ELSEVIER

Lymphocyte effector functions
Memory and unique subsets of lymphocytes
Editorial overview
Liisa K Selin

Current Opinion in Immunology 2004, **16**:257–258

This review comes from a themed issue on
Lymphocyte effector functions
Edited by Liisa K Selin

0952-7915/$ – see front matter

DOI 10.1016/j.coi.2004.03.017

Liisa K Selin

Department of Pathology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA
e-mail: Liisa-Selin@umassmed.edu

Liisa Selin's research interests are directed at understanding T-cell responses during viral infections in both mouse and human systems, with particular emphasis on the impact that immune responses to earlier infections have on subsequent unrelated infections — heterologous immunity. Specifically, she examines the influence of heterologous virus infections on the development of cross-reactive T-cell responses, T-cell receptor repertoire and immunopathology.

Abbreviations
IEL intraepithelial lymphocyte
TL thymic leukemia antigen
TCR T-cell receptor

Adaptive T-cell and B-cell immune responses work together with innate immune responses to eradicate pathogens, including viruses, bacteria and parasites. A function of the adaptive response not associated with the innate response is the generation of immunological memory. These memory responses are readily stimulated on re-exposure to the original pathogen and are able to patrol for pathogens that persist in the host at low levels. In our search for ideal vaccines it is imperative to have a good understanding of how effective T- and B-cell memory responses are generated. For T cells it can be difficult at times to draw the line between what defines an effector cell and a memory cell, which for B cells thus far seems to be more clearly defined. During B-cell activation there is generation of two separate lineages: terminally differentiated effector cells — the plasma cells that produce antigen-specific antibodies, and antigen-specific memory B cells, which are able, on re-exposure to the pathogen, to differentiate into antibody-producing plasma cells. Plasma-cell differentiation can occur with or without T-cell help. Memory B-cell differentiation, however, is thought to involve the germinal center reaction, and require $CD4^+$ T-cell help and CD40–CD40 ligand interactions.

Defining the differentiation pathways for T cells into effector and memory phenotypes has been more difficult. It has been generally agreed that this is a linear pathway with naïve cells becoming effector cells and then memory cells. T cells have previously been divided into multiple functional phenotypes on the basis of their surface expression of activation molecules (CD45R0, CD45RA), lymph node homing receptors (CD62L, CCR7) and molecules associated with co-stimulation (CD27,CD28). Memory T cells were found to be very heterogeneous in their expression pattern of these surface molecules, and there continues to be a great deal of controversy about whether these phenotypes represent either stages in a memory T-cell differentiation pathway or the initial and on-going antigen experience of the memory T-cell population. In the past year, however, three important observations, reviewed in this section, were made concerning $CD8^+$ T-cell differentiation into memory phase:

1. Similar to B-cell memory, $CD8^+$ T-cell differentiation requires $CD4^+$ T-cell help and CD40–CD40 ligand interactions.

2. The $CD8^+$ T cells expressing IL-7R during the effector phase of the response go on to become memory cells.
3. These IL-$7R^+$ cells also co-express CD8αα, a cell surface molecule associated with modulation of T-cell receptor (TCR) signaling.

Rocha and Tanchot [1] discuss the evidence for the newly defined role of $CD4^+$ helper T cells and CD40–CD40 ligand interactions that are required for the development of CD8 T cell memory. They point out the parallels that now exist between T- and B-memory-cell differentiation. Gangadharan and Cheroutre [2] discuss the evidence that antigenic stimulation of conventional CD8αβ T cells through the TCR results in induction of CD8αα. They provide evidence that signaling via CD8αα leads to enhanced survival and differentiation into memory $CD8^+$ T cells. These CD8αα memory cells were also found to co-express IL7R, another molecule reported to be associated with memory $CD8^+$ T-cell differentiation. Future studies will determine if these same requirements apply to memory $CD4^+$ T-cell differentiation.

Another important feature influencing the effectiveness of memory $CD8^+$ T cells is their ability to persist long-term throughout the host. Although memory $CD8^+$ T cells are reported to be stable over time, Welsh *et al.* [3] review the evidence that demonstrates that virus-induced memory $CD8^+$ T cells are quite volatile in the presence of other infections. This review examines how T-cell apoptosis and cross-reactivity are involved in accommodating and maintaining homeostasis in memory $CD8^+$ T-cell pools to many pathogens in a finite immune system. These authors also review the evidence for how altered rates of memory T-cell apoptosis are involved in maintaining higher frequencies of memory T cells in peripheral organs, such as the lung, at the site of viral entry.

Two reviews in this section address the issue of the unique features of T and B cells located at mucosal surfaces, the most frequent site of entry for all pathogens. The T-cell surface molecule CD8αα, as discussed by Gangadharam and Cheroutre [2], appears to have other unique functions in addition to its role in $CD8^+$ T-cell memory differentiation. CD8αα plays a role in thymic positive selection of self-reactive T cells, which ultimately migrate to the gut and become intraepithelial lymphocytes (IELs). Mucosal IELs, including TCRγδ and $CD4^+$ or $CD8^+$ TCRαβ T cells co-express the immunomodulatory CD8αα molecule, which can interact with its ligand, thymic leukemia antigen (TL), a non-classical MHC class I molecule, to modify TCR activation caused by antigen stimulation. IELs activated in the presence of the TL–CD8αα interaction show reduced proliferation and cytotoxicity, and enhanced cytokine production, suggesting that this partial interaction with self may protect gut epithelial cells while still controlling the pathogen. Are these gut IEL memory cells or unique T cells adapted to the environment of the gut? Is a similar mechanism of CD8αα interaction with a ligand-like TL modulating TCR signaling in conventional $CD8^+$ T cells, resulting in generation of memory?

The review by Fagaransan and Honjo [4] suggests that, in mucosal surfaces, the differentiation of B cells into plasma cells and memory B cells may not be as simple as previously thought, at least for the regulation of IgA synthesis. Antigen-specific B cells and plasma cells capable of producing IgA are generated not only in the germinal centers of Peyer's patches but also without T-cell help in the lamina propria of the gut, which is not an organized secondary lymphoid structure. Are these true memory B cells or unique adaptations in B-cell differentiation specific to mucosal surfaces? Much as IELs have unique functions, IgA-secreting cells appear to play a crucial role in immunomodulating anti-inflammatory effects in the gut.

References

1. Rocha B, Tanchot C: **Towards a cellular definition of $CD8^+$ T-cell memory: the role of $CD4^+$ T-cell help in $CD8^+$ T-cell responses**. *Curr Opin Immunol* 2004, **16**:259-263.
2. Gangadharan D, Cheroutre H: **The CD8 isoform CD8αα is not a functional homologue of the TCR co-receptor CD8αβ**. *Curr Opin Immunol* 2004, **16**:264-270.
3. Welsh RM, Bahl K, Wang XZ: **Apoptosis and loss of virus-specific $CD8^+$ T-cell memory**. *Curr Opin Immunol* 2004, **16**:271-276.
4. Fagarasan S, Honjo T: **Regulation of IgA synthesis at mucosal surfaces**. *Curr Opin Immunol* 2004, **16**:277-283.