Got IELs?

The majority of intraepithelial lymphocytes (IELs) that reside within the epithelia are fully differentiated CD8 effector memory T (T_{EM}) cells. These lymphocytes acquire their effector phenotype and functional differentiation in response to antigens in peripheral lymphoid organs.[1] Consequently, one of the major achievements of the immune memory process is the gradual seeding of nonlymphoid tissues with fully differentiated CD8 T_{EM} cells selected for the antigens present in the immediate environment. Their strategic localization suggests a critical role for these antigen-experienced cells as first-line defenders, capable of providing early immunity when invading pathogens are probably most susceptible to immune control.

In agreement with this, a recent study by Jiang *et al*.[2] showed that functionally differentiated skin-resident T_{EM} cells generated protective immunity against cutaneous infections and reinfections that was far superior to that provided by circulating, self-renewing, central memory T (T_{CM}) cells. These new findings join a growing body of evidence that preexisting, fully differentiated T_{EM} cells at peripheral interfaces, where most pathogens first enter, form one of the most critical arms of protective cell-mediated immunity.[3–8]

The role of CD8 memory T cells in providing protection against infections by intracellular pathogens, such as viruses, bacteria, and protozoan parasites, has been well recognized, and major efforts have been made to provide vaccine-induced, pathogen-specific CD8 T-cell immunity.[9] However, conventional vaccine strategies, which have been focused on the recall responses of T_{CM} cells in secondary lymphoid tissues, have largely failed in inducing effective protective immunity, especially against pathogens such as HIV that are naturally transmitted across mucosal borders.[10] This implies that the antigen-induced quantitative hallmark response of T_{CM} cells, which is required for their effector differentiation before they can migrate to the site of infection and participate in the protective response, might develop too slowly to provide the early adaptive immunity that could prevent transmission and systemic dissemination of invading pathogens. By contrast, other recent reports[5,7] showed that vaccine-induced mucosal CD8 T_{EM} cells were able, in the absence of neutralizing antibody, to effectively block establishment of systemic infection after mucosal challenge with a highly pathogenic simian immunodeficiency virus, presumably by interfering with the initial viral replication. In addition to achieving early pathogen control, the rapid responses of T_{EM} cells averted overt inflammatory responses that would impose a threat to the integrity of mucosal barriers.

Taken together, these new insights indicate that, to achieve effective vaccine-based protection, it will be important to establish close synergy between both a local qualitative T_{EM}-cell component and a systemic quantitative T_{CM}-cell component, with the former providing early preventive immunity at the site of infection and the latter serving as a second line of defense capable of clearing the pathogen in case the initial T_{EM}-cell barrier is breached.

The new advances also imply that the aim of improved or new vaccination strategies must be not only the generation of antigen-specific T_{CM} cells that can expand robustly upon rechallenge in secondary lymphoid tissues but also, equally important, the accumulation of preexisting, highly sensitive local T_{EM} cells at the mucosal interfaces. Nevertheless, the functional hallmarks that distinguish the protective efficacy of the memory T-cell subsets suggest that distinct mechanisms might drive their explicit generation and long-term maintenance. In support of this, data have shown that local induction and optimal activation conditions—for example, in the presence of efficient innate stimulation and proinflammatory cytokines such as interleukin-12 or in response to high-avidity/-affinity stimulation—preferentially lead to the differentiation of protective T_{EM} cells.[4,8,11–13] By contrast, systemic memory differentiation under conditions that preclude full activation, such as in the presence of the suppressive cytokine interleukin-10, as was shown recently,[14] interferes with effector differentiation and leads mainly to the accumulation of lymphoid T_{CM} cells.[14,15] In addition, we have previously shown that a unique survival mechanism—mediated by the activation-induced expression of CD8α homodimers (CD8$\alpha\alpha$), which function as T-cell-receptor repressors and counteract the coreceptor function of CD8$\alpha\beta$,[16]—results in the rescue of memory precursor cells from activation-induced cell death.[17] Induction of CD8$\alpha\alpha$ is proportional to the signal strength of activation, thereby marking the highest-avidity/-affinity memory precursor cells with the highest level of CD8$\alpha\alpha$ expression.[8] Interestingly, we also found that CD8$\alpha\alpha$ marked high-affinity/-avidity effector cells that were selectively preserved as mucosal memory precursor cells and that accumulated as T_{EM}-cell IELs in the intestine.[8] The data further showed that continuous selection pressure, enforced by the epithelium, enriched for the long-term survival of high-avidity/-affinity IELs, whereas less antigen-sensitive cells were constantly being eliminated from the pools of resident mucosal T_{EM} cells.[8]

These new insights into protective immunity have revealed that perhaps one of the most important, although underappreciated, functions of memory T-cell differentiation is the selective seeding of the mucosal barriers with highly sensitive and fully differentiated antigen-experienced IELs, which function as effective sentinels and rapidly respond before the pathogen or the systemic immune system has a chance to jeopardize the integrity of these critical surfaces. Therefore, the efficacy of the new generation of vaccination strategies will depend greatly on the answer to the question "Got IELs"?

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REFERENCES

1. Cheroutre, H. & Madakamutil, L. Mucosal effector memory T cells: the other side of the coin. *Cell. Mol. Life Sci.* **62**, 2853–2866 (2005).
2. Jiang, X. ***et al.*** Skin infection generates non-migratory memory CD8+ TRM cells providing global skin immunity. *Nature* **483**, 227–231 (2012).
3. Belyakov, I.M. *et al.* Impact of vaccine-induced mucosal high-avidity CD8+ CTLs in delay of AIDS viral dissemination from mucosa. *Blood* **107**, 3258–3264 (2006).
4. Belyakov, I.M., Isakov, D., Zhu, Q., Dzutsev, A. & Berzofsky, J.A. A novel functional CTL avidity/activity compartmentalization to the site of mucosal immunization contributes to protection of macaques against simian/human immunodeficiency viral depletion of mucosal CD4+ T cells. *J. Immunol.* **178**, 7211–7221 (2007).
5. Hansen, S.G. *et al.* Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. *Nat. Med.* **15**, 293–299 (2009).
6. Hansen, S.G. *et al.* Evasion of CD8+ T cells is critical for superinfection by cytomegalovirus. *Science* **328**, 102–106 (2010).
7. Hansen, S.G. *et al.* Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. *Nature* **473**, 523–527 (2011).
8. Huang, Y. *et al.* Mucosal memory CD8 T cells are selected in the periphery by an MHC class I molecule. *Nat. Immunol.* **12**, 1086–1095 (2011).
9. Ahlers, J.D. & Belyakov, I.M. Memories that last forever: strategies for optimizing vaccine T-cell memory. *Blood* **115**, 1678–1689 (2010).
10. Sekaly, R.P. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? *J. Exp. Med.* **205**, 7–12 (2008).
11. Ahlers, J.D., Belyakov, I.M. & Berzofsky, J.A. Cytokine, chemokine, and costimulatory molecule modulation to enhance efficacy of HIV vaccines. *Curr. Mol. Med.* **3**, 285–301 (2003).
12. Belyakov, I.M. *et al.* Enhancement of CD8+ T cell immunity in the lung by CpG oligodeoxynucleotides increases protective efficacy of a modified vaccinia Ankara vaccine against lethal poxvirus infection even in a CD4-deficient host. *J. Immunol.* **177**, 6336–6343 (2006).
13. Chowdhury, F.Z., Ramos, H.J., Davis, L.S., Forman, J. & Farrar, J.D. IL-12 selectively programs effector pathways that are stably expressed in human CD8+ effector memory T cells in vivo. *Blood* **118**, 3890–3900 (2011).
14. Cui, W., Liu, Y., Weinstein, J.S., Craft, J. & Kaech, S.M. An interleukin-21-interleukin-10-STAT3 pathway is critical for functional maturation of memory CD8+ T cells. *Immunity* **35**, 792–805 (2011).
15. Biswas, P.S. *et al.* Pathogen-specific CD8 T cell responses are directly inhibited by IL-10. *J. Immunol.* **179**, 4520–4528 (2007).
16. Cheroutre, H. & Lambolez, F. Doubting the TCR coreceptor function of CD8alphaalpha. *Immunity* **28**, 149–159 (2008).
17. Madakamutil, L.T. *et al.* CD8alphaalpha-mediated survival and differentiation of CD8 memory T cell precursors. *Science* **304**, 590–593 (2004).