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HIV PATHOGENESIS AND TREATMENT (AL LANDAY, SECTION EDITOR)

T Memory Stem Cells and HIV: a Long-Term Relationship

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Abstract In analogy to many tissues in which mature, terminally differentiated cells are continuously replenished by the progeny of less differentiated, long-lasting stem cells, it has been suspected that memory T lymphocytes might contain small numbers of stem cell-like cells. However, only recently have such cells been physically identified and isolated from humans, mice, and nonhuman primates. These cells, termed "T memory stem cells" (T_{SCM}), represent approximately 2–4 % of all circulating T lymphocytes, seem to be extremely durable, and can rapidly differentiate into more mature central memory, effector memory, and effector T cells, while maintaining their own pool size through homeostatic self-renewal. Although it is becoming increasingly evident that that these cells have critical roles for T cell homeostasis and maintaining life-long cellular immunity against microbial pathogens during physiological conditions, they also seem intrinsically involved in many key aspects of HIV/SIV disease pathogenesis. Current data suggest that CD4+ T_{SCM} cells represent a core element of the HIV-1 reservoir in patients treated with suppressive antiretroviral therapy (ART) and that relative resistance of CD4+ T_{SCM} cells to SIV represents a distinguishing feature of non-pathogenic SIV infection in natural hosts. This article summarizes recent studies investigating the role of T_{SCM} in HIV/SIV infection.

Keywords HIV · SIV · Memory T cell · T memory stem cell · HIV-1 reservoir · Persistence · Central memory · Effector memory · Stem cell · β-Catenin

Introduction

Memory T cells represent the largest lymphocyte population in the adult human body and play critical roles for maintaining life-long antimicrobial immune defense against specific pathogens. From an evolutionary perspective, memory T cells develop when antigen-specific naive CD4+ or CD8+ T cells become activated upon antigen exposure and subsequently undergo proliferative expansion and differentiation [1]. Whether naive T cells directly develop into memory T cells or first differentiate into effector cells of which a few are selected for immunological memory during a subsequent contraction phase is unclear at present [2]. Based on complementary studies in humans and mice, memory T cells can be divided into central memory (T_{CM}) and effector memory (T_{EM}) T cells [3–5]. T_{CM} cells represent a long-lasting cell population that express lymphoid tissue homing markers, secrete mostly IL-2 upon TCR stimulation, and have a high proliferative capacity and a prolonged in vivo half-life. In contrast, effector memory T cells are more short-lived, express chemokine receptors and adhesion molecules that allow for extravasation into inflamed tissues, and can more rapidly execute lymphocellular effector functions. Current

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experimental data and theoretical considerations suggest that these memory T cell populations evolve in a hierarchical developmental process during which more immature, long-lasting T cells serve as precursors for more differentiated, mature, and short-lived memory cell subsets [3, 6, 7]. Such a linear and progressive model of memory T cell development is reminiscent of the hierarchical developmental structure of the hematological and epithelial systems, in which small populations of multipotent, tissue-specific stem cells are able to constantly replenish large populations of differentiated effector cells, while maintaining their own life-long survival through homeostatic self-renewal. Such considerations have led to the provocative hypothesis that small populations of highly undifferentiated and long-lived memory T cells with stem cell-like properties could be the basis for the continual generation of central memory, effector memory, and effector lymphocytes from the memory pool [8–11] (Fig. 1a). Recently, immense progress has been made in identifying such stem cell-like memory T cell populations in humans and other species [12, 13, 14••], and emerging data suggest that these cells play a critical role in the pathogenesis of HIV and SIV infection in humans and nonhuman primates.

Discovery of T Memory Stem Cells

A population of CD8+ T cells with stem cell-like properties, later termed "T memory stem cells" (T_{SCM}), was first experimentally observed in a murine model of graft-versus-host disease [15]. These alloreactive CD8+ T cells demonstrated enhanced self-renewal capacity and multipotency and were able to differentiate into central memory, effector memory, and effector T cells. In this mouse model, these candidate memory stem cells were characterized by low surface expression of CD4 and high expression of CD62L, stem cell antigen-1 (Sca-1), CD122, CXCR3, and Bcl-2. Since that initial description, the properties of T_{SCM} have been explored in detail in mice [13], humans [12], and nonhuman primates [14••], in the healthy state as well as in the setting of cancer or HIV/SIV infection [16••, 17••, 18•, 19]. In these studies, T_{SCM} have been defined by the expression of naive T cell markers such as CD45RA and CCR7, in tandem with memory T cell markers including CD95 and CD122, among others (Table 1). Such cells were detected both within CD4+ and CD8+ T cell subsets and account for approximately 2–4 % of all cells in each compartment. As the defining functional characteristic,

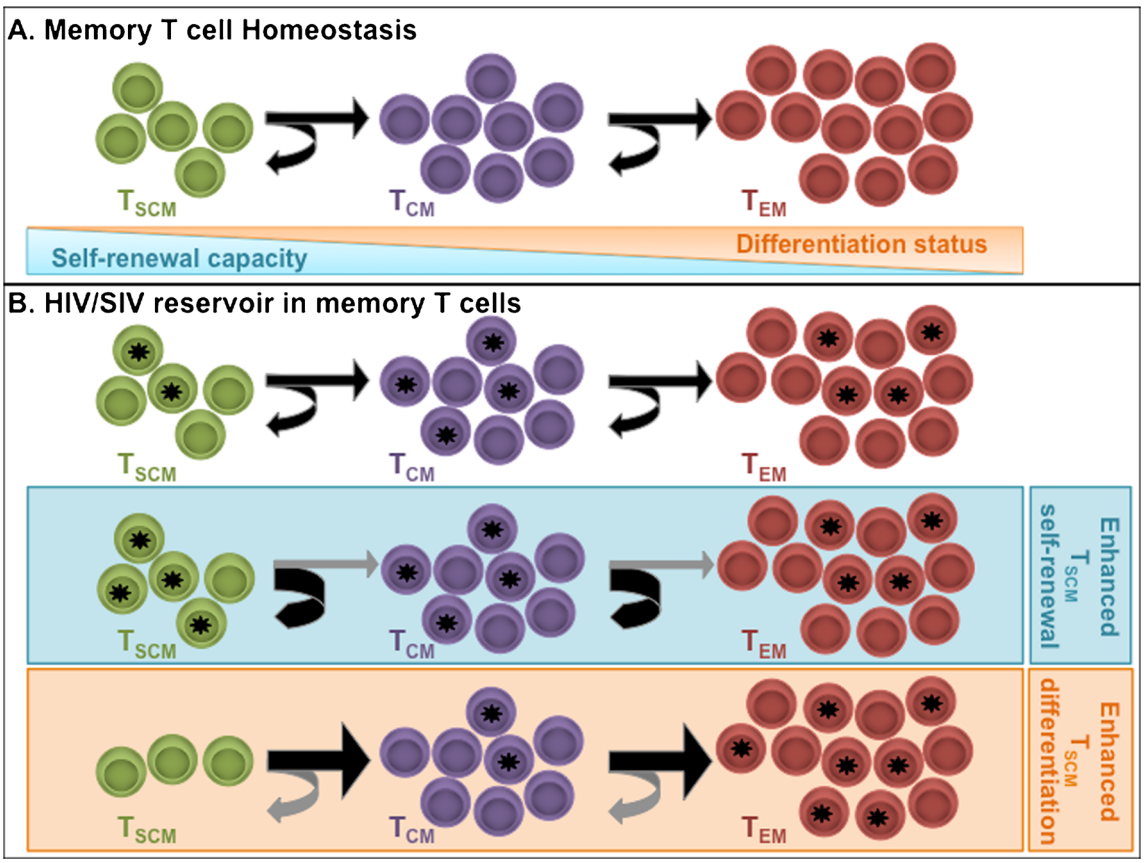

Fig. 1 Schematic of CD4+ memory T cell homeostasis (**a**) and proposed relative contribution of CD4+ T memory subsets to the persistent reservoir of HIV/SIV (**b**, *top panel*). In **b**, the potential effects of drugs promoting enhanced self-renewal (*middle panel*) or enhanced differentiation (*bottom panel*) of T_{SCM} on the overall CD4+ memory T cell reservoir are shown. *Stars* represent cells latently infected with HIV/SIV

Table 1 Phenotypic characterization of T memory stem cells (T_{SCM})

	CD45RA	CD45RO[a]	CCR7	CD62L[b]	CD27	CD28	CD95	CD122	CD58	CXCR3
Naive T cell	+	−	+	+	+	+	−	−	−	−
T_{SCM}	+	−	+	+	+	+	+	+	+	+[c]
T_{CM}	−	+	+	+	+	+	+	+	+	+
T_{EM}[d]	−	+	−	−	+/−	+/−	+	+	+	+/−

[a] Human cells only

[b] Can only be used to stain fresh cells

[c] More useful for CD8+ T_{SCM} than CD4+ T_{SCM} of nonhuman primates

[d] In several studies, subsets of T cells expressing a mix of T_{CM} and T_{EM} markers have been referred to as transitional memory T cells (i.e., CCR7+CD62L − or CCR7-CD62L-CD28+)

these long-lived T_{SCM} exhibit a multipotent developmental program that allows them to (i) continuously regenerate their own pool size through homeostatic self-renewal and (ii) repopulate more differentiated memory T cell subsets, including central memory, transitional memory, and effector memory T cells in vitro, as well as in vivo upon serial transplantation in animal experiments [8, 12, 13, 14••, 20, 21]. Further, T_{SCM} have been shown to be antigen-experienced T cells with a molecular signature that overlaps with but is still distinct from both naive and central memory T cells [12]. Homeostasis, proliferation, and differentiation of T_{SCM} seem to be governed by signaling pathways that are active in hematopoietic stem cells, thereby supporting the current nomenclature terming them "stem cell-like" memory T cells or, more simply, T memory stem cells. In vitro, T_{SCM} can be differentiated from naive T cells using TCR ligation along with co-stimulation through CD28 in the presence of IL-7 and IL-15 [22]. In this review, we will summarize recent advances in our knowledge of T_{SCM} in HIV and SIV infection, with an emphasis on their contribution to viral persistence, and describe the role of T_{SCM} in cellular immunity. Moreover, we will describe the signaling pathways that drive T_{SCM} self-renewal or proliferation and postulate how these pathways may be targeted for therapeutic purposes, including for HIV cure.

Role of T_{SCM} in Cellular Immunity

Despite the expression of several naive T cell markers, prior studies demonstrated that T_{SCM} could rapidly execute classical lymphocellular effector functions and secrete a number of different cytokines when stimulated with cognate antigen or experimental TCR ligands. Cytokines released by T_{SCM} upon antigenic challenge include IL-2, TNF-α, and IFN-γ [12], but the fraction of responding cells within the T_{SCM} compartment is typically smaller when compared to more mature T cell populations, consistent with the fact that T_{SCM} represent the least differentiated T cell subset. Other lymphocellular effector mechanisms, including cytotoxic activities and expression of lytic granules, have not yet been investigated in CD4+ or CD8+ T_{SCM}.

So far, the presence of CMV-, Flu-, SIV-, and melanoma-specific CD8+ T_{SCM} has been formally demonstrated [12, 14••], but CD4+ and CD8+ T_{SCM} are likely to contribute to cellular immune responses against any microbial pathogen that challenges the host and may also be inducible by vaccines or immunogens. Yet, the extent to which these cells may represent a correlate of immune protection, either during natural infection or after vaccination, is currently unknown. In the context of HIV-1 infection, a recent study demonstrated that in untreated patients, proportions of total CD8+ T_{SCM} were inversely correlated with levels of plasma viremia and with the degree of T cell-dependent immune activation [23], which represents an independent predictor of disease progression; moreover, there was a positive association with CD4+ T cell counts in the peripheral blood [23]. HIV-1-specific T_{SCM} have not yet been investigated, neither in the CD4+ nor in the CD8+ T cell compartment, and their role for antiviral immune defense is uncertain at present. However, given that more immature memory HIV-1-specific CD8+ T cells were preferentially observed in persons with natural control of HIV-1 [24], it is possible that HIV-1-specific T_{SCM} may contribute to HIV-1 restriction in this particular patient population. In the setting of SIV infection in rhesus macaques, prior studies demonstrated that SIV-specific CD8+ T_{SCM} are generated early after infection and persist throughout the disease process, but their contribution to the total number of SIV-specific CD8+ T cells recognizing a given epitope is low in the majority of cases [14••]. Notably, long-term persistence of SIV-specific T_{SCM} was demonstrated even after mutational escape of the targeted viral epitope, consistent with long-term antigen-independent persistence of antigen-specific CD8+ T_{SCM}. In contrast, many antigen-specific T_{CM} and T_{EM} cells recognizing the original wild-type epitope disappeared relatively rapidly after the emergence of viral escape mutations, indicating that they depend on continuous antigenic challenge to maintain their long-term survival. A better characterization of antigen-specific CD4+ and CD8+ T_{SCM} in HIV/SIV

infection and other chronic infections represents an important area of future research.

CD4+ T_{SCM} as an HIV-1 Reservoir During Treatment with ART

Given that CD4+ T_{SCM} seem to represent a very long-lasting cell population, they may represent a preferential cellular niche that supports long-term HIV-1 persistence in patients on suppressive antiretroviral therapy (ART) (Fig. 1b). To investigate this, prior studies initially analyzed the susceptibility of CD4+ T_{SCM} to HIV-1 [25–27]. Since hematopoietic stem cells seem to be largely resistant to HIV-1, it was hypothesized that CD4+ T_{SCM}, which appear to be regulated at least in part by stem cell-specific pathways, may possess cell-intrinsic immune defense mechanisms that protect this cell subset from retroviral infection. However, studies from a number of different laboratories demonstrated that CD4+ T_{SCM} express CCR5, although at low levels, and are able to support productive and latent infection with R5-tropic HIV-1. In addition, CD4+ T_{SCM} were highly permissive to ex vivo infection with a VSV-G pseudotyped HIV-1 virus and expressed comparatively low levels of cell-intrinsic viral restriction factors, such as SAMHD1, Trim5alpha, and APOBEC3G [16••]. Importantly, these investigations also demonstrated that CD4+ T_{SCM} from untreated HIV-1-infected patients harbored high levels of HIV-1 RNA, indicating that these cells are susceptible to HIV-1 in vivo. Using CD4+ T_{SCM} sorted from patients undergoing suppressive ART, subsequent studies demonstrated that CD4+ T_{SCM} harbor replication-competent virus that can be reactivated in viral outgrowth assays, further suggesting that CD4+ T_{SCM} can represent a reservoir for latent HIV-1 infection [16••, 18•]. Yet, due to their low frequency, the viral reservoir in CD4+ T_{SCM} only accounted for a small proportion of the total reservoir in CD4+ T cells in most patients [16••].

Interestingly, the relative contribution of CD4+ T_{SCM} to the total viral reservoir seems to critically depend on the timing and the duration of ART. For instance, in long-term treated patients who initiated ART early after infection and had a comparatively small total HIV reservoir, CD4+ T_{SCM} appeared to make a relatively larger contribution to the total viral reservoir size, as opposed to patients who started treatment during the chronic phase of the infection and had an increased total viral reservoir size [28•]. Moreover, the contribution of CD4+ T_{SCM} to the total viral reservoir seems to be inversely related to the total viral reservoir, an association that was exclusively observed for the CD4+ T_{SCM} compartment, and not for alternative CD4+ T cell populations. Longitudinal evaluations spanning more than 10 continuous years of suppressive ART indicated that HIV-1 DNA in CD4+ T_{SCM} remained largely stable, while decay of HIV-1 DNA in alternative CD4+ T cell populations was more obvious [16••, 18•]. Correspondingly, CD4+ T_{SCM} contributed only a small proportion to the viral reservoir after short-term ART. Yet, after longer-term ART, the fraction of the viral reservoir harbored by CD4+ T_{SCM} was significantly larger, while contributions made by other subsets, in particular short-lived CD4+ T_{EM} cells, declined [16••]. This disproportionate increase in the contribution of CD4+ T_{SCM} to the total viral reservoir over time is consistent with a role of CD4+ T_{SCM} as one of the most durable and stable reservoirs for HIV-1 that becomes increasingly visible after prolonged periods of ART.

A similar observation was made in a geographically distinct population of HIV-1-infected patients treated with antiretroviral agents for varying periods of time in France [18•]. Chromosomally integrated HIV-1 DNA was readily detectable in CD4+ T_{SCM} in all but three individuals out of a total study cohort of 38 ART-treated HIV-1-infected patients. Importantly, linear regression analyses of these data indicated that the half-life of HIV-1 DNA in CD4+ T_{SCM} was almost twice as long as in CD4+ T_{CM} cells, the compartment with the second-longest half-life of HIV-1 DNA, and more than three times longer than the half-life of HIV-1 DNA in CD4+ T_{EM} cells. Interestingly, analysis of data from this study also led to the conclusion that the relative proportion of HIV-1 DNA in the CD4+ T_{SCM} compartment progressively expands over time, while the fraction of HIV-1 DNA harbored by other CD4+ T cell subsets declined, with the net result of a contraction of the viral reservoir around a core of less differentiated, long-lasting memory CD4+ T cells. It should be mentioned, however, that these studies did not investigate whether and how HIV-1-infected CD4+ T_{SCM} may stabilize the viral reservoir by repopulating the pool of HIV-1-infected CD4+ T_{EM} and T_{CM} cells through transitional proliferation. Given that T_{SCM} can readily differentiate in more mature CD4+ T cell populations in in vitro assays and rapidly repopulate cellular immunity upon serial transplantation in animal models, it is expected that HIV-1-infected CD4+ T_{SCM} can indeed perpetuate HIV-1 persistence by homeostatic self-renewal as well as by continuously differentiating into more mature memory CD4+ T cell populations that are also infected with HIV-1; however, this remains to be formally demonstrated.

Role of T_{SCM} in SIV Pathogenesis

Asian rhesus macaques infected with SIV represent the best animal model of HIV infection due to many similarities in terms of early transmission events, viral and CD4+ T cell dynamics, establishment of reservoirs, and disease progression [29–33]. Similar to HIV-infected patients, SIV-infected rhesus macaques display a high viral load peak that falls to a set point level during the period of primary/acute infection. Viral loads during the chronic phase of infection are typically in the range of 10^4–10^7 and are accompanied by CD4+ T cell decline that progresses to AIDS and death over 1–2 years. African monkey species, such as

sooty mangabeys and African green monkeys, are naturally infected with SIV both in the wild and in captivity. Despite peak and set point viral loads that are comparable to those of HIV-infected humans and SIV-infected macaques, these "natural hosts" do not progress to AIDS and manifest only a minimal decline in peripheral CD4+ T cell counts [34]. One of the key features that differ between natural hosts and non-natural hosts (i.e., human and macaques) is the level of cell surface expression of the HIV/SIV co-receptor CCR5 [35]. In natural hosts, high-level expression of CCR5 is restricted to the effector memory subset of CD4+ T cells whereas central memory CD4+ T cells maintain low CCR5 levels even after exposure to activating stimuli in vitro or in vivo [36]. In fact, the level of CCR5 expression has been shown to correlate with the ability of SIV to infect specific cell subsets as well as with age at SIV acquisition [36–39]. These observations led to the hypothesis that differential SIV infection of CD4+ T_{SCM} (as a consequence of the level of cell surface CCR5) may distinguish pathogenic SIV infection of rhesus macaques from non-pathogenic SIV infection of sooty mangabeys (described further below).

The phenotypic and functional properties of T_{SCM}, both CD8+ and CD4+, in healthy and SIV-infected macaques were first described by the group of Mario Roederer [14••, 19]. Similar to their description in humans, T_{SCM} were identified using markers of naive T cells with further characterization as CD27+CD28+IL-7Ralpha+CD95+ in rhesus and pigtailed macaques. These cells represented about 2–3 % of circulating CD8+ and CD4+ T cells and were slightly more abundant in lymph nodes (for CD8+ T_{SCM} only) and less so at mucosal sites. Notably, during pathogenic HIV and SIV infection, a high level of direct infection of CD4+ T_{CM} cells is associated with depletion of CD4+ T cells as well as chronic immune activation [36, 40–44]. Although potentially less so than T_{SCM}, T_{CM} cells are thought to contribute to overall CD4+ T cell homeostasis due to their ability to undergo rounds of proliferation that maintain their pool as well as differentiate into the shorter-lived effector memory subset. Direct virus infection and killing of CD4+ T_{CM} cells therefore have implications for the maintenance of long-lived immunity as well as overall CD4+ T cell homeostasis. As the non-pathogenic SIV infection of sooty mangabeys is characterized by preservation of CD4+ T_{CM} cells [36], we postulated that CD4+ T_{SCM} would also be maintained and that this state of memory stem cell immunocompetence represents a hallmark of non-pathogenic SIV infection in natural hosts.

When directly compared, the levels of circulating CD4+ T_{SCM} in healthy rhesus macaques were slightly higher than in sooty mangabeys (1–8 vs. 0.5–3 %), although CD4+ T_{SCM} from mangabeys expressed higher levels of the proliferation marker Ki-67 [17••]. In addition, CD4+ T_{SCM} from sooty mangabeys demonstrated an almost complete absence of cell surface CCR5, unlike CD4+ T_{SCM} from macaques, suggesting a potential for differential levels of SIV infection. Indeed, a low level of SIV DNA in CD4+ T_{SCM} could only be detected in 2/10 SIV-infected sooty mangabeys, in contrast to 9/9 SIV-infected rhesus macaques with SIV DNA levels in CD4+ T_{SCM} that were comparable to those of other CD4+ T memory subsets [17••]. Furthermore, the pathogenic SIV infection of rhesus macaques was associated with a selective depletion of CCR5+CD4+ T_{SCM} whereas the percentage and absolute number of CD4+ T_{SCM} along with the percentage of CD4+ T_{SCM} expressing CCR5 did not differ in SIV-uninfected and SIV-infected mangabeys. Similar observations were also made in human viremic non-progressors, an exquisitely rare group of HIV-1-infected patients who maintain sufficient CD4+ T cell counts for prolonged periods of time in the setting of ongoing high-level HIV-1 replication, and in this way closely resemble the clinical picture of SIV infection in natural hosts. In these patients, the levels of HIV-1 DNA in CD4+ T_{SCM} were significantly lower than in normally progressing, untreated HIV-1-infected patients [45•], suggesting that the CD4+ T_{SCM} compartment of these specific patients does not support effective HIV-1 replication. Collectively, this work suggested that the relative resistance of CD4+ T_{SCM} to lentiviral infection in natural hosts of SIV infection and in HIV-1-infected viremic non-progressors is associated with protection against HIV/SIV disease progression. Vice versa, perturbed homeostasis of CD4+ T_{SCM} in SIV-infected rhesus macaques (manifested by both increased infection and depletion) likely promotes lentiviral pathogenesis. Based on these results in nonhuman primates as well as the recognized role of CD4+ T_{SCM} as an HIV-1 reservoir in ART-treated humans, experiments are underway in our laboratories to fully understand the contribution of CD4+ T_{SCM} to the total body SIV reservoir in ART-suppressed rhesus macaques and sooty mangabeys.

Signaling Pathways Active in T_{SCM}

The provocative observation that T_{SCM} seem to be able to imitate many of the functional characteristics conventionally ascribed to tissue-specific stem cells has raised considerable interest in the mechanisms controlling T_{SCM} behavior. Would it be possible that transcriptional programs and regulatory mechanisms of classical tissue-specific stem cells can be activated in T_{SCM}, despite the fact T_{SCM} represent committed lymphocytes? Recent data suggest that this is at least partially true, specifically for the molecular control of T_{SCM} fate decisions. In hematopoietic and epithelial stem cells, checkpoint decisions between self-renewal vs. differentiation into more mature cells are in part regulated by the phylogenetically conserved Wnt/β-catenin signaling pathway [46]. In the canonical Wnt/β-catenin signaling cascade, extracellular Wnt glycoproteins bind to 7-transmembrane Frizzled receptors and co-receptors LRP5 and LRP6, leading to phosphorylation of LRP5/6 and subsequent binding by Axin and other members of the β-catenin destruction complex [47]. In the absence of

Wnt binding, this destruction complex (made up of Axin, Dishevelled, GSK3, CK1, and APC) binds and phosphorylates β-catenin in the cytoplasm leading to ubiquitination and degradation of β-catenin by the proteasome. In the presence of Wnt signaling, however, β-catenin is released from the destruction complex and can move freely into the nucleus where it binds to the TCF/LEF family of transcription factors, resulting in transcription of target genes [47, 48]. Hypothesizing that Wnt/β-catenin is also involved in regulating cell fate decision of T_{SCM}, Gattinoni et al. demonstrated that induction of the Wnt signaling pathway using a pharmacological inhibitor of GSK-3β in the presence of antigen in CD8+ T cells led to an accumulation of β-catenin, blocked T cell differentiation, and promoted the generation of self-renewing multipotent T_{SCM} in vitro [13]. These observations are in line with prior studies showing that mice lacking the *TCF7* gene, which encodes for a downstream effector of the Wnt/β-catenin pathway, exhibited a more differentiated T cell phenotype [49] and that decreasing expression of Lef1 and TCF7 was associated with progressive differentiation of T cells in humans and mice [50]. Moreover, high-level expression of β-catenin was associated with an increased ability to form functional memory cell responses in vivo [51]. Together, these data suggest stem cell physiology and regulatory pathways involved in stem cell fate decisions can at least transiently be activated in non-stem cells such as lymphocytes and allow for a stem cell-specific functional profile in committed lymphocytes that is otherwise exclusively encountered in traditional stem cells. Whether other stem cell-specific signaling pathways, such as the Notch or sonic hedgehog signaling cascade, are also involved in regulating T_{SCM} behavior represents an important aspect of future investigations.

Opportunities to Target T_{SCM} to Reduce the HIV/SIV Reservoir

Although once regarded as an elusive goal, the development of clinical strategies that can lead to a long-term drug-free remission of HIV-1 infection has become a more and more realistic objective. This is in part related to the recent identification of patients with a sterilizing or functional cure of HIV-1 infection, which provides living evidence that at least in principle, a complete or near-complete eradication of residual HIV-1 reservoirs is possible [44, 52, 53]. Most clinical approaches that are currently evaluated as strategies to reduce HIV-1 persistence despite ART focus on the "shock and kill" strategy, which is based on the use of pharmaceutical agents that can reverse viral latency, followed by immune-based interventions that may kill cells in which viral reactivation has been successfully induced. Although this concept is currently being tested in a number of pre-clinical and clinical studies, it is uncertain whether this strategy would be effective in targeting the latent viral reservoir in CD4+ T_{SCM} and T_{CM} cells, which arguably represents the most durable and long-lived site for long-term viral persistence and the most critical barrier to HIV-1 cure. As an alternative to the shock and kill approach, strategies that specifically destabilize the viral reservoir in these long-lasting CD4+ T_{SCM} and T_{CM} cells may therefore represent promising and possibly more effective avenues for future clinical interventions to reduce HIV-1 persistence. Such approaches will likely have to specifically target molecular pathways that are responsible for self-renewal, survival, and proliferation of CD4+ T_{SCM} and T_{CM} cells. As described above, homeostasis of the CD4+ T_{SCM} and T_{CM} cell pool seems to be maintained at least in part by molecular mechanisms that are similar or identical to stem cell-specific, phylogenetically conserved signaling cascades regulating the "stemness" (i.e., multipotency, self-renewal, and long-term persistence) of classical hematopoietic or epithelial stem cells. These pathways are currently also under active investigation for targeting cancer stem cells, a small subset of long-lived cancer cells with high oncogenic potential that in many cases are responsible for persistence and recurrence of malignant diseases despite treatment [54–57], and in that sense may represent the functional analog to the reservoir of HIV-1-infected CD4+ T_{SCM} and T_{CM} cells that persist despite antiretroviral therapy in patients. Therefore, drugs designed to manipulate cancer stem cells through interference with stem cell-specific signaling pathways may offer novel opportunities to specifically target the long-lived core components of the HIV-1 reservoir and reduce long-term viral persistence in HIV-1-infected CD4+ T_{SCM} and T_{CM} cells. This strategy, whereby long-lived, latently HIV-1-infected T_{SCM} and T_{CM} cells are forced to differentiate into T_{EM} and effector T cells with a much shorter half-life, could be termed "push and vanish" (Fig. 1b, bottom panel). Such approaches recognize the structural and developmental heterogeneity of HIV-1-infected CD4+ T cells in ART-suppressed patients and provide a more specific molecular strategy for selectively eliminating the cells that arguably seem most relevant for maintaining and perpetuating HIV-1 persistence.

Conclusions

The discovery of T_{SCM} as the stem cells of cellular immune memory may have critical implications for understanding the ontogeny and the evolution of cellular immune responses and for designing immunological interventions, adoptive immunotherapy, and vaccination strategies. In the context of HIV-1 infection, the idea that HIV-1 can infect stem cells, the most long-lasting cells in the human body, to establish life-long viral persistence has remained conceptually appealing for many years [58, 59]; however, data to support HIV-1 infection of classical tissue-specific stem cells, in particular hematopoietic stem cells, remain controversial [60, 61], since these cells appear to possess defined cell-intrinsic resistance mechanisms to inhibit retroviral infection [62]. Infection of the readily susceptible CD4+ T_{SCM} as a stem

cell-like cell compartment may allow HIV-1 to exploit the stem cell characteristics of cellular immune memory to propagate viral persistence indefinitely. As evidence to support this hypothesis increases, HIV-1 CD4+ T_{SCM} may move into the center of current efforts to reduce persistence of replication-competent HIV-1 during ART and offer novel opportunities for targeted destabilization of long-lived viral reservoirs. For instance, genetic manipulation of CD4+ T_{SCM} through gene therapy-induced reduction of CCR5 surface expression may generate a long-lasting population of CD4+ T cells that does not support HIV-1 replication and may increase a patient's ability to maintain at least a transient drug-free remission of his or her disease. In addition, rapid introduction of ART during the hyperacute stage of HIV-1 infection may spare infection of CD4+ T_{SCM}, in which case a finite course of ART may be curative, or at least allow for longer periods of viral control after treatment discontinuation. A finite course of ART may also be sufficient to destabilize persistent viral reservoirs in natural hosts of SIV infection, in whom CD4+ T_{SCM} seem to be at least partially resistant to SIV infection. Finally, pharmaceutical interventions that transform long-lived HIV-1-infected CD4+ T_{SCM} into short-lived effector cells through interference with molecular programs governing CD4+ T_{SCM} survival and homeostasis may represent a promising approach for reducing long-term HIV-1 persistence that would be applicable to larger populations of ART-treated HIV-1-infected patients.

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Compliance with Ethics Guidelines

Conflict of Interest Ann Chahroudi, Guido Silvestri, and Mathias Lichterfeld declare that they have patent pending on Wnt pathway inhibitors for treating viral infections.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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