ND = not determined.

reported to inhibit several interferon-stimulated genes, thus likely contributing to the increased susceptibility of T_{FH} cells to HIV replication.[112] Blimp-1 on the other hand, directly interacts with interferon-stimulated response elements within the HIV proviral sequences and prevents transcription processivity, contributing to the establishment of latent infection in memory T cells.[113] Blimp-1 is also upregulated in T cells that display exhausted phenotypes.[36,114] Exhausted T cells have been shown to have provirus in HIV-infected individuals,[115] but whether Blimp-1 is involved in the repression of HIV transcription in these cells has not been demonstrated.

Latent HIV infection appears to be preferentially contained within the central memory $CD4^+$ T cell compartment.[116–121] However, all T cell subsets that have been surveyed carry HIV provirus, including naive T cells.[115–122] Latent infection of naive T cells has been largely ignored partly due to the very low frequency of these cells in HIV-infected individuals. It has been recently suggested that latent infection in naive $CD4^+$ T cells is more difficult to reverse.[123] This observation may suggest that intrinsic factors within naive cells may promote a ''deep'' latency that may be difficult to target by latency-reversing agents, thus having implications for strategies to reduce the size of the latent reservoir.

Cellular Mechanisms That Establish HIV Latent Populations

Latent infection has been suggested to be established by two mechanisms: (1) during the resolution of a T cell response when a subset of activated cells transition to a quiescent or resting state or (2) by direct infection of quiescent or resting T cells (Fig. 2). As mentioned in the previous section, most studies have found that the majority of latently infected T cells in treated individuals are memory T cells. This evidence suggests that the process of infected activated $CD4^+$ T cells returning to a resting state is an important mechanism for the generation of latent infection *in vivo*.[124]

Many *in vitro* models used for studying transcriptional regulation of latent infection are dependent on activated T cells returning to a resting state and extinguishing HIV proviral transcription.[91,125–129] Such experimental models have shown that proviral transcription is limited in latently infected cells by three main biochemical mechanisms: (1) absence of positive transcription factors, such as NF-κB, to initiate proviral transcription, (2) epigenetic changes to chromatin and proviral DNA, and (3) repressive factors that prevent the processivity of the transcriptional machinery.[130–133] However, it remains unclear if specific cellular factors are involved in the

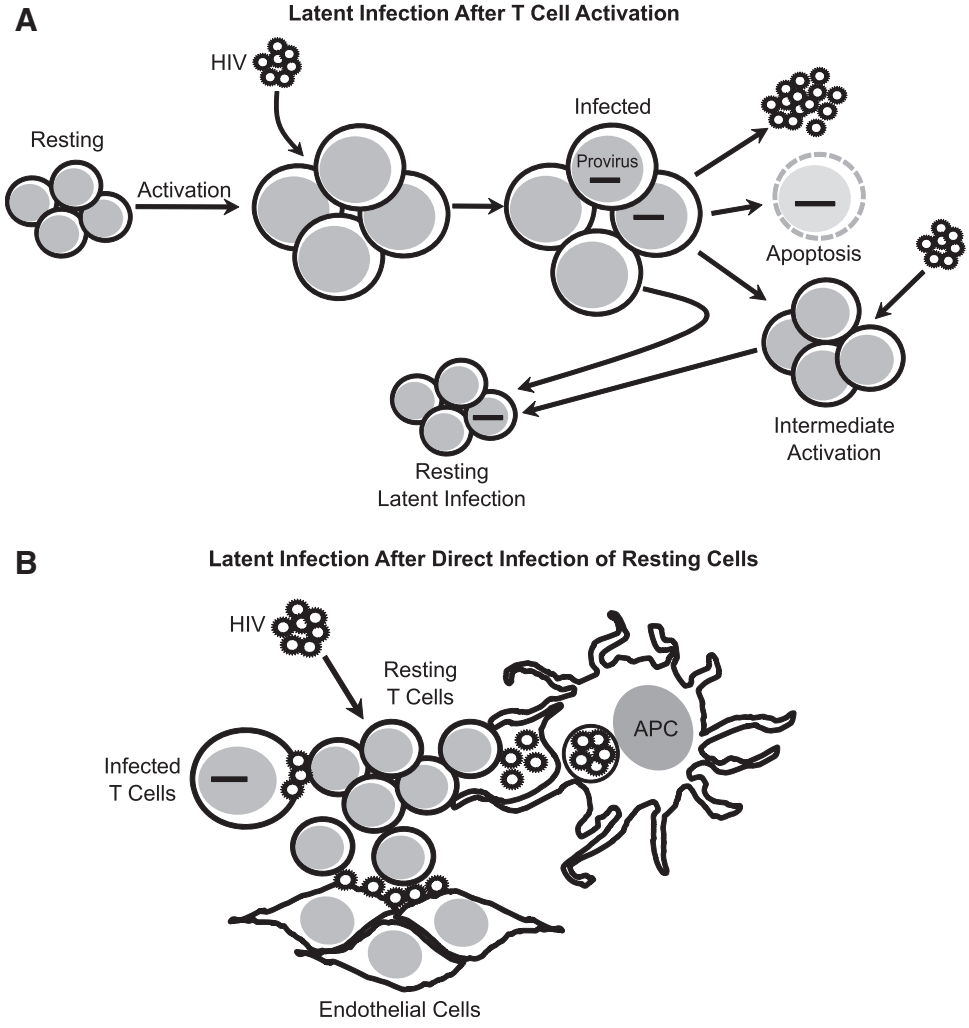

FIG. 2. Cellular mechanisms for the generation of latent infection in $CD4^+$ T cells. **(A)** Latent infection can be established during the transition of activated $CD4^+$ T cells to a quiescent/resting state. When fully or intermediately activated, $CD4^+$ T cells become infected with HIV, a proportion will undergo apoptosis due to the cytopathic effects of viral replication, and a proportion will survive infection and return to a resting state in which viral replication is suppressed.[124,149] **(B)** Latent infection can also be established by direct infection of quiescent/resting $CD4^+$ T cells with cell-free particles,[94,136,137,150–152] or by cell-to-cell transmission from productively infected T cells (Agosto and Henderson, unpublished work), from APC,[96,97,141] and from endothelial cells.[98] APC, antigen-presenting cells.

establishment and regulation of HIV transcription and latency when resting T cells are infected directly.[134]

Direct infection of quiescent or resting $CD4^+$ T cells could explain the presence of proviral DNA in some quiescent T cell subsets such as naive cells and exhausted T cells.[135–137] Interestingly, just as in activated $CD4^+$ T cells, HIV integration in resting T cells is favored near transcriptionally active chromatin regions,[138,139] yet infectious virus production is repressed. Despite the inability of infected resting $CD4^+$ T cells to produce infectious particles, it has been observed that these cells do express some spliced HIV RNA.[95] These RNAs in infected resting cells have been demonstrated to be translated into viral proteins, such as Gag and Nef, but little production of Tat, Rev, and Env is detected.[95,140] Read-through of RNAP II from neighboring cellular genes or yet-to-be-identified cellular transcription factors may account for this pattern of HIV expression in latently infected resting cells.

Resting $CD4^+$ T cells can also become infected through cell–cell contact. The best characterized mode of infection of resting cells by cell–cell contact is that mediated by dendritic cells.[96,97,141] Dendritic cells capture particles through receptors such as Siglec-1/CD169 and DC-SIGN, which are then preserved in intracellular compartments.[142–144] Upon interaction with T cells while probing for antigen-specific cells, particles are transferred and ultimately infect T cells. Dendritic cell maturation and functional subsets will directly influence whether this cell–cell interaction is productive or latent.[96]

Non-APCs have also been shown to transmit HIV directly to resting T cells, including endothelial cells[98] and productively infected T cells. Although cell-to-cell transmission to resting $CD4^+$ T cells has been suggested to be a highly inflammatory process resulting in the apoptosis of target and bystander resting T cells,[145–147] recent work from our laboratory indicates that a proportion of target resting $CD4^+$ T cells become latently infected through this process (Agosto and Henderson, unpublished observations). Interestingly, our work suggests that latent infection generated by cell-to-cell transmission between T cells is more difficult to reverse through TCR/CD28 signaling compared with latent infection generated by cell-free infection. This observation suggests that cell-to-cell transmission either modifies the transcriptional program in target T cells and a number of specific factors may be involved in tightly repressing HIV transcription or that this mode of viral transmission preferentially targets resting cells with a strongly repressive transcriptional program.

Conclusion

HIV transcription and the establishment of proviral latency are regulated by multiple biochemical and cellular mechanisms which will reflect how cells are activated, cell maturation, and differentiation. Two main strategies have been proposed for targeting the latent reservoir.[148] The first strategy, known in the field as ''shock and kill,'' proposes to pharmacologically reactivate latent proviruses with the aim of inducing death of infected cells due to the cytopathic effects of viral replication or cytotoxic immune responses. The second strategy, known in the field as ''block and lock,'' proposes to suppress HIV transcription long term, thus eliminating the need for antiretroviral therapy. Regardless of which strategy will be used to target the latent reservoir, it will be critical that all populations that are harboring latent HIV are targeted to assure efficacy of a cure; thus, underscoring the importance of understanding the events of latency in multiple cell subsets in different tissue environments.

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