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REPLY

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

Ross M. Kedl and Jason T. White

In their present Correspondence on our recent Opinion article (Antigen-inexperienced memory CD8$^\pm$ T cells: where they come from and why we need them. *Nat. Rev. Immunol.* **17**, 391–400 (2017)[1]), Kawabe *et al.* present a compelling case for the consideration of CD4$^+$ T cell memory developing in the absence of foreign antigen encounter (Foreign antigen-independent memory-phenotype CD4$^\pm$ T cells: a new player in innate immunity? *Nat. Rev. Immunol.* https://doi.org/10.1038/nri.2018.12 (2018)[2]). They make this conclusion based both on their own published data[3], as well as on recent data from Charlie Surh who identified memory phenotype (MP) CD4$^+$ T cells in both germ-free (GF) and 'antigen-free' (GF mice raised on an elemental diet free of potential food and foreign antigens) mice[4]. Collectively, with their recent publication, the authors do well to support their assertion that "a memory-like phenotype associated with innate immune function is a feature of both CD4$^+$ and CD8$^+$ T lymphocytes."

That said, the data are not entirely consistent with the conclusion that the CD4$^+$ T cell compartment contains memory analogous to CD8$^+$ innate memory T (T_{IM}) or virtual memory T (T_{VM}) cells. Our previous article on T_{IM} and T_{VM} cells centred on the clarification of these subsets as antigen-inexperienced memory cells[1], that is, T cells that arise without any overt stimulation through their T cell receptor (TCR). While it is clear that Kawabe and colleagues have shown that memory CD4$^+$ T cells can be produced independently of encounter with foreign antigens[3], they do not show that they can occur in the absence of any antigen encounter, a characteristic thus far unique to T_{IM} and T_{VM} cells. Bill Paul and colleagues showed that an established subset of MP CD4$^+$ T cells can undergo rapid proliferation independently of MHC class II[5], but conversion of naive CD4$^+$ T cells into an MP appears to be fully dependent on MHC class II and CD28, consistent with the requirement for TCR stimulation[3]. As highlighted in our review, CD49d staining is an effective way to delineate antigen-experienced (CD49d^{hi}) versus antigen-inexperienced (CD49d^{low}) T cell memory[1]. Although this cellular marker has yet to be shown on the foreign antigen-independent CD4$^+$ memory T cells studied by Kawabe and colleagues, I would suspect that its analysis would reveal a history of antigen encounter. Given this, we suggest that MP CD4$^+$ T cells can indeed arise as a result of self-antigen encounter. For reasons yet to be elucidated, the context of this self-antigen encounter inspires dramatic proliferation and conversion, not into regulatory T cells, but into T-bet-expressing T helper 1 (T_H1) cells with bystander protective capacity[3]. Taken together, it appears that while the CD8$^+$ T cell pool can develop memory subsets independently of any antigen encounter, the CD4$^+$ T cell pool has memory subsets that develop independently of foreign antigen encounter but still require antigen stimulation (from self antigens). Regardless of the mechanisms underlying these differences, there is a larger point highlighted by both sets of data; memory T cells are unquestionably useful and the host seems bent on deriving them by whatever means possible.

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Competing interests
The authors declare no competing interests.