LINK TO ORIGINAL ARTICLE
LINK TO AUTHOR'S REPLY

Foreign antigen-independent memory-phenotype CD4$^+$ T cells: a new player in innate immunity?

Takeshi Kawabe, Jinfang Zhu and Alan Sher

In an Opinion article published in May 2017 (Antigen-inexperienced memory CD8$^\pm$ T cells: where they come from and why we need them. *Nat. Rev. Immunol.* **17**, 391–400 (2017)[1]), Ross Kedl and colleagues provided a comprehensive review concerning foreign antigen-inexperienced CD8$^+$ T lymphocytes with a memory phenotype (MP). This population develops without foreign antigen recognition and consists of thymus-derived innate memory (T_{IM}) and peripherally generated virtual memory (T_{VM}) cells. Importantly, these CD8$^+$ MP lymphocyte subsets exert innate effector function in terms of cytokine production[2] and/or host resistance to infection *in vivo*[3].

From available evidence, these authors argued that CD4$^+$ T cells fail to generate a corresponding foreign antigen-independent MP population in lymphoreplete mice while likely doing so in humans[1]. They based this hypothesis in part on the observations that most murine CD44^{hi} CD4$^+$ T cells are CD49d$^+$ (a marker for antigen-specific effector and/or memory CD8$^+$ T cells)[4], and that CD44^{hi} CD4$^+$ T cells are virtually absent in T cell receptor (TCR)-transgenic *Rag*-deficient mice in steady state[5].

Nevertheless, the late Charles Surh and colleagues demonstrated the existence of CD4$^+$ T cells with a MP (CD44^{hi} CD62L^{lo}) in mice and, importantly, showed that this population is present equally in specific-pathogen-free, germ-free, and antigen-free mice[6]. As antigen-free mice are germ-free animals raised on an elemental diet free of potential food antigens and thus unexposed to virtually all foreign antigens, self-reactivity may serve as a key driving factor in the development of MP CD4$^+$ T lymphocytes in a lymphoreplete environment, although commensal antigen recognition may contribute to the generation of these cells in lymphopenic settings[7,8]. Moreover, distinct from typical memory CD4$^+$ T cells, CD4$^+$ MP cells rapidly proliferate under steady-state conditions[9]. We suggest that MP CD4$^+$ T cells were not detected in TCR-transgenic *Rag*-deficient mice because they possess an overabundance of cells showing homogeneous expression of a TCR with low affinity for self-antigens; consequently, these cells may out-compete those precursors that would normally differentiate into MP cells during homeostatic proliferation.

Recently, we have found that in a lymphoreplete environment MP CD4$^+$ T cells are spontaneously generated from peripheral naive T cell precursors and in particular from those expressing high levels of CD5 (REF. 10), a reliable marker for self reactivity[11]. In the steady state, the CD4$^+$ MP population consists of both T-bet^{hi} and T-bet^{low} subsets, the former of which differentiates as a consequence of tonic IL-12 signalling acting through a T-bet-dependent positive feedback loop. Importantly, in infectious settings, these T-bet^{hi} MP cells produce IFNγ in response to pathogen-induced IL-12 in the absence of foreign antigen recognition and thereby contribute to innate resistance and enhancement of T helper1 (T_H1)-type effector immunity. Thus, the T-bet^{hi} CD4$^+$ MP subset can be seen as a continuously generated lymphocyte population that provides an additional layer of innate immunity beyond that provided by CD8$^+$ T_{IM} and T_{VM} cells, natural killer cells, natural killer T cells, and innate lymphoid cells.

We propose that spontaneous acquisition of a memory-like phenotype associated with innate immune function is a feature of both CD4$^+$ and CD8$^+$ T lymphocytes, although T_{IM} cells are restricted to the CD8$^+$ T cell lineage. As TCR-bearing T cells that possess innate activity, MP cells present a striking example of the intersection of the innate and adaptive immune systems.

Takeshi Kawabe[1], Jinfang Zhu[2] and Alan Sher[1]

[1]Immunobiology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA.

[2]Molecular and Cellular Immunoregulation Section, Laboratory of Immune System Biology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA.

Correspondence to T.K. and A.S.
takeshi.kawabe@nih.gov; asher@niaid.nih.gov

doi:10.1038/nri.2018.12
Published online 26 Feb 2018

1. White, J. T., Cross, E. W. & Kedl, R. M. Antigen-inexperienced memory CD8$^+$ T cells: where they come from and why we need them. *Nat. Rev. Immunol.* **17**, 391–400 (2017).
2. Weinreich, M. A. *et al.* T cells expressing the transcription factor PLZF regulate the development of memory-like CD8 + T cells. *Nat. Immunol.* **11**, 709–716 (2010).
3. White, J. T. *et al.* Virtual memory T cells develop and mediate bystander protective immunity in an IL-15-dependent manner. *Nat. Commun.* **7**, 11291 (2016).
4. Sosinowski, T. *et al.* CD8alpha + dendritic cell *trans* presentation of IL-15 to naive CD8 + T cells produces antigen-inexperienced T cells in the periphery with memory phenotype and function. *J. Immunol.* **190**, 1936–1947 (2013).
5. Moon, J. J. *et al.* Naive CD4(+) T cell frequency varies for different epitopes and predicts repertoire diversity and response magnitude. *Immunity* **27**, 203–213 (2007).
6. Kim, K. S. *et al.* Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine. *Science* **351**, 858–863 (2016).
7. Kieper, W. C. *et al.* Recent immune status determines the source of antigens that drive homeostatic T cell expansion. *J. Immunol.* **174**, 3158–3163 (2005).
8. Kawabe, T. *et al.* Homeostatic proliferation of naive CD4 + T cells in mesenteric lymph nodes generates gut-tropic Th17 cells. *J. Immunol.* **190**, 5788–5798 (2013).
9. Younes, S. A. *et al.* Memory phenotype CD4 T cells undergoing rapid, nonburst-like, cytokine-driven proliferation can be distinguished from antigen-experienced memory cells. *PLoS Biol.* **9**, e1001171 (2011).
10. Kawabe, T. *et al.* Memory-phenotype CD4(+) T cells spontaneously generated under steady-state conditions exert innate TH1-like effector function. *Sci. Immunol.* **2**, eaam9304 (2017).
11. Mandl, J. N. *et al.* T cell-positive selection uses self-ligand binding strength to optimize repertoire recognition of foreign antigens. *Immunity* **38**, 263–274 (2013).

Acknowledgements
The authors are grateful to R. N. Germain and the late W. E. Paul for their invaluable discussions and contributions to the work on this topic. T.K., J.Z. and A.S. are funded by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Competing interests
The authors declare no competing interests.