Human stem memory T cells (T_{SCM}) as critical players in the long-term persistence of immune responses

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Adaptive immunity relies on the generation of memory lymphocytes from naive precursors of the host immune repertoire (1). To achieve a long-term capacity to respond to natural antigens derived from a broad diverse spectrum of pathogens and tumor cell antigens, the immune system needs to develop special lymphocyte differentiation programs to ensure the perpetuation of a given antigen-specific immune response (1,2). For T lymphocytes, long-lasting immune protection is achieved by the differentiation of naïve T cells upon antigen stimulation events into distinct cell programs consisting of central memory (TCM) and the terminally committed effector memory T cells (TEM). This differentiation model of memory cells is well described for murine models but the translation to human is hampered by the limited sort of immunological compartments studied and the different lifespan of the organisms (3). Although it has been consistently demonstrated that memory T lymphocytes can be present for several years after primary infection or vaccination, little is known about the requirements for long-term persistence of these cells.

Recently, some studies have shed light on this issue with the identification of memory stem T cells (T_{SCM}). Memory stem T cells are long-lived lymphocytes able to persist in the host in the absence of antigen. They are maintained at a constant size in the host repertoire due to its self-renewing capacity. Human memory stem T cells were shown to be multipotent in providing a potential reservoir for T cell memory throughout life (4). With the advent of T cell-based gene therapy, the possibility to monitor antigen-specific T cells and their *in vivo* dynamics and homeostasis has provided important insights on T cell persistence throughout the human lifespan. Recently, a relevant study was conducted in a cohort of patients undergoing hematopoietic stem cell transplantation (HSCT) to investigate the dynamics of long-term memory T cells (5). This therapy involves the intravenous infusion of autologous or allogeneic stem cells to restore the hematopoiesis and immune system in patients whose bone marrow is functionally defective. In the study, post-transplanted patients received an infusion of donor-derived gene-modified memory T lymphocytes expressing the herpes simplex virus thymidine kinase (HSV-TK) suicide gene (5).

The HSV-TK is a suicide gene, the expression of which in donor lymphocytes confers lethal sensitivity to the selective antiviral drug ganciclovir. The suicide gene-based therapies have allowed the overcoming of the toxicity of graft-versus-host disease (GVHD) while preserving the host T cell repertoire of HSCT transplanted patients (5). In the case of GVHD, the administration of ganciclovir leads to the "suicide pathway" activation that ultimately is responsible for deletion of HSV-TK genetically modified T cells, without interfering with the natural recovery of hematopoietic cell lines that follows HSCT. In order to detect and monitor the HSV-TK genetically modified donor T cells circulating in treated patients, the authors combined the expression of the low-affinity nerve growth factor receptor (LNGFR) in the infused T cells as a selection marker (5). The tracking of HSV-TK genetically modified lymphocytes for up to 14 years in HSCT treated patients has revealed the relative contribution of infused T cell subsets to the dynamics of long-term persistent immune

responses (5).

The HSV-TK genetically modified infused memory cells bearing the LNGFR selection marker were profiled from peripheral blood for the different subsets of memory T cells based on the phenotype of major clusters, including TSCM ($CD3^+CD45RA^+CD62L^+$), TCM ($CD3^+CD45RA^-CD62L^+$) and TEM ($CD3^+CD62L^-$) cells (5). TCR sequencing for clonal tracking to study long-term memory T cells found a preferential expansion and maintenance of clones from TSCM or TCM subsets. The results demonstrate a positive correlation between the frequency of TSCM cells infused with the magnitude of T cell expansion and long-term persisting immune responses (5). These findings point toward a determinant role of TSCM in promoting *in vivo* expansion and persistence of memory T cells (5). The therapeutic manipulation of the TSCM compartment could have implications on the acquisition of prolonged immune protection for new approaches to vaccine development against human pathogens and cancer.

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Footnote

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