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REVIEW
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Immunotherapeutic Potential of T Memory Stem Cells

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Memory T cells include T memory stem cells (T_{SCM}) and central memory T cells (T_{CM}). Compared with effector memory T cells (T_{EM}) and effector T cells (T_{EFF}), they have better durability and anti-tumor immunity. Recent studies have shown that although T_{SCM} has excellent self-renewal ability and versatility, if it is often exposed to antigens and inflammatory signals, T_{SCM} will behave as a variety of inhibitory receptors such as PD-1, TIM-3 and LAG-3 expression, and metabolic changes from oxidative phosphorylation to glycolysis. These changes can lead to the exhaustion of T cells. Cumulative evidence in animal experiments shows that it is the least differentiated cell in the memory T lymphocyte system and is a central participant in many physiological and pathological processes in humans. It has a good clinical application prospect, so it is more and more important to study the factors affecting the formation of T_{SCM}. This article summarizes and prospects the phenotypic and functional characteristics of T_{SCM}, the regulation mechanism of formation, and its application in treatment of clinical diseases.

Keywords: T memory stem cells, stemness, tumor immunotherapy, HIV, autoimmune diseases

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INTRODUCTION

Immunotherapy has become one of the most promising strategies in cancer treatment, and has shown good efficacy in clinical trials (1). In particular, chimeric antigen receptor-engineered T cells (CAR-T) can specifically and effectively kill tumor cells, bringing new hopes for the treatment of patients with malignant tumors (2–7). However, whether it is traditional immune cell therapy or new CAR-T cells and T-cell receptor T cells (TCR-T) therapy, all are based on terminally differentiated effector T (T_{TE}) cells, making it difficult to exert long-lasting anti-tumor effects in the body (8). Adoptive T cell therapy (ACT) is the *in vitro* expansion and reinfusion of tumor-reactive T cells, and is a potential treatment method for the treatment of advanced cancer (9–14). In infections and cancers, T lymphocytes expand and differentiate into effector cells and memory cells that clear pathogens. These cells can survive for a long time and ensure that they have a protective effect against pathogens when they are re-attacked by antigens (15). Human T lymphocytes are generally divided into naive T cell (T_N), central memory T cell (T_{CM}), effector memory T cell (T_{EM}) and effector T cell (T_{EFF}). In 2005, in the study of graft *versus* host disease (GVHD) in mice, a group of special memory T cell subsets with super proliferation and differentiation ability was observed for the first time. It produces persistent graft-*versus*-host disease, which the researchers named "stem like memory T cells" (T_{SCM}) (16). Studies have shown that adoptively infused young T cells can

self-renew and differentiate in mice, having the ability to survive for a long time, and exhibit significantly better anti-tumor capabilities than T_{TE} cells. The progressive differentiation of T lymphocytes leads to a gradual loss of function and therapeutic potential. These studies suggest that poorly differentiated immune cells may have more application potential in clinical treatment (17–21).

T_{SCM} cells have great potential in overcoming the limitations of current T cell-based immunotherapy (22–24). In mouse tumor models and human hematopoietic stem cell transplantation (HSCT) patients, T_{SCM} cells have higher antitumor activity and survival rate. However, the proportion of T_{SCM} cells in peripheral blood is low, which limits its application in immunotherapy. In this review, we summarize the latest findings, and discuss in depth the phenotype, function, differentiation mechanism and clinical application of memory T cells. It is hoped that using the therapeutic potential of T_{SCM} cells for adoptive immunotherapy provides new ideas. The conceptual work and key discoveries that formed this field of investigation are shown in **Figure 1** (25–38), which mainly summarizes the main discoveries in the process of T_{SCM} cell research in recent years and the new research on the occurrence and development of diseases, some of which are introduced in articles.

PHENOTYPIC AND FUNCTIONAL CHARACTERISTICS OF MEMORY T CELLS

T_{SCM} is a T cell subset with self-renewal ability and pluripotency potential. This group of memory T cells can play the role of acquired immune function in the process of the body's fight against viruses or tumors (36, 39). T cell populations are classified by some surface markers, and distinguished according to their functions and sources, and the production of their effector cytokines. Memory T cells can be divided into T_{CM} and T_{EM}. T_{EM} cells and T_{CM} cells circulate in the blood and target the secondary lymphoid tissues. The degree of differentiation of T_{CM} cells is lower than that of T_{EM} and effector cells, and its telomeres are found to be longer, and the expression of perforin, granzyme and other effector molecules is lower (40). In addition, the T_{SCM} pool should be limited to lymph nodes and secondary lymphoid organs, which are T cells that have antigen experience. The current research results also show that T_{CM} has the function of T memory stem cells. T_{CM} has stronger immune replacement ability and stronger survival ability *in vivo* than T_{EM} cells. T_{SCM} is developed from naive T cells in a resting state. It is a group of cells between T_N and T_{CM}. It also has the characteristics of T_N cells and memory T cells (T_M), and then differentiates into T_{CM} and T_{EM}. Good et al. (41) used single-cell mass cytometry to track the proliferation history of T cells. By analyzing the changes in phenotype and protein expression of T cells at different times and in different division states, it assisted in confirming the T cell differentiation theory: $T_N \rightarrow T_{SCM} \rightarrow T_{CM} \rightarrow T_{EM}$. It is worth noting that only naive T cells and T_{SCM} cells can reconstruct the heterogeneity of the entire memory T cell subset. At present, malignant tumors are one of the important diseases threatening human health, and there is no effective method to treat them. Due to their own characteristics, T_{SCM} cells have shown their strong potential for tumor therapy.

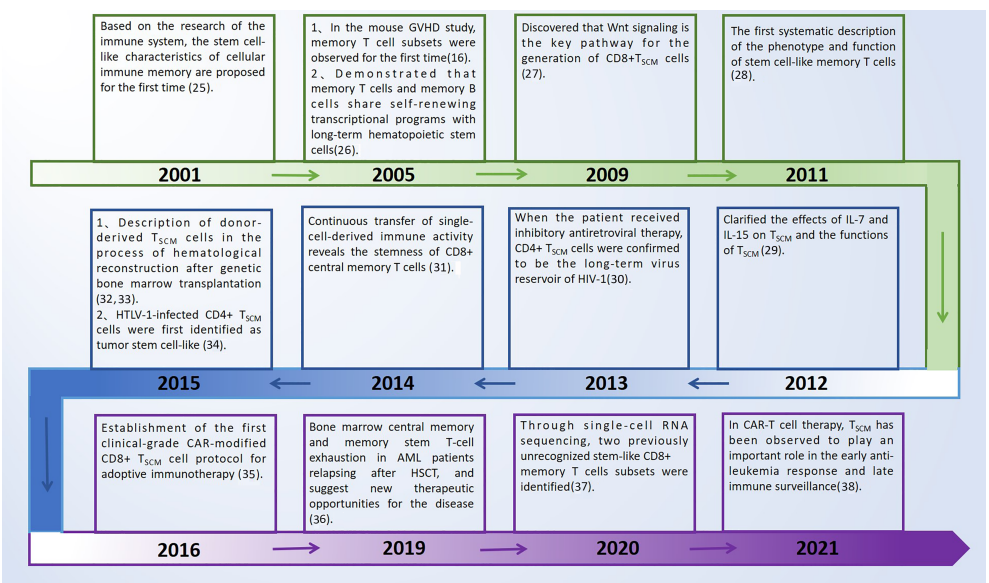

FIGURE 1 | Key discoveries on T_{SCM} cells. GVHD, graft *versus* host disease; T_{SCM} cells, T memory stem cells; HTLV-1, human T cell lymphotropic virus type 1; HIV-1, human immunodeficiency virus type 1; CAR-T, chimeric antigen receptor-engineered T cells; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation.

According to the different expressions of cell surface chemokine receptor (CCR7) and lymph node homing molecules (CD62L), memory T cells are divided into T_{CM} and T_{EM}. T_{CM} highly expresses CCR7 and CD62L, homing to secondary lymphoid organs, but low expression in T_{EM}, which preferentially transports to peripheral tissues and mediates rapid effector functions. T_{SCM} cells express naive cell phenotypes (CD45RA, CD62L, CCR7, CD95, CD27, CD122), and are characterized by rapid response to antigens, expression of a variety of effector molecules, and generation of memory effector cells. $CD45RA^+$ is closely related to its memory ability. Naive cells express two molecules CD27 and CD45RA at the same time. Memory and effector cells only express CD27 or CD45RA respectively. T_{SCM} cells highly express IL-2, IFN-γ, TNF-α, Bcl- 2. IL-7 and other molecules related to early differentiation of T cells, low expression of CD57 and other molecules related to T cell senescence, showing stronger degranulation ability and the ability to produce inflammatory cytokines. Recent studies have found that by detecting the expression of CD122 or CXCR3 in healthy people by flow cytometry, the T_{SCM} $CD122^{hi}$-expressing subset demonstrate greater proliferation, greater multipotency and enhanced polyfunctionality with higher frequencies of triple positive (TNF-α, IL-2, IFN-γ) cytokine-producing cells upon exposure to recall antigen. The cell proliferation and multifunctional cytokine production of the T_{SCM} $CXCR3^{lo}$ population are also significantly increased (42). Loss of CXCR3 promotes stem-like memory precursor differentiation (43). According to these surface markers, T_{SCM} cells can be accurately distinguished. T_{SCM} cells represent a subset of minimally differentiated T cells, which are characterized by phenotypic and functional characteristics that connect naive and conventional memory cells.

The above mainly describes the surface markers of human T cell subsets. In addition to the specific T cell receptor (TCR), both human and murine T_{SCM} express common markers of memory T cells (mouse CD62L, human CCR7, human CD45RO), and anti-apoptotic marker molecules (Bcl- 2), the cytokine receptor markers related to survival and proliferation CD122 (co-receptor of IL-2, IL-7 and IL-15) and CD127 (IL-7 receptor), stem cell marker (Sca-1). Human and murine T cell subsets are defined by different phenotypes (16, 27) (**Table 1**).

DEVELOPMENT OF T_{SCM} CELLS

Manipulation to Produce T_{SCM} Cells in *(Ex) Vivo*

The relative scarcity of circulating T_{SCM} cells limits their use in tumor therapy, which has led to manufacturing protocols that expand this cell type *in vitro*. As an important participant in the function of T cells, cytokines play an important role in the maintenance and expansion of T_{SCM} subset. Recently reported related cytokines that can promote T_{SCM} expansion are shown in **Figure 2**. A large number of studies have shown that adding different cytokines to the immune cell culture system can make it differentiate into memory or effector T cells (44–47). γc-cytokine IL-2, as a T cell growth factor, is still the most common cytokine used to expand therapeutic T cell products for patients (29, 48–50). γc-cytokine IL-2, as a T cell growth factor, is still the most common cytokine used to expand therapeutic T cell products for patients. However, high IL-2 levels reduced the overall production of early memory T cells by reducing central memory T cells and augmenting effectors. The number of early memory T cells in the T cell subset could be increased by simply reducing the amount of IL-2 (51). In the *in vitro* expansion process, repeated use of IL-2 to stimulate T cells would also cause T cell depletion and reduced T cell persistence (52). IL-7 could also promote the proliferation of T_{SCM} cells by down-regulating the expression of programmed cell death protein 1 (PD-1) and Foxp3, and promoted the ability of $CD4^+$ T cells to produce IFN-γ, IL-2, TNF-α and granzyme B. The involvement of STAT5 in IL-7-induced polyfunctionality, this the polyfunctional phenotype driven by IL-7 is associated with increased histone acetylation effector gene promoters and reveals previously unknown characteristics of IL-7 (53–56). The current study, CAR-T cells expanded in IL-15 (CAR-T/IL-15) preserved a less-differentiated T_{SCM} phenotype, defined by expression of $CD62L^+CD45RA^+CCR7^+$, as compared to cells cultured in IL-2 (CAR-T/IL-2). What's more, CAR-T/IL-15 cells exhibited reduced expression of exhaustion markers, higher anti-apoptotic properties, and increased proliferative capacity when it was attacked by antigens (57). The combined use of IL-7 and IL-15 can preserve the T_{SCM} phenotype and enhance the effectiveness of CAR-T cells (11, 29, 58–61). IL-21 was critical for the long-term maintenance and functionality of

TABLE 1 | Phenotypic markers of memory T cells.

Subset	Phenotype (Human)	Phenotype (Mice)	Characteristics
T_N	$CD45RA^+$,$CD45RO^-$,$CCR7^+$,$CD62L^+$,$CD127^+$,$CD122^+$,$CD27^+$,$CD44^-$,$CD28^+$,$CD43^-$,$CD95^-$, $CD57^-$,$CD58^-$,$CD11\alpha^-$,$(IL\text{-}7R\alpha)^+$,$CXCR3^-$,$(IL\text{-}2R\beta)^-$	$CD44^-$, $CD62L^+$, $CCR7^+$, $CXCR5^-$, $CXCR3^-$	Multidirectional differentiation ability
T_{SCM}	$CD45RA^+$,$CD45RO^-$,$CCR7^+$,$CD62L^+$,$CD127^+$,$CD122^+$,$CD27^+$,$CD44^{+/-}$,$CD28^+$, $CD43^-$, $CD95^+$,$CD57^-$,$CD58^+$,$CD11\alpha^+$,$(IL\text{-}7R\alpha)^+$,$CXCR3^+$,$(IL\text{-}2R\beta)^+$	$CD44^-$, $CD62L^-$,$(Sca\text{-}1)^+$,$CD122^+$, $(Bcl\text{-}2)^+$,$CCR5^+$,$CXCR3^+$	Self-renewal capacity and multipotency
T_{CM}	$CD45RA^-$,$CD45RO^+$,$CCR7^+$,$CD62L^+$,$CD127^+$,$CD122^+$,$CD27^+$,$CD44^+$,$CD28^+$, $CD43^-$,$CD95^+$, $CD57^-$,$CD58^+$,$CD11\alpha^+$,$(IL\text{-}7R\alpha)^+$,$CXCR3^+$,$(IL\text{-}2R\beta)^+$	$CD44^+$, $CD62L^+$, $CCR7^+$	Long-lasting immune memory
T_{EM}	$CD45RA^-$,$CD45RO^+$,$CCR7^-$,$CD62L^-$,$CD127^+$,$CD122^+$,$CD27^{+/-}$,$CD44^+$,$CD28^{+/-}$,$CD43^{+/-}$, $CD95^+$,$CD57^{+/-}$,$CD58^+$,$CD11\alpha^+$,$(IL\text{-}7R\alpha)^{+/-}$, $CXCR3^+$,$(IL\text{-}2R\beta)^+$	$CD44^+$, $CD62L^-$, $CCR7^-$	Immediate effector function
T_{TE}	$CD45RA^-$,$CD45RO^-$,$CCR7^-$,$CD62L^-$,$CD127^+$,$CD122^-$,$CD27^-$,$CD44^-$,$CD28^-$,$CD43^+$,$CD95^+$, $CD57^+$,$CD58^+$,$CD11\alpha^+$,$(IL\text{-}7R\alpha)^-$,$CXCR3^-$,$(IL\text{-}2R\beta)^+$	$CD44^-$, $CD62L^+$	Terminally differentiated effector T cells

"+" positive expression; "–" negative expression; T_N, naive T cell; T_{SCM}, stem cell memory T cell; T_{CM}, central memory T cell; T_{EM}, effector memory T cell; T_{TE}, terminal effector T cell.

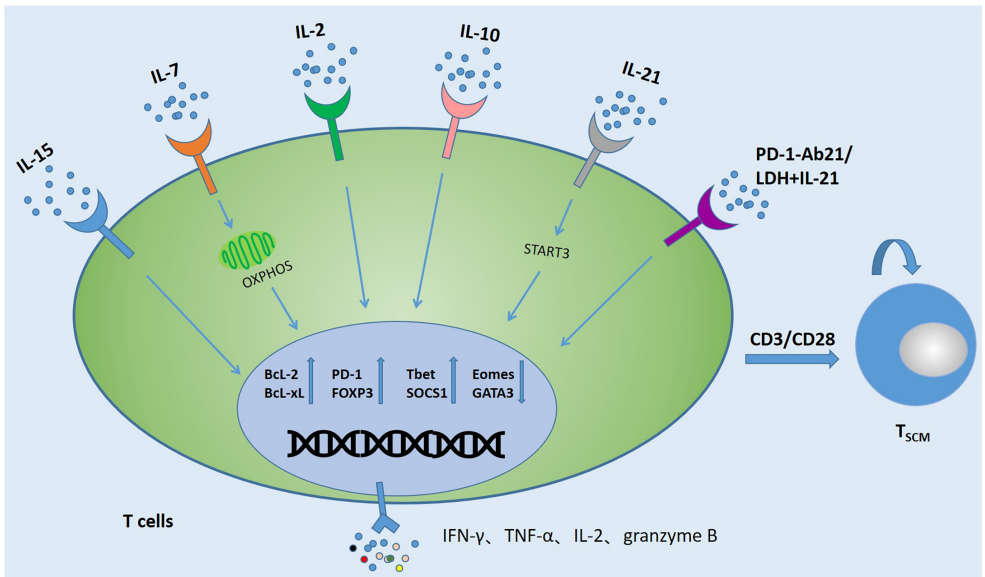

FIGURE 2 | Several strategies to induce the generation of T_{SCM}. Activating T cells (CAR-T cells, TCR-T cells, TILs, VSTs) with anti-CD3/CD28 antibodies and co-cultivating them with cytokines or combined with PD-1 and LDH can promote the production of T_{SCM} cells and change the expression levels of related anti-apoptotic proteins and metabolic molecules. In addition, the expression of TNF-α, IFN-γ, IL-2 and Granzyme B also increased significantly.

$CD8^+$T cells and the control of chronic lymphocytic choriomeningitis virus (LCWV) infection in mice. In the process of chronic infection, cell-autonomous IL-21 receptor (IL-21R)–dependent signaling by $CD8^+$ T cells was required for sustained cell proliferation and cytokine production (62, 63). IL-21 also can promote the generation of T_{SCM} cells. It activates the Janus kinase signal transducer and activator of transcription 3 pathway by upregulating signal transducer and activator of transcription 3 phosphorylation and thereby promoting the expression of T-bet and suppressor of cytokine signaling 1, while decreasing the expression of eomesodermin (Eomes) and GATA binding protein 3 (64). In the absence of IL-10, IL-21 or STAT3, virus-specific $CD8^+$ T cells (VSTs) maintain the terminal effect (T_E) differentiation state and couldn't mature into self-renewing T_{CM} cells. The maturation of protective memory T cells and memory $CD8^+$ T cell precursors was an active process that depended on the IL-10-IL-21-STAT3 signal (64, 65). Whether the formation of T_{SCM} depends on this pathway still needs further research, but it provides new ideas for subsequent research. Lactate dehydrogenase (LDH) inhibition combined with IL-21 could increase the formation of T_{SCM} cells, thereby producing more profound antitumor responses and prolonging the survival time of the host (66). In addition, a new study found that by fusion of IL-21 to anti-PD-1 antibody, IL-21 can target tumor-reactive T cells to promote T_{SCM} production. PD-1Ab21 therapy has shown greater antitumor effects in established tumor-bearing mice (67). At present, a large number of experiments have confirmed that these cytokines can promote the production of T_{SCM} and have potential antitumor effects. However, the mechanism of using cytokines, drugs and checkpoint blockade to promote the differentiation of memory T cells remains to be studied.

Oxidative Metabolic Pathway of T_{SCM} Cells

The naive T cells in the circulation are quiescent and have low metabolic requirements. They mainly use oxidative phosphorylation (OXPHOS) to produce ATP (53, 68). Generally speaking, differentiated T cells use glycolysis to proliferate, while memory T cells tend to use fatty acid oxidation (FAO)-dependent oxidative phosphorylation (OXPHOS) to produce ATP, which helps to perform long-lasting antitumor response in the tumor microenvironment (69–74). In the tumor microenvironment, tumor cells inhibit the metabolic reprogramming of T cells by competitively using glycolysis, so that the formation of memory T cells is inhibited (75, 76). It is reported that important transcription factors and cytokines, as well as MEKi and other inhibitors in the process of T cell differentiation, induce the generation of T_{SCM} by regulating T cell-related metabolic enzymes (77–79) (**Figure 3**).

Signals from TCR, costimulatory molecules, and growth factors lead to the activation of signaling pathways that promote transcriptional programs that are critical to effector function (80–82). In memory T cells, cellular stress, such as growth factor deprivation or a low ratio of ATP/AMP, will activate AMP-activated protein kinase (AMPK) and inhibit mTOR signaling (83). IL-15 also showed a similar function (57, 83).

Good et al. (41, 84) have proved through a large number of experiments that blocking the mTOR pathway by adding inhibitors can allow T cells to differentiate towards T_{SCM}-like cells, such as ITK

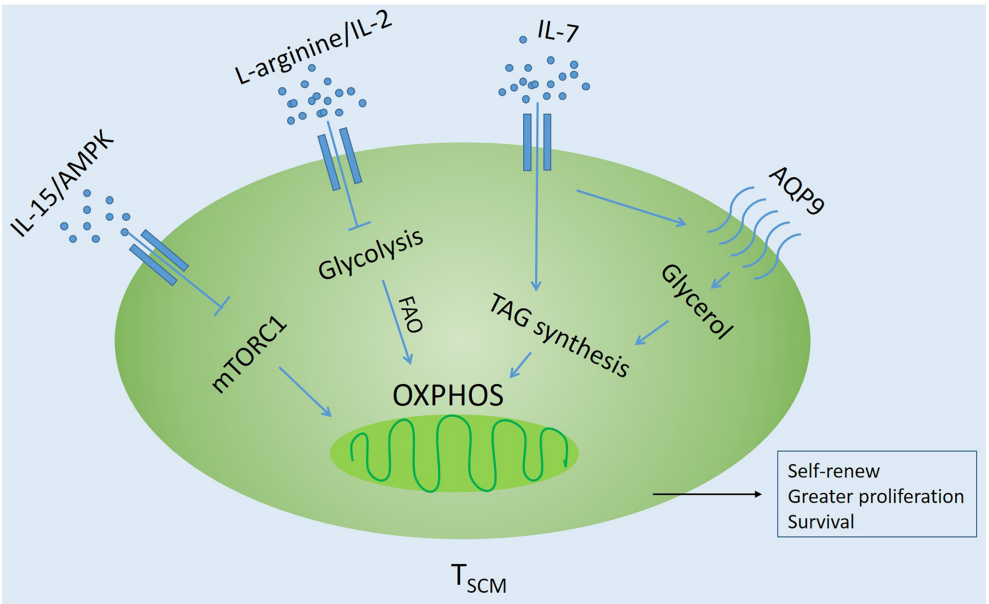

FIGURE 3 | Influencing factors regulating oxidative metabolism of T_{SCM} Cells. Inhibit glycolysis through different pathways and promote fatty acid oxidation (FAO)-dependent oxidative phosphorylation (OXPHOS). AQP9, Glycerol channel aquaporin 9; AMPK, AMP-activated protein kinase; TAG, triglyceride; mTORC1, Rapamycin Complex 1.

(IL-2-inducible T-cell kinase), TWS119 and BTK (Bruton's tyrosine kinase) inhibitors. In addition, the glycolytic function of T_{SCM} cells is reduced, and different inhibitors promote the *in vitro* generation of T_{SCM}-like cells with unique metabolic characteristics and retained polyfunctionality. It is worth noting that the drug-induced T_{SCM} cells have superior functional characteristics and self-renewing capacity after adoptive transfer. The research compound Akt inhibitor VIII inhibits AKT *in vitro*, which can preserve the differentiation and function of minor histocompatibility antigen (MIHA)-specific $CD8^+$ T cells. Moreover, transcriptome profiling revealed that AKT-inhibited $CD8^+$T cells clustered closely to naturally occurring stem cell-memory $CD8^+$ T cells. Moreover, AKT-inhibited MiHA-specific $CD8^+$ T cells showed increased polyfunctionality with co-secretion of IFN-γ and IL-2 upon antigen recall (79). Glycerol channel aquaporin 9 (AQP9) deficiency could impair the entry of glycerol into memory $CD8^+$ T cells for fatty acid esterification and triglyceride (TAG) synthesis and storage. While IL-7 could induce expression of the AQP9 in virus-specific memory $CD8^+$ T cells, but not naive cells. AQP9 is essential for their long-term survival. TAG synthase could restore the survival of lipid storage and memory T cells through ectopic expression, and it was found that TAG synthase is the central component of IL-7-mediated survival of human and mouse memory $CD8^+$ T cells (75). Three transcription factors, BAZ1B, PSIP1 and TSN, could regulate the level of L-arginine and promoted the survival of T cells. Activated T cells transform from glycolysis to oxidative phosphorylation, which promotes the production of T_{SCM} with higher survival ability and has antitumor activity in mouse models (85). Recent new studies have found that T_{SCM} induced by Meki/2 inhibition (Meki) has a natural phenotype, self-renewal ability, and enhanced pluripotency and proliferation. It is also achieved by regulating metabolism without affecting T cell receptor-mediated activation. DNA methylation analysis showed that Meki-induced T_{SCM} cells exhibited plasticity and loci-specific profiles, similar to those of T_{SCM} truly isolated from healthy donors, and had similar characteristics to naive and T_{CM} cells. Meki treatment of tumor-bearing mice also showed strong immune-mediated antitumor effects (86). These studies indicate that the regulation of glycolysis and metabolism is the key factor in inducing the formation of T_{SCM}. Therefore, targeted metabolic checkpoints can make T cells differentiate into memory and provide more young T cells for immunotherapy (74, 81, 82, 86).

The Molecules of Exhausted T Cells

T cell exhaustion is a phenomenon widely observed in humans. T_{SCM} or CAR-modified T_{SCM} expresses high levels of PD-1, TIM-3 or CTLA-4 after infiltrating the tumor, indicating that they have become exhausted T cells. Mostly due to T cell exhaustion and dysfunction by continuous TCR and cytokine stimulation. In addition, the effect of immune checkpoint inhibitors is very dependent on endogenous T cell function. However, they cannot reverse the exhaustion of T cells in cells that have undergone epigenetic changes. Therefore, this limits the long-term efficacy and wide application of cancer immunotherapy. Therefore, an in-depth understanding of the mechanism of T cell exhaustion is necessary for the study of T_{SCM} and its better clinical application. The term " exhausted T cells" was originally derived from a mouse model of LCMV. It is

now widely used to define the dysfunction state of T cells under chronic infection or tumor-induced long-term high antigen load stimulation (87). Enhanced and sustained T cell receptor stimulation is a key driver of T cell exhaustion. In recent years, the definition and identification of exhausted T cells have been divided from phenotype to transcriptional and epigenetic levels (88–90). Exhausted T cells are characterized by increased expression levels of inhibitory receptors such as PD-1, LAG3, 2B4, TIM-3 and CD28, and the gradual loss of effector functions, including impaired ability to secrete IFN-γ and tumor necrosis factor (91–95). PD-1 is mainly expressed on the surface of activated T cells and can inhibit T cell activation and proliferation. It is an important immunosuppressive molecule that plays an important role in suppressing immune responses and promoting self-tolerance (96–98). Programmed cell death ligand 1 (PD-L1) is a transmembrane protein, which is mainly expressed on the surface of antigen-presenting cells (APCs) such as dendritic cells (DCs), and can also be expressed on the surface of cancer cells and tumor infiltrating lymphocytes (TIL) (99–102). TOX is a nuclear DNA binding protein. TOX plays an important role in the development of thymus $CD4^+$ T cells, NK cells and intrinsic lymphocytes, and is critical in the differentiation of tumor-specific T cells. Recent studies have described the important role of TOX in the differentiation of exhaustive $CD8^+$ T cells and its molecular mechanism. It is unanimously found that the high expression of TOX is related to the high expression of a variety of inhibitory receptors (PD-1, TIM-3, TIGIT, CTLA-4, etc.) and the low expression of TCF1 (103). So inhibiting TOX expression may hinder the exhaustion of T cells (104–109). Many laboratories have identified a kind of exhausted T cell precursors (TPEX), which highly express molecules related to memory T cells, such as TCF1. TCF1 is a transcription factor and histone deacetylase (HDAC), which is related to the formation of T cell memory. Through single-cell RNA sequencing (scRNA-seq) and lineage tracing, the $TCF1^+Ly108^+PD\text{-}1^+CD8^+$ T cell population was identified. It was found that PD-1 stabilized the $TCF1^+$TeX precursor cell pool and confirmed that PD-1 was this early stage protector of the TCF1 population (91, 110). Exhaustion first appeared in $TCF1^+$ precursor T cells and then spread to the antigen-specific T cell pool. These findings will be important in the future to further investigate the developmental relationships in the later stages of exhaustion (111, 112).

At present, the specific mechanism of T cell exhaustion has not been fully elucidated. T cell exhaustion may be a parallel process with T cell differentiation. T cells at any stage of differentiation can be induced into exhausted T cells, which involves changes in different phenotypes and molecules. Excessive stimulation of precursor cells may be the origin of T cell failure. Under chronic infection or long-term tumor antigen stimulation, memory T cells and exhausted T cell precursors show different differentiation characteristics. Whether there is a link between the differentiation between these two subgroups should be a priority research area in the future. The possible potential developmental trajectories of exhausted T cells are shown in **Figure 4**.

At present, drugs for T cell exhaustion are still in the laboratory research or clinical trial stage. By reducing T cell exhaustion to promote the self-renewal ability and polyfunctionality of T_{SCM} cells (**Table 2**). Therefore, we do not know how to regulate the exhaustion process of T cells and reverse the exhausted state. Is it feasible to reach a certain effector state, and will there be side effects? Whether T_{SCM} can be designed to be exhaustion resistant? In general, the molecular mechanism of T_{SCM} cell formation is very complicated, and we describe them as clearly as possible in the review. More and more evidence supports the therapeutic potential of targeting exhausted T cells (115–118). We have already begun to understand the molecular mechanism of T cell exhaustion and early memory formation. Transforming exhausted T cells into rejuvenated T_{SCM} cells is the goal of our research.

CLINICAL APPLICATION

The Antitumor Effect of T_{SCM}

T_{SCM} cells are the least differentiated cells located at the top of the memory T lymphocyte hierarchy system. Compared with other T cells, they have stronger self-renewal ability and anti-tumor ability (84, 119, 120). As early as in previous studies, it has been found that T_{SCM} is considered a key determinant of immune memory and is involved in diversification of immune memory after allogeneic HSCT (32, 33). Play an important role in adult T-cell leukemia (34). With the FDA approval of CAR-T cell therapy for hematological malignancies, ACT has become a hot spot of continuous attention (63, 121–128). The clinical application of T_{SCM} cells is hindered because they are relatively rare in the circulation. According to reports, the CAR-T cell-modified T_{SCM} was cocultured with IL-2, IL-7 or IL-15 and then injected intravenously into tumor-bearing mice. It was found that the CAR-T/IL-15 group have the best anti-tumor effect (57). Guan et al. (129) prepared allogeneic antigen-specific $CD8^+$ T_{SCM}. It showed a proliferation history and rapidly differentiated into effector cells upon the E007 [the EB virus (EBV) transformed B lymphoblastoid cell lines (LCLs)] re-stimulation. Importantly, the prepared T_{SCM} cells could survive for a long time and reconstituted other T cell subsets *in vivo*, and could effectively eliminate E007 cells after being transferred to LCL burden mice. KUN et al. (120) presented a novel tumor therapeutic modality of the cryo-thermal therapy. After 90 days of cryo-thermal therapy, it can enhance the cytolytic function of $CD8^+$ T cells, induce $CD8^+$ T cells to differentiate into T_{SCM}, and $CD4^+$ T cells to differentiate into dominant $CD4^-$ CTL, Th1 and TFH subets. Cryo-thermal therapy not only inhibits lung metastasis, but also promotes the regression of implanted melanoma and prolongs survival time (35, 130, 131). It was found that after antigen chimeric modification of T_{SCM}, CD19-specific CAR T cell adoptive transfer has a significant antitumor effect on leukemia and lymphoma, and the therapeutic potential seems to be related to persistence *in vivo* (128, 129, 132, 133).

In SIP (an ex-vivo culture system modeled after the temporal changes of essential cytokines in an acute infection), TIL in the

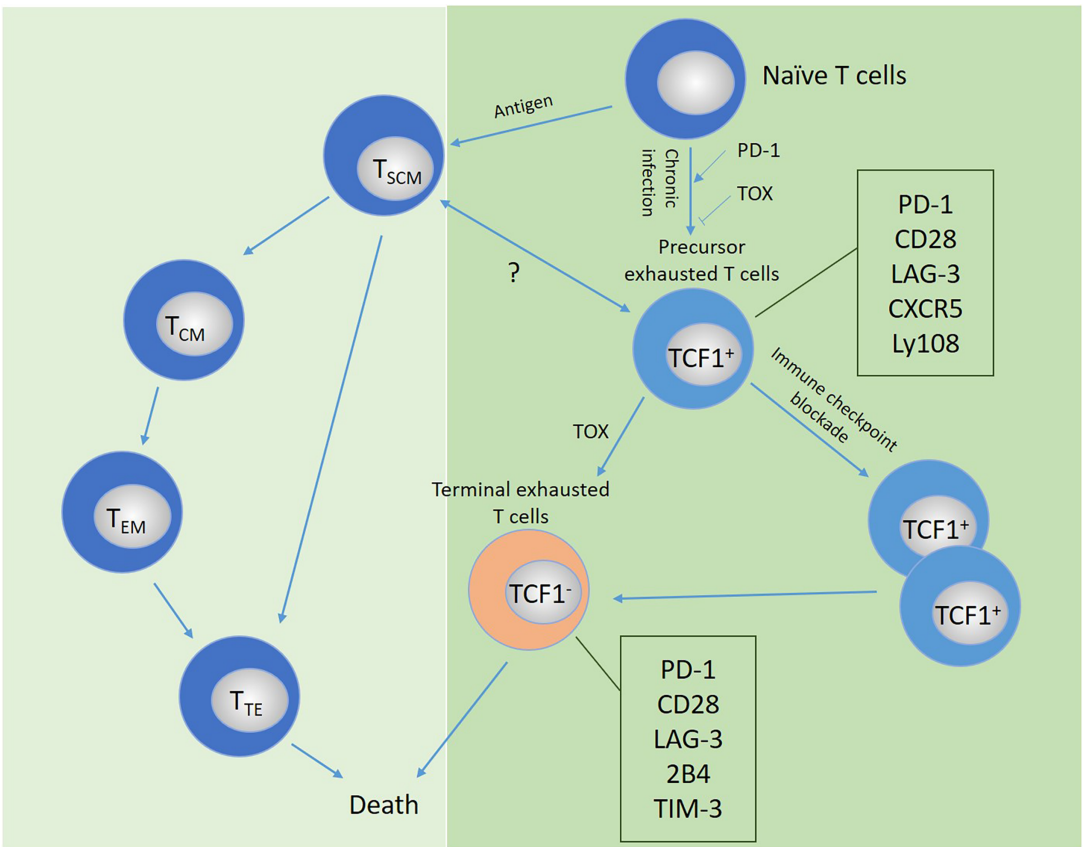

FIGURE 4 | Possible developmental trajectory of exhausted T cells and the comparison and relationship with memory or effector T cells. Under continuous antigen stimulation, T cells transform from precursor exhausted cells into terminally exhausted T cell populations, which mainly depends on the expression of the transcription factor TCF-1, accompanied by the high expression of a variety of inhibitory receptors. The relationship between the differentiation of T cell subsets and exhausted T cells remains to be explored. PD-1, PD ligand 1; TCF1, T cell factor-1; TIM-3, T-cell immunoglobulin domain and mucin domain protein 3; LAG-3, lymphocyte activation gene 3; TOX, thymocyte selection-associated high-motility group (HMG) box protein.

TABLE 2 | Key discoveries in the formation of induced culture T_{SCM}.

Year	Authors	Discovery
2013	Nicoletta Cieri et al.	IL-7 and IL-15 instructed the generation of human memory stem T cells from naïve precursors (29).
2016	Lenka V. Hurton et al.	IL-15 could maintain the long-term persistence of CAR-T modified T_{SCM} (48, 57).
2016	Godehard Scholz et al.	Promote the generation of T_{SCM} by inhibiting the mTORC1 pathway (39, 84).
2016	Alvarez-Fernandez, C et al.	IL-21, IL-7 and IL-15 could effectively promote the generation of T_{SCM} under short anti-CD3/CD28 costimulation (113).
2017	T aisuke Kondo et al.	Coculture of activated T cells and stromal cells expressing Notch ligand could produce T_{SCM} cells with low expression of inhibitory receptors (89).
2017	TANJA KAARTINEN et al.	Simply reducing the amount of IL-2 could promote the generation of T_{SCM} (51).
2018	Charlotte M. Mousset et al.	AKT inhibitors promoted the *in vitro* generation of T_{SCM}-like $CD8^+$ T cells with a unique metabolic profile and retained polyfunctionality (79).
2018	Taisuke Kondo et al.	The coculture of activated T cells with IL-7, IL-15 and op9-hdll1 cells could effectively generate T_{SCM} cells (58).
2018	Yingshi Chen et al.	IL-21 promoted the generation of T_{SCM} cells more effectively than other common γ-chain cytokines (64).
2020	Taisuke Kondo et al.	The Notch-foxm1 axis played a key role in the metabolism of CAR-T modified T_{SCM} (74).
2020	Dalton Hermans et al.	LDH inhibition combined with IL-21 increase the formation of T_{SCM} cells (66).
2020	Pilipow, K et al.	Promote the formation of T_{SCM} by adding antioxidants (114).
2021	Ying Li et al.	IL-21 fusion anti-PD-1 antibody promoted the generation of T_{SCM} (67).
2021	Vivek Verma et al.	Meki was confirmed to induce reprogramming of $CD8^+$ T cells into T_{SCM} (86).

Op9-hdll1, op9 cells expressing notch ligand, delta-like 1; Foxm1, forkhead box m1.

bone marrow of patients diagnosed with acute myeloid leukemia (AML) was treated with similar SIP, and it was found that these lymphocytes can be re-transformed into mutant $CD45RA^+$ central memory T lymphocytes (T_{CMRA}) with similar characteristics of T_{SCM}. The expression of pro-inflammatory cytokines, TNF-α, IFN-γ and IL-2 increased, and T_{CMRA} also exhibited cytotoxicity against autologous AML blast cells (134). In addition, similar effects have been shown in the treatment of Hodgkin's lymphoma. It showed a survival advantage, had higher tumor invasion and enhanced antitumor effect (133). Tumor immunotherapy is a promising treatment method. Transfect antigen-specific TCR gene or CAR vector to T_{SCM} to obtain CAR-T cells with poor differentiation and greater proliferation ability (135–139). A clinical trial study found that the genetically modified T_{SCM} can survive in the body for up to 12 years and has good safety and function (140). Recent studies have found that through integration site analysis, it is possible to study the fate of different types of CAR-T cells in patients, and it has been observed that T_{SCM} plays a central role in the early anti-leukemia response and late immune surveillance (38). This shows that this small portion of T cells is critical to the long-term success of CAR-T cell therapy. This new insight may help us improve CAR-T cell therapy and find out which patients are at higher risk of recurrence, and may benefit from stem cell transplantation after CAR-T cell therapy.

To date, CAR-T cells have achieved remarkable results in the treatment of hematological malignancies. However, despite extensive research, CAR-T cells have not been so successful in the treatment of solid tumors (141). Therefore, how to increase the trafficking and extravasation of T cells to the tumor sites and encourage the proliferation of T cells in the tumor is a problem that needs to be solved urgently. T_{SCM} have been shown to eradicate large tumors even when limited numbers of cells were transferred (28). Studies have found that chimeric T cells with multiple antigens may be a new direction for the treatment of solid tumors (71, 141, 142). At present, there are relatively few reports on the treatment of solid tumors with CAR-T-modified T_{SCM}, so it is more challenging for CAR-T-modified T_{SCM} to target solid tumors. The future should be a priority research area. In summary, memory T cell subsets have good clinical application prospects in clinical antitumor immunotherapy, and can provide personalized treatment plans for improving the prognosis of patients (134, 143). In short, these studies provide a strong scientific basis and practical methods for the rapid advancement of T_{SCM} cells in clinical trials of human adoptive immunotherapy.

The Importance of T_{SCM} in HIV-1 Immunotherapy and Vaccine Research

T_{SCM} cells play a key role in the pathogenesis of human immunodeficiency virus (HIV) infection (30, 144–146). The exhaustion of these cells will lead to the deterioration of the immune system and the development of AIDS. HIV-1 is an important part of the virus reservoirs. During HIV-1 infection, $CD4^+$ T_{SCM} cells are confirmed to be the longest-lived HIV-1. Virus storage is one of the factors that cause persistent HIV-1 infection (147, 148). Therefore, $CD4^+$ T_{SCM} cells can be used as a new target to clear the HIV-1 virus reservoir. The virus-latent cells are mainly concentrated in $CD4^+$ T_{SCM}. $CD4^+$ T_{SCM} expresses lower levels of CCR5, but can still support the production and latent infection of R5-tropic HIV-1 (149, 150). In addition, $CD4^+$ T_{SCM} is highly permissible for VSV-G-HIV-1 virus infection *in vitro*, and expresses relatively low levels of intracellular viral restriction factors, such as SAMHD1, Trim5alpha, and APOBEC3G. Moreover, these restriction factors can prevent HIV-1 from replicating in myeloid and dendritic cells (151–153). It was found that the $CD4^+$ T_{SCM} of untreated HIV-1 infected persons contained high levels of HIV-1 RNA, which all indicated the sensitivity of $CD4^+$ T_{SCM} cells to HIV-1. The study also found that in patients undergoing antiretroviral therapy (ART), $CD4^+$ T_{SCM} cells also have viral DNA that can be activated. Moreover, among the subsets of $CD4^+$ T memory cells, the number of HIV-1 DNA in T_{SCM} cells is the highest. During HIV infection, T cells play an important role in controlling virus replication. In patients receiving inhibitory antiretroviral therapy, $CD8^+$ T_{SCM} with stem cell characteristics was found to be more abundant than untreated patients (154). In addition, prolonging the treatment time can increase the ratio of $CD8^+$ T_{SCM}, and preferentially secrete IL-2 under viral stimulation, indicating that $CD8^+$ T_{SCM} is an important part of the cellular immune response to HIV-1. Able to maintain long-term, non-antigen-dependent cellular immune memory for HIV-1, which plays a key role in HIV control, but it seems unable to survive and proliferate during untreated infections (149). It is worth noting that HIV-1 specific $CD8^+$ T_{SCM} cells may not directly participate in the antiviral process, but play a role by secreting IL-2 to maintain their own proliferation and differentiation (155–157). Recent studies have found that vaccination of the subtype C prophylactic HIV-1 vaccine candidate can induce more T_{SCM} and antiviral. Compared with MVA alone and placebo, it induces more peripheral $CD8^+$ T_{SCM} cells and a higher level of $CD8^+$ T cell-mediated inhibition of the replication of different HIV-1 branches can respond to acute HIV infection or effectively control the chronic replication of HIV (152). Recently, a cross-sectional study of 20 cases of HIV-infected patients on treatment alone and 20 cases of ART has revealed a new subset of $CD4^+$ T cells: follicular regulatory T cells (TFR). The TFR of HIV^+ patients had anti-apoptotic properties, high proliferation rate and T_{SCM}-like properties, which leaded to the expansion of TFR, which in turn leaded to the dysfunction of TFH. Therefore, TFR cells may also become a new and potential therapeutic target for the treatment of HIV infection (158). How to target T_{SCM} therapy to provide new ideas for the development of new strategies for HIV-1 vaccines and immunotherapy still needs to continue to be explored and studied.

T_{SCM} and Autoimmune Diseases

T_{SCM} cells provide long-term protective immunity for anti-tumor immunity, which is probably based on reactivity to self-antigens. Therefore, as a by-product of antitumor, T_{SCM}-

mediated autoimmunity is inevitable (18, 159). Recent related studies have reported that T_{SCM} cells are associated with a variety of autoimmune diseases. Systemic lupus erythematosus (SLE) is a chronic connective tissue disease involving multiple organs that occurs in young women. Compared with healthy controls, the percentage of $CD4^+$ and $CD8^+$ T_{SCM} cells in SLE patients increased significantly. Differentiated TFH cells increase the antibodies produced by their own B cells. T_{SCM} cells play a role in the pathogenesis of SLE by maintaining TFH cells (132). Moreover, compared with healthy controls, the $CD4^+$ T_{SCM} of rheumatoid arthritis (RA) patients increased significantly (160). In the presence of IL-6, TCRs are easily activated to produce inflammatory cytokines. T_{SCM} cells may be a continuous source of the pathogenicity of RA (161). In patients with immune thrombocytopenia (ITP), the ratio of $CD4^+$ and $CD8^+$ T cells in the peripheral blood is unbalanced. The percentage of $CD8^+$ T_{SCM} in peripheral blood of ITP patients was significantly reduced after glucocorticoid treatment, indicating that the imbalance of the ratio of $CD8^+$ T_{SCM} may be involved in the occurrence and development of ITP (162). In addition, the frequency of acquired aplastic anemia (AA) $CD8^+$ T_{SCM} after immunosuppressive treatment was significantly higher than that of healthy controls. The frequency of $CD8^+$ T_{SCM} is also elevated in patients with autoimmune uveitis or sickle cell disease (130). B-cell-specific $CD8^+$ T_{SCM} cells with high expression of glucose transporter 1 (GLUT1) can be detected in T1D patients. WZB117, a selective inhibitor of Gult-1, effectively inhibits T_{SCM} cells in type 1 diabetes (T1D) patients by inhibiting glucose metabolism (53). Long-term autoreactive or abnormally activated T_{SCM} cells may induce self-renewing inflammatory cell responses. Studies have found that rapamycin (mTORC1 inhibitor) is outstanding in the treatment of autoimmune diseases (163). The above studies indicate that T_{SCM} may be a potential therapeutic target for these autoimmune diseases. The possible role of T_{SCM} cells in other diseases with severe cellular immune response, such as autoimmune hepatitis, thyroiditis, and certain types of glomerulonephritis, is currently unclear, but represents a priority research area in the future.

CONCLUSION

T_{SCM} is a long-lived memory cell with self-renewal ability and multi-differentiation potential. Different subsets of memory T cells can be identified based on their surface markers, gene expression profiles, and metabolic methods. At the same time, clinical-grade memory T cells can be obtained through *in vitro* induction and culture for cell transfer. The formation of memory T cells in the body has been confirmed in pre-clinical trials. The genetically modified T_{SCM} can survive in the body for up to 12 years and has good safety and function (140, 164). Convincing evidence in mice and humans shows that T_{SCM} cells are an important tool for adoptive immunity in tumor immunotherapy (143, 162). On the contrary, it is precisely because of their powerful immune reconstruction ability that they play a double-edged role in human diseases, and they are also potential therapeutic targets for autoimmune diseases and HIV (**Figure 5**). However, there are still many problems that need to be solved, elucidating the molecular mechanism of maintaining the phenotype of T_{SCM} cells and the influence of epigenetic modification, how to obtain a sufficient number of clinical grade T_{SCM} for induction culture. The infused T_{SCM} cells are easily affected by the immune microenvironment and are difficult to exert antitumor effects, and how the T_{SCM} cells target the tumor site to kill tumor cells is a

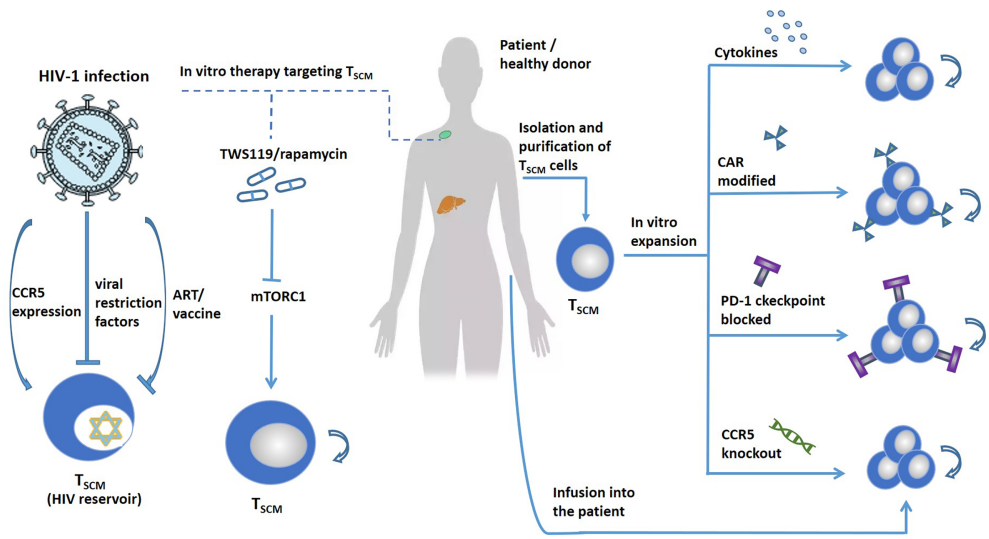

FIGURE 5 | Target T_{SCM} cells to treat human diseases. T_{SCM} cells can exacerbate human disease. Left, treat T_{SCM}-driven diseases, such as autoimmune diseases, HIV, etc., by blocking the production of T_{SCM}. The expression of CCR5 promotes the infection of T_{SCM} cells with HIV. Viral restriction factors and vaccines can target T_{SCM} cells to treat HIV. Blocking the mTORC1 pathway promotes the self-renewal and differentiation of T_{SCM}. Right, T_{SCM} cells are expanded *in vitro* by adding cytokines, CAR modification, immune checkpoint blocking, and gene editing. Stars represent cells latently infected with HIV.

problem worthy of attention at present. CAR-modified T_{SCM} cells, although there is good preclinical evidence that they have anti-tumor activity, when they are intravenously infused into solid tumor patients, they still lack persistence and efficacy (71, 133, 142). At the same time, it is worth noting that a single treatment method cannot effectively eliminate tumor cells. Immune cell therapy should be combined with PD-1 monoclonal antibody, CTLA-4 monoclonal antibody or radiotherapy, chemotherapy and other treatment methods, so that patients can get better efficacy (165). T_{SCM} has long existed in the HIV-1 virus reservoir, so future research is necessary to determine whether the low virus accumulation in T_{SCM} cells represents a significant feature of HIV-1 infection. More effort is needed to clarify the changes between the different states of T_{SCM} cells in health and disease. Although significant progress has been made in tumor therapy, there is still a gap in our understanding of the role of T_{SCM} cells in autoimmunity and viral infections.

AUTHOR CONTRIBUTIONS

YL designed the study and wrote the manuscript. DW and XY collected the literature. All authors contributed to the article and approved the submitted version.

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