Editorial

Lifelong protection mediated by stem cell-like CD8$^+$ T memory subset cells (Tscm) induced by vaccination

Alexandre Morrot

Departamento de Microbiologia Geral, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Correspondence to: Dr. Alexandre Morrot. Instituto de Microbiologia, Universidade Federal do Rio de Janeiro (UFRJ), CCS-Sala D1-035, Av. Carlos C hagas F ilho, 373-Cidade Universitária, CEP 21.941-902, Ilha do Fundão, Rio de Janeiro, RJ, Brazil. Email: morrot@micro.ufrj.br.

Submitted Apr 06, 2016. Accepted for publication Apr 13, 2016.
doi: 10.21037/atm.2016.05.38
View this article at: http://dx.doi.org/10.21037/atm.2016.05.38

The immune response is in its most fundamental aspect an orchestrated battle of host cells against intruders that threaten tissue homeostasis. One of the hallmarks of the immune system is its capacity to monitor tissues for pathogens or transformed malignant cells (1). One could view immune cells as sentinels distributed over the entire body. The saying *"tell me where you live and I'll tell you who you are"* could well apply to the distinctive functions of different components of the immune system because cells of the immune system not only circulate continuously through the tissues but also establish tissue-resident populations of memory T (T_{RM}) cells that mount a first response against an intruder (2).

T_{RM} cells are phenotypically and functionally distinct from circulating central (T_{CM}) and effector (T_{EM}) memory T cells. Like naive T cells, they patrol secondary lymphoid organs and undergo a rapid proliferative burst when their T cell antigen receptors recognize antigen-presenting molecules and then differentiate into effector cells (3). At this stage, they lose their lymph node homing receptors (CD62L and CCR7) and migrate to peripheral non-lymphoid tissues where they can destroy invading pathogens or transformed cells by means of effector cytokines or cytolysis of infected host cells (2,3). T cell recirculation is a dynamic process that is regulated during all phases of the immune response and is crucial in the fight against pathogens or transformed cells (4).

During antigen-mediated immune responses, inflamed lymph nodes are enriched with cytokines such as type I interferon (IFN), interleukin-33 (IL-33), and tumor necrosis factor-α (TNFα) and others that promote the expression of the C-type lectin CD69 on activated T cells together with reduced expression of the transcription factor kruppel-like factor 2 (KLF2), a positive regulator of sphingosine-1 phosphate receptor 1 (S1PR1) (5). Inhibition of S1PR1-dependent chemotactic responses is thought to represent an important checkpoint in the commitment of the T_{RM} lineage. This event prevents the exit of T_{RM} cells from the tissues in which they reside (3). In contrast, recirculating Tem cells do not express CD69 and make increased levels of S1PR1, which allows them to chemotax to S1P1 and migrate from draining afferent lymphatics to secondary lymph nodes (3).

The fate of T_{RM} cells is also governed by the cytokine milieu. Transforming growth factor β (TGF-β) has been shown to induce αEβ7 expression on T_{RM} cell precursors, and expression of αEβ7 integrin is required for T_{RM} subsets to be retained within mucosal tissues and epidermal epithelia (6). In an experimental model of cutaneous leishmaniasis, blocking integrin αv *in vivo* increased the burden of *Leishmania major* parasites in the skin; moreover intravital multiphoton imaging indicated that the failure to control parasite infection was associated with inhibition of the αv integrin-dependent interstitial motility of T cells in the inflamed dermis (7).

Other experimental models have shown that T_{RM} cells control cell-mediated adaptive immune responses against pathogen infection in a number of different organs. In an experimental model of influenza infection, CD4$^+$ T_{RM} cells were found to be responsible for protective immunity against respiratory lung infection (8). These studies demonstrate that T_{RM} cells are located in the peripheral non-lymphoid tissues most often occupied by microbes at the outset of an infection, and respond immediately to the

infection.

The existence of different subsets of T memory cells present in the various tissue compartments as blasts or effector T cells, with distinct properties, tissue-residency "zip codes" and motilities, optimizes pathogen detection (2,3). Their existence can be seen as helpful for the development of new therapeutic interventions and vaccination technologies. In this regard, much attention is being paid to the factors that regulate the proliferation, maintenance, and longevity of the different T cell memory subsets. There is evidence that cytokine IL-15 controls the size of the memory $CD8^+$ T cell compartment (9). However, this control seems to apply to central and effector memory $CD8^+$ T cell populations, while its application to T_{RM} cells is controversial (3).

In humans, much effort is being dedicated to better understanding the mechanisms underlying the development and long-term maintenance of persisting memory T cells but there have been few studies of long-term T cell responses associated with protection against infectious and malignant diseases. However, recent discoveries in vaccines against yellow fever (YF) have shed new light on this area (10). Thus, live-attenuated vaccines against YF-17D and YF-17DD strains are known to induce protective responses in human populations, and lead to long-lasting and robust YF-specific proliferative responses of $CD8^+$ T cells. Furthermore, these vaccines induce stable populations of polyfunctional $CD8^+$ T cells with distinct activation and memory differentiation patterns that correlate with the effectiveness of protection (10).

Interestingly, analysis of the frequencies and differentiation status of YF vaccine-induced T cells in a large cohort of patients over time showed that the YF-specific $CD8^+$ T cell responses were stable for decades, being detectable for at least 25 years after vaccination (10). This stability relies on the fact that the vaccine induces sets of YF-specific memory $CD8^+$ T cells with a naïve-like $CD45RA^+$ $CCR7^+$ phenotype with the capacity to respond to cognate peptide and undergo the IL-15-driven proliferation characteristic of memory cells (10). At the same time these cells have an unconventional phenotype: unlike naïve cells they express activation markers such as CD95 (Fas/APO-1), granzyme A and chemokine receptor CXCR, among other products characteristic of antigen-experienced T cells (10).

This combination of memory cell and naive T cell characteristics leads the classification of these cells as stem cell-like memory T cell populations: they possess steady-state activation profiles combined with the self-renewing "stemness" of undifferentiated cells able to undergo antigen-driven differentiation into central memory, effector memory and effector T cells, and this permits them to confer robust adaptive immunity (10,11). Further elucidation of the cellular and biological mechanisms governing the fate and self-renewing capacity of these human stem cell-like memory T cells as well as their relationship to other T cell memory lineages promises to provide insight into the design of new vaccines and T cell therapies.

Acknowledgements

This work was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico do Brasil (CNPq), Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAP ERJ). Alexandre Morrot is recipient of fellowships from CNPq.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Morrot A. Lifelong protection mediated by stem cell-like CD8$^+$ T memory subset cells (Tscm) induced by vaccination. Ann Transl Med 2016;4(11):221. doi: 10.21037/atm.2016.05.38

