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Memory T cells officially join the stem cell club

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Abstract

In this issue of *Immunity*, Graef et al. demonstrate self-renewal and multipotency of a single CD62L$^+$ memory T cell across serial adoptive transfers and infection-driven re-expansions, providing evidence of true stemness within the T cell memory compartment.

Long-term maintenance of tissue homeostasis relies on somatic stem cells, which ensure efficient replacement of short-lived, specialized cells while maintaining themselves through a process of self-renewal (Simons and Clevers, 2011). Analogous to other organ systems, life-long immunological memory is thought to depend on stem cell-like memory cells, as the ability of hematopoietic stem cells (HSCs) to provide for antigen-specific immunity is constrained by stochastic recombination of the T cell receptor and thymic involution in early adulthood (Fearon et al., 2001). Over the past decade, it has become increasingly recognized that memory T cells display core molecular signatures and functional attributes characteristic of stem cells (Gattinoni et al., 2012). For instance, memory T cells share a partially conserved transcriptional profile with HSCs and, similar to stem cells, they can undergo asymmetric division and activate telomerase to maintain telomere length and replicative potential (Gattinoni et al., 2012). Furthermore, several signaling pathways regulating stem cell self-renewal have been found to be active in T cells to promote memory and limit effector T cell differentiation (Gattinoni et al., 2012). However, self-renewal and multipotency, the defining qualities of stem cells, have only been inferred by reconstitution studies analyzing the developmental potential of T cell populations rather than studying individual cells, which is essential to determining the true stemness of a given cell type. These population-based studies have revealed a hierarchical organization of the T cell memory compartment. T memory stem cells (T_{SCM}), a subset of cells displaying a naïve-like phenotype (CD44$^-$ CD62L$^+$ in mice; CD45RA$^+$ CD62L$^+$ in human and nonhuman primates) together with the expression of the memory markers interleukin-2 receptor (IL2R) β and the chemokine C-X-C motif receptor 3 (CXCR3) have been shown to be the most undifferentiated memory subset (Gattinoni et al., 2012). In this hierarchical structure, CD62L$^+$ central memory (T_{CM}) cells are located at an intermediate position between T_{SCM} cells and CD62L$^-$ effector memory (T_{EM}) cells, which are committed progenitor cells prone to effector (T_{EFF}) differentiation (Gattinoni et al., 2012). While these studies focusing on

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population analyses helped shape our current understanding of T cell differentiation, they cannot unequivocally establish the developmental potential of individual cells.

In this issue of *Immunity*, Graef et al. evaluate the stemness of the $CD8^+$ memory T cell compartment by measuring self-renewal and multipotency of a single T_{CM} cell throughout a series of *in vivo* clonogenic assays. It was an extraordinary undertaking, performing a serial tri-generational single cell transfer, an experiment that was never attempted before for any type of mammalian stem cells. The authors found that following pathogen-stimulation, a single T_{CM} cell could propagate itself while giving rise to a diverse progeny comprising T_{EM} and T_{EFF} cells. Remarkably, progeny size, diversity and long-term maintenance were highly reproducible across serial transfers, demonstrating stem cell behavior of individual T_{CM} cells (Figure 1). In keeping with the stem cell parallel, it was striking to observe that a progeny from single T_{CM} cells could be detected in about 20% of mice, a recovery rate comparable to the reconstitution efficiency originally reported for a single HSC (Osawa et al., 1996). A hallmark of adult stem cells is the ability to confer functional tissue reconstitution. Graef et al. showed that minuscule numbers of tertiary T_{CM} cells, whose ancestors had passed through three generations of single T cells – a naïve T cell, a primary T_{CM} cell and a secondary T_{CM} cell, were capable of reconstituting full immunocompetence and protecting severely immunodeficient hosts from a lethal bacterial challenge (Figure 1). Collectively, these findings further buttress the conclusion that $CD62L^+$ memory T cells functionally behave as adult stem cells.

It is currently unclear whether T_{CM} cells have a persistent broad developmental potential or if they accumulate inherited restrictions as a result of their replicative history. The authors concluded in favor of the first hypothesis, as they observed no correlation between the degree of expansion that had originated from a single ancestor and the proliferation of its T_{CM} daughter cells. However, it should be noted that the degree of expansion of a single cell progeny does not necessarily reflect the replicative history of T_{CM} daughters, as the size of large colonies is primarily driven by T_{EM} and T_{EFF} cells. Conversely, paralleling other types of adult stem cells, whose stemness is often preserved by enforcing cellular quiescence (Simons and Clevers, 2011), the reconstitution potential of individual T_{CM} cells might also be conditioned by their past proliferation. Indeed, the authors observed that about 20% of single T_{CM}-derived progenies that were detectable at the peak of expansion failed to persist for the long-term, indicating a stochastic loss of stemness, possibly reflecting heterogeneity of replicative history in the T_{CM} compartment. These results underscore that, akin to other types of tissue stem cells (Simons and Clevers, 2011), T cell memory stemness is maintained not only at single cell level but also through the "robustness" of the $CD62L^+$ memory pool.

It is unfortunate that T_{SCM} cell stemness could not be evaluated in this study, as the experimental conditions employed by Graef et al. did not support the formation of this memory subset. Pathogen-specific T_{SCM} cells have yet to be reported in mice but have been described in human and nonhuman primates (Gattinoni et al., 2011; Lugli et al., 2013). More importantly, it is becoming clear that these cells are fundamental for the maintenance of immune homeostasis as perturbation of the T_{SCM} cell compartment has been linked to the pathogenesis of simian immunodeficiency virus infection in rhesus macaques (Cartwright et al., 2014). The authors contended that since naïve T cells and T_{CM} were virtually

indistinguishable in their capacity for immune reconstitution, intermediates are unlikely to do better. It should be stressed that naïve and T_{CM} cells are not functionally identical. Like two paths leading to the same destination, naïve and T_{CM} cells might exhibit comparable efficiencies for immune reconstitution as a result of different functional properties. For example, a single naïve T cell might be outcompeted for antigen access by increased numbers of endogenous naïve T cells specific for the same epitope, impairing its reconstitution efficiency. T_{CM} cells, instead, might have a defective reconstitution potential compared to naïve T cells that could be compensated by CXCR3-mediated migratory advantages facilitating their encounter with pathogens (Sung et al., 2012). Thus, it is possible to envision that an intermediate subset possessing the “best of both worlds” could outperform naïve and T_{CM} cell ability for reconstitution. In fact, while there were not significant differences in the engraftment and expansion of human naïve and T_{CM} cells adoptively transferred into highly immunodeficient NOD.Cg-Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ mice, T_{SCM} cells outpaced both subsets generating 10- to 100-fold more progenies in both lymphoid and peripheral tissues (Gattinoni et al., 2011). Nevertheless, the data presented here by Graef et al. clearly indicated that T_{CM} cells are sufficient to propagate T cell memory and reconstitute epitope-specific immunocompetence of the host.

Graef et al. also provide new experimental evidence that helps resolve the ongoing debate regarding the ontogeny of memory cells. The findings that even 100 T_{EM} cells could not be propagated across serial adoptive transfer strongly argue against a linear model of differentiation where T_{CM} cells develop from T_{EFF} cells through maturational transition into T_{EM} cells (Wherry et al., 2003). Instead, these results are consistent with a developmental model of differentiation where cells progressively lose their proliferative and developmental potential as they differentiate from CD62L$^+$ T cells to T_{EM} and T_{EFF} cells.

The findings reported here by Graef et al. have important therapeutic implications and add to the mounting evidence that less-differentiated CD62L$^+$ T cells are the ideal cell population to use in cellular therapies targeting intracellular pathogens and cancer (Gattinoni et al., 2012). Long-term persistence of adoptively transferred T cells have been shown to correlate with objective tumor responses across multiple clinical trials employing either naturally occurring or gene-engineered tumor-reactive T cells (Gattinoni et al., 2012). However, cell products currently employed in adoptive immunotherapy studies predominantly comprise T_{EFF} and T_{EM} cells, which have a limited life span. Adoptive transfer of long-lived, multipotent CD62L$^+$ memory T cells might significantly improve persistence and potentiate the therapeutic efficacy of adoptive immunotherapies. New clinical trials employing T_{CM} or CD62L$^+$-derived T cells have been initiated and hopefully will translate into increased tumor response rates. Finally, the experimental demonstration that tiny numbers of CD62L$^+$ memory cells can fully reconstitute immunocompetence emphasizes the idea that large numbers of cells are not necessary for therapeutic success if memory stem cell populations are employed. The use of small numbers of CD62L$^+$ memory cells might reduce the cost and complexity of the treatment and, ultimately, allow the widespread application of adoptive immunotherapies.

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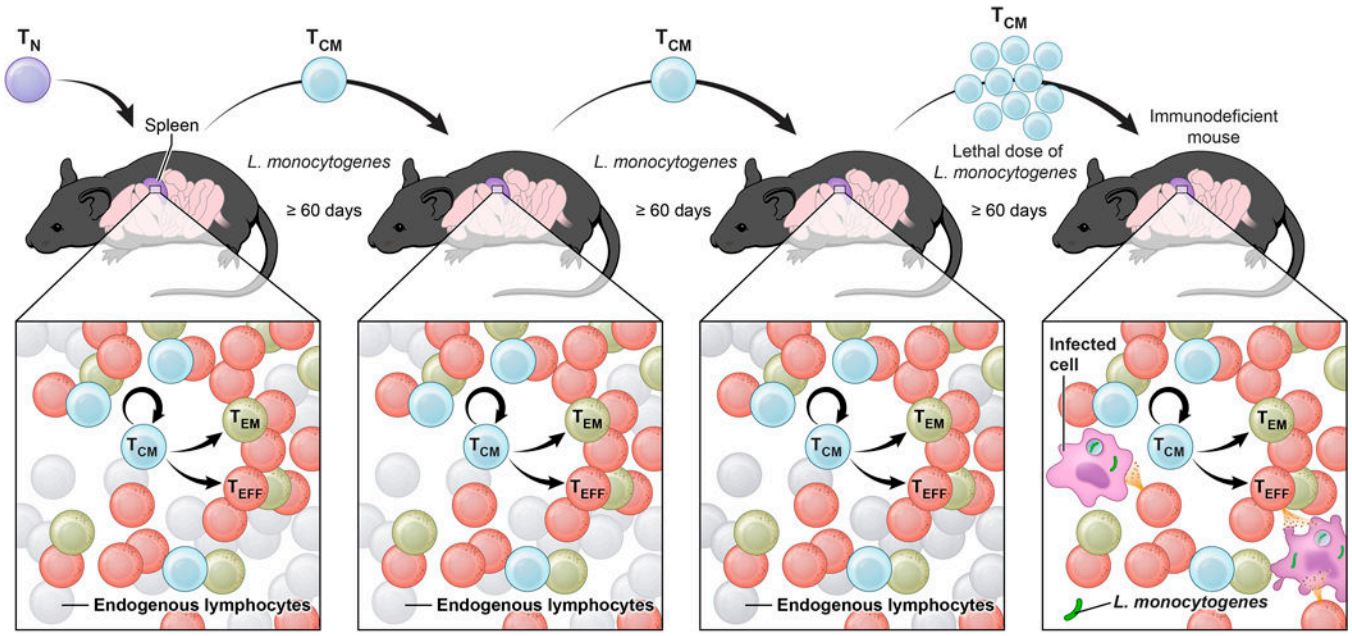

Figure 1: T_{CM} cells function as adult stem cells.

Self-renewal and multipotency of a single central memory T cell (T_{CM}) across serial adoptive transfers and infection-driven re-expansions ensure full immunocompetence. T_N, naïve T cell; T_{EM}, effector memory T cell; T_{EFF}, effector T cell.