MINIREVIEWS

Stem cell-like memory T cells: Role in viral infections and autoimmunity

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Abstract

Stem cell-like memory T (T_{SCM}) cells possess stem cell properties including multipotency and self-renewal and are being recognized as emerging players in various human diseases. Advanced technologies such as multiparametric flowcytometry and single cell sequencing have enabled their identification and molecular characterization. In case of chronic viral diseases such as human immunodeficiency virus-1, CD4+ T_{SCM} cells, serve as major reservoirs of the latent virus. However, during immune activation and functional exhaustion of effector T cells, these cells also possess the potential to replenish the pool of functional effector cells to curtail the infection. More recently, these cells are speculated to play important role in protective immunity following acute viral infections such as coronavirus disease 2019 and might be amenable for therapeutics by *ex vivo* expansion. Similarly, studies are also investigating their pathological role in driving autoimmune responses. However, there are several gaps in the understanding of the role of T_{SCM} cells in viral and autoimmune diseases to make them potential therapeutic targets. In this minireview, we have attempted an updated compilation of the dyadic role of these complex T_{SCM} cells during such human diseases along with their biology and transcriptional programs.

Key Words: Stem cell-like memory T cells; Viral infections; Autoimmune diseases; Effector T cells; Memory T cells

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Core Tip: This article discusses the contrasting roles of stem cell-like memory T (T_{SCM}) cells during chronic viral infections and autoimmune diseases. During chronic viral infections, such as human immunodeficiency virus-1, the T_{SCM} cells serve as reservoirs for latent viruses, which can be activated to make them susceptible to cytotoxic T cell responses. However, during acute viral infections, the T_{SCM} cells have the ability to replenish the diminished effector T cell population. In autoimmune diseases, like type-1 diabetes, these cells contribute to the disease pathogenesis by persistent generation of autoreactive effector T cells. A better understanding of the key signaling pathways and mediators regulating T_{SCM} cells could lead to novel approaches to target or manipulate these cells for immunotherapeutic applications.

INTRODUCTION

Memory T cells with stem cell properties were identified more than a decade ago and since then they have gained tremendous attention as important players in several disease conditions owing to their self-renewal and multipotent properties[1,2]. Typically, the stem cell-like memory T (T_{SCM}) represent the earliest developmental stage of memory T cells capable of differentiation upon antigen re-challenge[1]. These cells proliferate extensively and have long lifespans because of the maintenance of the length of their telomeres attributed to an active telomerase that preserves the potency of these cells[3]. T_{SCM} cells express a combination of molecules on their surface including: CD45RA, CD45RO, CD62L, CCR7, CD27, CD28, CD127, CD95, and CD122. These cells also express CXCR3, Bcl-2, and LFA-1 and display characteristics that are intermediate between naive and central memory T-cells.

In chronic viral infections, T_{SCM} cells have been known to harbor viruses like human immunodeficiency virus-1 (HIV-1) or hepatitis C virus (HCV) and serve as their long-term latent reservoirs (Figure 1). This T cell subset harbors the highest amount of proviral DNA and contributes significantly as an HIV-1 reservoir as compared to other reservoirs[4]. The stem cell signaling pathways operational in these cells have been elucidated in a few studies[5]. Studies on cancer stem cells have further shed light on the role of canonical Wnt/Notch signaling as a fundamental pathway mediating self-renewal of these cells which might be probably involved in latency during HIV-1 infection. Wnt proteins are secreted glycoproteins that bind and activate the seven transmembrane receptors, Frizzled. Binding of Wnt to Frizzled receptor results in the activation of cytosolic proteins belonging to the Dishevelled family of proteins, leading to internalization of the Frizzled receptor. Activation of Wnt after binding to its receptors leads to downstream signaling events that further lead to the translocation of cytosolic β-catenin proteins into the nucleus. These proteins act as a transcriptional coactivators of factors belonging to the T cell factor 1 (TCF-1)/lymphoid enhancer factor (LEF) family leading to the transcription of Wnt/β-catenin target genes[6,7]. Turning off these pathways may favor memory T cell differentiation, influencing HIV-1 replication and making these cells susceptible to either anti-retroviral drugs or cytotoxic T cells. Besides Wnt/β-catenin pathways, other pathways such as Notch or Sonic Hedgehog pathways might also be functional in these cells, however, this remains to be an important area of future research.

Unlike viral infections, autoimmune diseases are characterized by an exaggerated immune response against self-antigens involving various cell types including T_{SCM} cells (Figure 1). Studies in the past few years have drawn attention to the role of T_{SCM} cells in the sustenance of autoimmune cells for longer durations, posing a big hurdle toward immuno-therapeutic approaches. It is believed that owing to their high differentiation potential these cells continue to generate effector T cells that further exacerbate the immune homeostasis and contribute to disease pathogenesis. An understanding of the key transcription factors and their signaling mechanisms could lead to the design of approaches to specifically target these cells.

Although it has been more than a decade since the T_{SCM} cells were first identified, there is a scarcity of literature on the role of these cells in various diseases suggesting further research on this important T cell subset through a greater number of studies. In this minireview, we have tried to compile the available literature on the role of T_{SCM} cells in common viral infections like coronavirus disease 2019 (COVID-19), HIV-1, HCV, and autoimmune diseases like type 1 diabetes (T1D) and attempted to suggest a few strategies to target these cells.

STEM CELL-LIKE MEMORY T CELLS AND COVID-19 INFECTION: EMERGING CONCEPTS

Severe acute respiratory syndrome virus (SARS-CoV-2), a new virus that emerged in 2019 was responsible for the COVID-19 pandemic which caused havoc worldwide. The era witnessed the rapid development of a wide variety of vaccines against COVID-19 for the induction of long-term protective immunity in the general population, an attribute of immunological memory. The infection subsides after clearance of the virus leaving a small proportion of T and B memory cells that have the potential to differentiate into virus-specific effector cells and neutralizing antibodies in response to a new episode of infection. Studies using MHC multimers and activation-induced markers have demonstrated that the T_{SCM} cells are generated in both the CD4 and CD8 compartments of T cells peaking approximately at 120 d and persisting up to
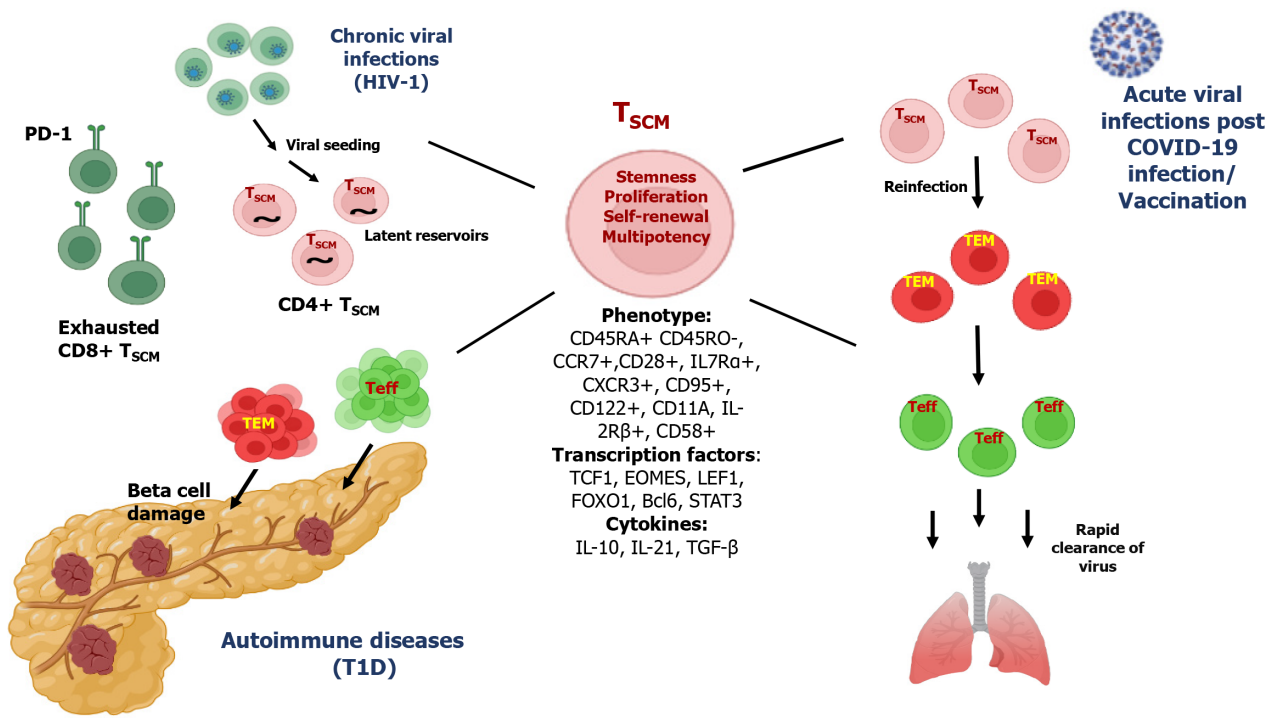
Figure 1 Varying roles of stem cell-like memory T cells during chronic (human immunodeficiency virus-1) and acute (COVID-19) viral infections and autoimmune diseases (type 1 diabetes). In chronic human immunodeficiency virus-1 (HIV-1) infection, the CD4+ stem cell-like memory T (T_{SCM}) cells act as latent reservoirs of HIV-1, whereas the CD8+ T_{SCM} cells exhibit an exhausted phenotype with upregulation of inhibitory molecules like programmed cell death 1. In case of post coronavirus disease 2019 infection or vaccination, viral specific T_{SCM} cells are generated that provide long term protective immunity. In autoimmune responses, such as during type 1 diabetes, T_{SCM} cells generate autoreactive effector-memory (T_{EM}) and effector T (Teff) cell subsets that perpetuate the ongoing inflammatory responses. HIV-1: Human immunodeficiency virus-1; PD-1: Programmed cell death 1; T1D: Type 1 diabetes; T_{SCM}: Stem cell-like memory T; COVID: Coronavirus disease 2019.

8 mo to 10 mo post-infection[8,9].

Further, gene expression profiling and using computational framework methods, the host genetic responses that influence immune cell subsets including CD8+ memory T cells were studied in COVID-19[10]. The CXCR6+ memory CD8+T cells were enriched in genes involved in cytokine, chemokine, T cell activation, proliferation, and migration, indicating their potential contribution to protection from the severe form of COVID-19. In fact, a timely generation of T_{SCM} cells determines the durability of vaccine-induced memory CD8+ T-cell responses[11]. Hence, there appears to be a direct correlation between protective immunity and memory stem cells either after natural infection with the virus or post-vaccination. Similarly, in another study, BNT162b2 vaccine induced various immune-competent cell populations including T_{SCM} cells that serve as indicators of a protective immune response[12]. The frequencies of both CD4+ and CD8+ T_{SCM} cells correlated positively with antibody titers as well[13]. Since the T_{SCM} cells are associated with virus control and induction of long-lived immunity, it may be assumed that these cells are an indicator of success of vaccine efficacy. Whether the T_{SCM} cells or their progenitors are able to migrate to regional lymph nodes or mucosal sites of viral entry is another parameter of durable protection. Nevertheless, a deeper understanding of the genesis and sustenance of T_{SCM} cells could provide the basis for the improvement and development of newer vaccines against COVID-19 and its variants.

STEM CELL-LIKE MEMORY T CELLS AND HIV-1: A PARADIGM

During HIV-1 infection, the virus utilizes a variety of cells like tissue macrophages, myeloid cells, brain microglial cells, gut epithelial cells, and hematopoietic stem cells (HSCs) and more importantly CD4+ T_{SCM} cells as its latent reservoir, making it inaccessible to the antiretroviral therapy (ART). Consequently, the patients need to be on life-long ART since any interruption in their therapy leads to virus rebound from these reservoirs. Hence, this reservoir poses a big hindrance to the cure of HIV infection. The establishment of reservoirs begins early during the acute phase of infection and keeps on accumulating during the subsequent phases[14]. While the establishment of viral reservoirs is almost inevitable, early and timely initiation of ART leads to a reduction in the size of this reservoir[15,16]. Earlier research in this regard suggested that prevention of reservoirs is not possible even if therapy is initiated before the presentation of symptoms, as early as 10 days despite the successful control of plasma viremia[17]. In this context, the expansion of the T_{SCM} cells has been documented to be correlated to HIV disease progression[4]. The contribution of T_{SCM} to the total HIV reservoir becomes appreciable when the total CD4+ T cell population contracts with disease progression and hence contributes largely to the long-term persistence of the virus[18]. Earlier, one of our own studies showed an increased frequency of T_{SCM} cells in HIV

patients with a break in ART as compared to patients on regular ART. It may be noted that a greater number of these cells might not be protective since the CD8+ T_{SCM} also expressed high levels of inhibitory molecule, programmed cell death 1 (PD-1) on their surface making them functionally incompetent[19]. In this scenario, latency reversal agents (LRA) in combination with PD-1 blockade might serve to target viral reservoirs besides revival of cellular functions. CD8+ T cells expressing PD-1 and TCF-1 retain long-term survival capacities and proliferation potential, hence they constitute an important armory against the virus. These cells hold greater promise in T cell therapies since they have higher cytolytic potential of these cells and could be helpful in controlling viral replication. These cells have been associated with slow progression in pediatric HIV-positive patients[20]. The HIV-specific CD8+ T cell population expressing PD-1 and TCF-1 represents a promising target for T cell therapies because of the long-term survival and proliferative capacity of these stem-like cells.

The cell signaling pathways that aid in the establishment of latency, are incompletely understood. It is suggested that the process of formation of HIV reservoirs mimics those that are operational in the maintenance of T cell memory, hence insights from the studies in cancer stem cells might shed light into their development programs. Strategies to reactivate viruses from this reservoir have been continually evolving and various hypotheses to explain the generation and maintenance of these reservoirs have been put forward. After encountering the antigen, a state of chronic activation is achieved. During this stage, these T_{SCM} may undergo a process of asymmetric division that replenishes the pool of latent reservoirs[21]. Another hypothesis is that gamma chain cytokines such as IL-7 and IL-15 may lead to the homeostatic proliferation of these cells owing to a higher expression of cytokine receptors on these cells[22]. The observation that the cells expressing PD-1 retain higher levels of HIV-DNA as compared to cells that are PD-1 Low, suggests that certain pathways collating with negative regulators or inhibitory receptors might be favoring the sustenance of T_{SCM} cells as viral reservoirs[23].

Several strategies have been tried including activating the cells carrying the latent HIV-1 with some LRA so that these cells become targets of the cytolytic machinery of the host[24]. Many such agents have been identified and include histone deacetylase inhibitors[25,26]; disulfiram[27,28]; and the bromodomain-containing protein 4 inhibitor JQ1[29]. These agents either function through the activation of some epigenetic programs or cell signaling pathways that lead to cellular activation. There are other agents that act *via* activating T cells like protein kinase C agonists such as phorbol esters, prostratin[30], bryostatin-1[31] which reverse latency in cell models. Using 3 assay systems, Bullen *et al*[24] did a comparison of all these agents, however, none of the agents significantly interrupted the maintenance of latent reservoirs. This could be explained by the resistant nature of these cells to cell death which is inefficiently induced by these agents. The only agent that demonstrated relatively better results was the PKC agonist, bryostatin-1, however, its clinical application is limited due to a high degree of associated cellular toxicity and a lack of pharmacokinetic studies[24].

STEM CELL-LIKE MEMORY T CELLS AND HEPATITIS C INFECTION

Chronic HCV infection is found to be associated with a suboptimal interferon response and exhaustion of cytotoxic T cell responses leading to the viral escape of immune responses and persistence of the virus. Similar to HIV-1 infection, complete clearance of HCV also does not occur with antiviral agents with a consequent dysfunctional state of memory CD8+ T cells. In such a scenario, CD8+ T_{SCM} cells with long life, multipotency, and self-renewal properties can rescue the dysfunctional immune state. It has been observed that higher frequencies of these cells were associated with low viral loads and less immune activation, indicating a role of T_{SCM} cells in protective immunity. More recently, the same group depicted an increased proportion of CD8+ memory stem cells during HCV infection and in HCV/HIV dual-positive patients. In fact, the proportions of these cells had a positive correlation with central memory cells. Also, they were associated with lower viral load, a likely impact on controlling immune activation, and ultimately an effective and protective immunity[32].

It was also observed that vaccination in chimpanzees for HCV-induced memory T cells along with control of virus replication concurrent to attenuation of inhibitory receptors on T cells[33]. Therefore, it could be speculated that such a response would mean more differentiation of the effector T cells from the memory stem cell reservoir.

STEM CELL-LIKE MEMORY T CELLS AND AUTOIMMUNE DISEASES

Since memory stem cells are endowed with self-renewal properties and can differentiate into effector T cells with the maintenance of their pool size, these cells are proposed to play a substantial role in the progression of autoimmune diseases particularly type 1 diabetes, systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis, aplastic anemia (AA) and autoimmune uveitis[34-36].

T1D

A chronic autoimmune disease characterized by a strong islet-associated inflammatory response cause the destruction of pancreatic β-cells leading to deficiency in insulin synthesis[37]. Genetic predisposition and environmental factors be linked although the mechanisms are not completely understood[38]. Another strong hypothesis suggested that underlying microbial infections exacerbate islet inflammation in genetically susceptible individuals[39,40]. The disease leads to the production of islet-specific autoantibodies as well as islet-specific autoreactive CD8+ T cells that are present in large numbers in the insulitis lesions. Such autoreactive CD8+ T cells are mainly responsible for the destruction of β-

cells besides the contribution of other immune cells like B cells, macrophages, and NK cells[41].

An important observation in T1D patients is that some of the autoimmune cells display properties that coincide with the appearance of T_{SCM} cells along with the expression of memory cell markers[42]. These cells probably act as stable reservoirs which can differentiate into other autoreactive T cells that might lead to disease progression. One of the earlier studies did show that T1D patients possess memory stem cells with a higher proliferative capacity to generate memory autoimmune T cell repertoire[43]. The mechanisms involved in the generation of memory stem cells are being elucidated. The cytokine, IL-7 has been proposed to play an important role during the differentiation of T cells from naïve precursors [44]. IL-7 promotes the uptake of glucose *via* overexpression of glucose transporter 1 (GLUT1) and upregulation of the glycolytic enzyme hexokinase 2. The process of pyruvate oxidation in the mitochondria has been linked to the differentiation of T_{SCM} cells from the naïve cell precursors. The T1D patients had a higher expression of GLUT1, which is a hallmark of circulating memory stem cells. Moreover, it has been shown that in such patients, WZB117, an inhibitor of GLUT1 could be used to target glucose uptake and was found to interfere with the generation of memory stem cells[45]. A large number of T_{SCM} cells can be obtained *in vitro* from the naïve precursors with the use of a combination of IL-7 and IL-15 through the engagement of CD3/CD28[46]. This will facilitate rapid exploitation of these cells in adoptive cell therapy. A higher frequency of both CD4+ and CD8+ circulating T_{SCM} cells has been observed in T1D suggesting a possible association with disease pathogenesis[34]. The effector functions could be attributed to their capacities to secrete the cytokines tumour necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ), and IL-2, enabling them high pathogenicity in T1D.

Besides memory stem cells, closely related cell types or more specifically stem-like autoimmune progenitor T cells have also been shown to play an important role in the pathogenesis of autoimmune diseases. These stem-like cells are CD44highTCF1+CXCR6- which convert into effector CD44highTCF1-CXCR6+ CD8+ T cells which mediate destruction of target cells have been identified in NOD mice[47]. Using single-cell RNA sequencing and clonal analysis, researchers discovered that autoimmune CD8+ T cells represent distinct T cell differentiation phases and distinct traits that drive the switch from autoimmune progenitor to the autoimmune mediator. It could be speculated that strategies that could be employed to target the stem-like progenitors could serve as powerful immunotherapeutic tools in the future for T1D as well[48].

SLE

SLE is a multiorgan systemic disease in which autoantibodies develop against nuclear antigens and affect multiple body organs. Immune complexes comprising antigens and their cognate anti-nuclear antibodies accumulate in various organs such as skin, kidneys, or brain that trigger activation of immune cells leading to increased pro-inflammatory cytokine production that ultimately damages the affected organ[49]. Immunosuppressive therapies are not completely effective in suppressing the formation of autoantibodies making the disease incurable and there is only partial remission[50]. Similar to T1D, an increased frequency of CD4+ T_{SCM} cells exist in patients with SLE. A vicious series of events is initiated with enhanced secretion of cytokines that boost their differentiation of T follicular helper (Tfh) cells that also increase the production of autoantibodies from B cells that further perpetuate the disease[51]. Further, these T_{SCM} cells are more proinflammatory in nature indicative of their contribution to disease pathogenesis.

Aplastic anemia

Aplastic anemia (AA) is an autoimmune disease in which cytotoxic CD8+ T-cells attack autologous HSCs and is mainly characterized by an acquired immune-mediated bone marrow failure syndrome. The disease is sustained by increased levels of type I interferons that polarize the immune system towards Th1 responses in the early stage of the disease. On the other hand, the late-stage and severe form of the disease is characterized by Th17 cells and effector memory CD8+ T-cells[52].

It has been reported that AA patients had a higher frequency of both CD4+ and CD8+ effector memory T cells. This increased frequency was observed in both circulation as well as bone marrow, contributing to abnormal immune status and correlating with disease pathogenesis[53]. Next, there was a correlation between the memory stem cells and disease severity, treatment response, disease relapse, and response to immunosuppressive therapy[35]. An inverse relation was observed between these T_{SCM} cells and their effector memory or effector T cell counterparts since these cells serve as their progenitors. A hyperimmune activation seen in patients with autoimmune diseases might be the reason for an aberrant immune cell repertoire encompassing a higher number of memory stem cells, although this remains to be a hypothesis and needs to be confirmed further. In AA as well, the T_{SCM} cells serve as a source of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-2 in response to TCR stimulation. As compared to healthy controls, *in vitro* stimulation of TCR in AA patients resulted in a higher production of these cytokines from both CD4+ and CD8+ T_{SCM} cells with a greater expansion of these cells as well[54].

As far as memory stem cells are concerned, they also expressed higher PD-1 levels and are thus implicated as an exhausted T cell subset[35]. The expression of PD-1 also gets upregulated during AA and is associated with aberrant regulation of T cell activation[55]. However, this does not suggest a lower functional capacity of these cells since in healthy controls, a higher PD-1 expression correlated with a higher differentiation capacity making these cells self-reactive rather than a dysfunctional state[56]. Therefore, these two properties of T_{SCM} cells, *i.e.*, higher PD-1 expression, and higher cytokine production are evidence of clonal expansion capacity, similar to those of tumor-infiltrating CD8+ T cells. A complete understanding of these cells is warranted in the future and may help in the identification of novel therapeutic targets against these cells which probably applies to other autoimmune diseases as well.

Other autoimmune diseases

There is a scarcity of literature on these cells in other autoimmune diseases such as autoimmune uveitis, immune thrombocytopenia, and juvenile idiopathic arthritis. Autoimmune uveitis is an inflammatory disease that occurs as a result of an autoimmune reaction to self-antigens with foci of ocular lesions. An earlier observation was an increased proportion of CD8+ lymphocytes at the site of inflammation in the retina during the later stage of the disease[57]. Only one study has so far reported a reduced number of CD4+ T_{SCM} cells as compared to healthy controls, however an elevated frequency of CD8+ T_{SCM} cells was observed in the same set of patients[35]. Another observation in these patients was a positive correlation between these T cell subsets. Therefore, T_{SCM} cells could fuel ongoing immune activation and serve as biomarkers of disease severity.

Autoimmune thrombocytopenia (ITP) is characterized by a deficiency of platelets, purpura, and episodes of hemorrhages in which the antiplatelet autoantibodies mediate the destruction of platelets[58]. Evidence suggests that platelets express MHC class I molecules and therefore possess the ability of MHC-dependent antigen processing. These platelets could then be recognized by CD8+ T-cells initiating a series of events culminating in the apoptosis of platelets in ITP[59]. ITP patients have hyper-activated CD8+ T-cells with an increased degranulation and cytotoxic potential[60]. One study investigated the effect of T_{SCM} cells on the pathogenesis of ITP[36]. This study depicted a higher percentage of circulating CD8+ T_{SCM} cells in these patients as compared to healthy controls. These cells play an important role in immune activation and such an aberrant immune response could further upregulate the memory stem cell numbers exacerbating the disease. T_{SCM} cells could also serve as an indicator of treatment efficacy since glucocorticoid treatment significantly decreased their numbers.

APPROACHES TO AUGMENT AND TARGET MEMORY STEM CELLS IN VARIOUS DISEASES

With increased recognition of the role of memory stem cells during infectious as well as autoimmune diseases, various approaches to manipulate these cells have been defined and are summarized in Table 1. Memory stem cells are only scarcely present in the circulation which limits their clinical potential, however, *ex vivo* expansion of these cells is possible. CD8+ T_{SCM} cells are an important part of the cellular immune response against viruses like HIV-1 which maintain their pool through secretion of IL-2. Cytokines like IL-7 and IL-15 could be used to generate and expand CD8+ T_{SCM} cells from the naïve precursor cells. Using a combination of beads coated with CD3/CD2/CD28-specific antibodies or a combination of cytokines such as IL-7 and IL-15, effective expansion could be achieved *in vitro*[2,46]. Good manufacturing protocols have led to their expansion making their utility possible in many immunodeficiency conditions. Recently, an *ex vivo* expansion of these cells has been attempted in a mouse model using urolithin A (UA), a natural metabolite present in pomegranates. The authors have unraveled a novel mechanism in which UA-induced memory stem cell formation through Pink-1 mediated mitophagy through induction of mitochondrial phosphatase Pgam5, that further dephosphorylates β-catenin and drive Wnt signaling in these cells[61].

Blocking the inhibitory receptors on T cells augments the CD8+ T cell immunity and this kind of immunotherapy has already been applied in the field of cancer and holds great promise for infectious diseases as well[62]. It is widely held that the process of exhaustion drives CD8+ T cells into a transcriptionally distinct lineage that comprises "precursor exhausted" and "terminally exhausted" subsets. The precursor-exhausted CD8+ T cells infrequently express inhibitory receptors and more commonly express certain transcription factors, including TCF-1, encoded by T cell factor 7 (*TCF7*), which is the downstream transcription factor of the canonical Wnt signaling pathway[63]. CD8+ T cells expressing high levels of TCF1 (TCF1^{high}) exhibit a stem-cell-like phenotype, which maintained a better proliferative capacity and could further differentiate into both TCF1^{high} and TCF1^{low} CD8+ T cell subsets[64]. Therefore, it could be speculated that certain agonists of Wnt signaling pathways can improve TCF-mediated signaling that may promote the survival of these functional cells and prevent their differentiation into an exhausted phenotype and reinvigorate their effector function. Most of the reported studies have been performed in animal models of chronic viral infections and strategies to augment the expression of TCF-1 have shown promising results in such models. This approach could represent a promising immunotherapeutic strategy against not only chronic HIV-1 infection but also other chronic viral infections by reinvigorating the effector function of exhausted CD8+ T cells.

In the case of tumors and malignancies, the same approach has been applied to impart stemness or stem-cell-like phenotype in chimeric antigen receptor (CAR)-T cells, especially CAR-modified CD8+ T cells that have shown great promise[65,66]. In the case of conventional CAR T cells, a major disadvantage was their lack of persistence owing to the acquisition of exhaustion phenotype and loss of proliferative abilities. With advances in genetic manipulation methods and identification of novel transcription factors, it is now possible to generate clinical grade CAR T cells that carry the stem-cell-like phenotype that is functionally more competent, carry the memory phenotype, and are enriched with genes to promote their sustained proliferation. These modified T_{SCM}-like CAR-T cells have shown initial success in clinical trials in various solid tumors, lymphomas, and other malignancies. At the same time, T_{SCM}-like CAR-T cells are being explored in the area of infections and autoimmune diseases as well[67-69]. In one such first preclinical study, hematopoietic stem/progenitor cells derived T cells bearing a protective CD4 chimeric antigen receptor (CD46CD4CAR) were used to redirect against simian HIV (SHIV) infection in pigtail macaques. Owing to their stem-cell-like phenotype, these infused CAR-T cells were found to persist for over two years, retaining their immunological memory and abilities of multilineage engraftment without any toxic side effects[70]. In a relatively recent study, genetically modified, anti-HIV duo-CAR-T cells comprising predominantly CCR7+ T_{SCM} and central memory T cells expressing a few effector molecules were injected in the spleens of HIV-infected humanized mice. These cells were efficient in killing HIV-infected PBMCs including activated CD4+ T cells, monocytes, and macrophages[71]. Likewise in other viral infections, wherever CAR-T cells are

Table 1 Summary of approaches to target memory stem cells in different disease conditions

No.	Disease	Approach	Target molecules	Ref.
1	HIV-1 infection	*Ex vivo* expansion of CD8+ T_{SCM} cells with IL-7 & IL-15 with CD3/CD28	T cell receptor	[46]
2	Immunodeficiency, tumor	*Ex vivo* expansion of CD8+ T_{SCM} cells with urolithin A	Pink-1 mediated mitophagy. Dephosphorylation of β-catenin through action of Wnt signaling	[61]
3	Tumors and malignancies	Use of T_{SCM}-like CAR-T cells (particularly CAR modified CD8+ T cells)	Various tumor/lymphoma antigens	[65-67, 69]
4	Chronic viral infections	Increased survival of CD8+ T_{SCM} through Wnt agonists	Increased expression of TCF1	[64]
5	HIV-1 infection	Nanoparticles or aptamers targeting latent reservoirs by inducing differentiation of T_{SCM} cells to effector memory subsets	Key molecules of Wnt-β-catenin pathway	[1]
6	HIV-1 infection	Shock and kill strategy to reactivate HIV from CD4+ T_{SCM} cells with LRAs + TLR agonists to activate CD8+ T cells	Killing of activated reservoirs by cytotoxic T cells	[76]
7	HIV-1 infection	Block and Lock strategy by HIV Tat inhibitors	No HIV replication by blocking of HIV promoter	[77]
8	Autoimmune diseases	Nanoparticles or siRNA to suppress T_{SCM} cells	Inhibition of key molecules of NF-κB signaling	[79,80]
9	Autoimmune diseases	Wnt agonists or shRNA or inhibitors such as PRI-724 to disrupt T_{SCM} cells by inducing differentiation to EM cells	TCF7, CBP/β-catenin pathway	[1,81]
10	Autoimmune diseases	Induced differentiation of T_{SCM} cells to short lived EM cells	Molecules of mTOR/AMPK pathway	[1]
11	Type-1 diabetes	Selective inhibition of metabolic machinery of T_{SCM} cells	Decreased glucose metabolism through inhibition of GLUT1	[5]
12	Type-1 diabetes	Antibodies to block CCR7 to target T_{SCM} cells	CCR7	[86]

HIV-1: Human immunodeficiency virus-1; GLUT1: Glucose transporter 1; T_{SCM}: Stem cell-like memory T; CAR: Chimeric antigen receptor; CBP: Cyclic AMP-response element-binding protein-binding protein; LRA: Latency reversal agents; EM cell: Effector memory; TLR: Toll-like receptor.

developed, there are options for inducing stem-cell-like phenotype in these cells to generate long-term protection against the pathogenic viruses.

Researchers discovered a relationship between the size of the CD8+ T_{SCM} compartment and HIV-1 disease progression in a group of chronically infected subjects. The findings indicate that ART restores a normal frequency of CD8+ T_{SCM} and that natural retention of this subset in the context of untreated HIV-1 infection is associated with enhanced viral control and immunity. As a result, the CD8+ T_{SCM} population may be a predictor of protection in chronic HIV-1 infection, which is directly relevant to the development of T cell-based vaccines, adoptive immunotherapy methods, or the pharmacologic induction of T_{SCM} cells[72-75]. As far as the role of CD4+ T_{SCM} cells as latent reservoirs of viral infections are concerned, they need to be destabilized if these pockets are to be reduced. It has been proposed that targeting key molecules of stem cell signaling pathways such as Wnt through antagonists or silencing RNAs could be used to skew the stem cell signaling machinery to induce differentiation to short-lived effector memory T cell subsets[1]. Similarly, nanoparticles or aptamers against the key molecules of the Wnt-β-catenin pathway, a key driver of stemness could also be utilized to target these reservoirs to reverse the latency. Another strategy could be concomitant activation of the immune system and the LRA so that as soon as the HIV-1 gets reactivated from latency, it becomes a target of CTLs. A combinatorial approach has been investigated in which a synergistic interplay between TLR 8-matured dendritic cells and LRAs is successful in reinvigorating the exhausted CD8+ T cell machinery to kill the latently infected cells[76]. Reactivation of latent HIV-1 could be prevented using a block and lock strategy in which compounds prevent the reactivation of latent HIV-1 from the reservoirs. For example, transcriptional expression of HIV-1 transactivator of transcription (Tat) protein can be inhibited using dCA or Tat inhibitors. In the absence of tat protein, transcription from the integrated HIV-1 promoter does not take place and hence HIV-1 does not replicate[77]. More such inhibitors are under development and active research is going on targeting Tat.

Another approach is to induce a state of deep latency in which the proviral HIV-1 is maintained in a dormant state in these reservoirs so that the virus would not rebound even after discontinuation of anti-retroviral therapy[78]. Since many strategies have been evaluated but none have proven completely successful. Intravenous immunoglobulin (IVIG) has been used as an adjuvant therapy to ART. As a result, there was viral blip and HIV-RNA remained undetectable even after several months of ART discontinuation. IVIG treatment activated HIV from the reservoirs, hence a transient increase in plasma viral load also occurred. This encouraging data envisages studies exploring combination therapies of immunomodulatory agents and LRAs in the future.

In the case of autoimmune disorders, anti-inflammatory and immunosuppressive therapies have limited success and are often associated with relapse, which could be attributed mainly to the persistence of immunological memory. The expression of inflammatory molecules by T_{SCM} cells suggests that key inflammatory signaling molecules can be targeted. In this context, NF-κB signaling which is involved in the maintenance and generation of cytokines by T_{SCM} cells offers the

possibility of changing aggressive' TSCM cells into 'limited T$_{SCM}$ cells. While, systemic NF-κB blocking may have negative side effects, targeted strategies including the use of nanoparticles could be beneficial for the selective administration of anti-inflammatory agents such as benzoyl aconitine or siRNA targeting NF-κB signaling in inflammatory lesions[79,80].

Similar to latent viral infections, Wnt antagonists or short hairpin RNA (shRNA) can target the key molecules of their respective signaling pathways. One such molecule is *TCF7* which offers another option in autoimmune diseases to induce the differentiation of long-lived memory stem cells to short-lived subsets to curtail their sustenance[1]. PRI-724, a Wnt/β-catenin pathway inhibitor, has been shown to prevent the connection between cyclic AMP-response element-binding protein-binding protein (CBP) and β-catenin to direct cellular differentiation instead of proliferation[81]. In one such attempt, TCF-1 deletion did not induce differentiation of T$_N$ cells into memory T cells, although effector differentiation was detected and this deletion did not cause any developmental abnormality[82]. These studies imply the need for a better target and timing of intervention in the Wnt signaling pathway while targeting T$_{SCM}$ cells.

Another major pathway, the mTOR/AMPK system regulates T$_{SCM}$ cell stress and survival by balancing glycolysis and mitochondrial metabolism. Reduced mTORC1 activity and increased AMPK activity promote the formation of memory T cells, which rely on mitochondrial metabolism and fatty acid oxidation (FAO)[83,84]. Earlier studies have demonstrated that TRAF6-deficient CD8+ T cells have altered the expression of genes that regulate fatty acid metabolism. In response to growth factor withdrawal, activated CD8+ T cells lacking TRAF6 exhibit impaired AMPK activation and mitochondrial fatty acid oxidation (FAO)[83]. The AMPK pathway thus offers another possibility to target T$_{SCM}$ cells.

Another opportunity to target T$_{SCM}$ cells is selective inhibition or manipulation of metabolic machinery. It has been found that T1D patients have β-cell-specific CD8+ T$_{SCM}$ cells with elevated expression of GLUT1. *In vivo*, IL-7 is necessary for the maintenance of self-reactive CD8+ T$_{SCM}$ cells. IL-7 increases glucose absorption by overexpressing GLUT1 and the glycolytic enzyme hexokinase 2. In one such attempt, WZB117, a GLUT-1 specific inhibitor, effectively inhibited T$_{SCM}$ cells in T1D patients by decreasing glucose metabolism[45]. Even though metabolism is dependent on glucose absorption, pyruvate oxidation in the mitochondria is required for the formation of T$_{SCM}$ cells from naive precursors. The mitochondrial pyruvate transporter inhibitor UK5099 has been utilized for metabolic manipulation in cancer cells, however, metabolic manipulation of T$_{SCM}$ cells using similar agents could be explored in the future[85].

The chemokine receptor CCR7 and its ligands CCL19 and CCL21 direct T-cell homing and recruitment in lymphoid organs. T$_{SCM}$ cells express high levels of CCR7 which can be targeted using anti-CCR7 antibodies and potential antagonists in localized sites of inflammation or autoimmunity. Treatment of humanized CCR7 mice with anti-human CCR7 monoclonal antibodies, 8H3-16A12, resulted in near-total inhibition of the development of collagen-induced arthritis[86].

Taken together, there are numerous approaches available to target, augment or manipulate T$_{SCM}$ cells under various pathological conditions and many such approaches are being tested in clinical trials.

CONCLUSION

Memory stem cells (T$_{SCM}$ cells) contribute to the latency of viruses on one hand and autoimmunity on the other hand. During chronic viral infections like HIV-1 or HCV, these cells, particularly CD4+ T$_{SCM}$ cells serve as reservoirs where viruses remain in a dormant state inaccessible to any pharmaceutical agent. However, with discontinuation of therapy, the virus rebounds from these pockets and there is an outburst of viremia that overwhelms the limits of our immune system. With the recent development of strategies like shock and kill, block and lock, and deep latency, it is possible to either restrict the virus in these pockets for a long time or activate the virus using LRAs and making them susceptible to cytotoxic T cell (CTL) armory. However, CTLs including T$_{SCM}$ cells are not entirely functional in immunodeficient conditions because of immune exhaustion. Strategies to boost these cells after the blockade of inhibitory receptors or reinvigoration of CTL functions have been experimentally successful. More recently, in acute viral infections such as COVID-19, these cells have been proposed to exacerbate the inflammatory conditions because of increased activation of signaling pathways that increase the proinflammatory cytokines. Therefore, depending on the type of viral infection and the state of immune cells, different strategies could be employed to either restrain or augment these cells.

Autoimmune diseases that result from the loss of tolerance to self-antigens are also influenced by T$_{SCM}$ cells, however, the molecular programs that result in the persistence of these cells are still incompletely elucidated. Experience from the field of cancer stem cells has unraveled strategies to manipulate the metabolic machinery of T$_{SCM}$ cells during autoimmunity to restrict the proliferation of these cells or skew their differentiation to short-lived subsets. More detailed understanding in the context of genetic or epigenetic evaluation in this regard is warranted in the future. The stem-like autoimmune progenitor T cells can continuously seed the niches with self-proliferating memory stem cells, therefore, strategies that target the progenitors could emerge as novel therapeutic approaches in the future.

FOOTNOTES

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