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Editorial: T cell memory

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There is perhaps no more important function of the adaptive immune system than to confer protection from reinfection by pathogens previously encountered and defeated. Within the T cell lineage, this property of remembering past antigenic threats resides in the small subset of memory cells which persist long after the disappearance of the short-lived effector cells that arise to meet the original challenge. A question of current and enduring interest concerns the lineage relationship between effectors and memory cells, and the identity of the signals and factors that determine the establishment and maintenance of immune memory at the cellular level. The articles in this volume will consider these issues from a variety of perspectives as they apply to T cell memory.

Memory T cells can be divided into two main subsets based on their location, surface phenotype, and functional capacity. Central memory cells (T_{CM}) express the homing receptors CCR7 and CD62-L, thus ensuring their residence within lymph nodes where they can respond to antigen re-encounter with a proliferative burst that generates a new cohort of effectors. Effector memory cells (T_{EM}) do not express these lymph node homing receptors and are instead found mostly in peripheral tissues where they are thought to serve a sentinel function at sites where infectious pathogens are likely to first be re-encountered. Although the memory CD8+ T cells have been the subject of a greater number of studies to-date due their greater proliferative response to the model pathogens used in experimental animal models, the article by MacLeod et al focus on CD4+ T cell memory and discusses the types of models used to study this subset and how the data these generate influences our concepts of what a memory CD4+ T cell is and what functional properties it should possess. Rather than focusing solely on phenotypic markers or physiological location, MacLeod et al make a compelling case for understanding CD4 memory through function, specifically through the capacity to mediate protection from a variety of pathogens that might involve a range of ultimate effector mechanisms.

Stemberger et al address the clonal origins of the functional and phenotypic heterogeneity represented in memory T cells. Following up on their recent surprising finding that the entire repertoire of CD8+ effector and memory (T_{CM} and T_{EM}) that arises in response to infection can be generated from a single precursor cell, these authors discuss the implications of the 'stem-cell' qualities that memory subsets can display and how this may influence the strategic use of these cells through vaccination or adoptive transfer. These are critical issues to the field, as defining the point(s) during memory cell development that this inherent plasticity can be manipulated to generate the type and magnitude of T cell responses desired for a given purpose will significantly improve the clinical application of immunotherapy in a variety of disease settings.

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The remaining articles in this volume address an area of the field that will only expand in the coming years: identifying the genetic and biochemical factors that govern the establishment, maintenance, and functional manifestation of T cell memory. Although memory T cells have long been thought to be independent of the costimulatory signals which are required for priming of naïve T cell responses such as CD28 and various TNF family members, recent *in vivo* evidence has shown that optimal recall responses of both CD4+ and CD8+ T cells and clearance of challenge pathogens are dependent on classical 'signal two' costimulatory molecules. Boesteanu and Katsikis provide a thoughtful review of this literature, including their own groundbreaking work in this area, and offer perspectives on how these findings can fundamentally influence the development of vaccination and immunotherapeutic strategies.

Moving from the cell surface to the nucleus, Nakayama and Yamshita focus on a set of new findings concerning the role of polycomb (PcG) and Trithorax (TrxG) complexes in the establishment and maintenance of CD4+ T cell memory. These gene products are involved in the regulation of developmental genes such as those controlling homeobox factors as well as maintenance of hematopoietic and cancer stem cells, and are known to antagonize each other in the same developmental processes. Using a novel experimental system for the molecular analysis of CD4+ memory T cells, these authors have defined a role of PcG and TrxG proteins in the regulation of both Th1 and Th2 CD4+ T cell memory. These interesting findings greatly expand our understanding of the genetic regulation of T cell memory, and provide significant insights into how nature can regulate seemingly disparate cellular functions through common molecular components.

The biochemical and genetic regulation of CD4+ T cell recall responses is the subject of the article from Donna Farber, and represents an area to which her laboratory has made a series of seminal contributions. Drawing from a number of sources of experimental data including her own research, her article reveals the common signaling and genetic pathways that regulate the rapid production of cytokines in memory CD4+ T cells and the rapid activation of innate effectors in response to inflammatory stimuli, as well as revealing the functional coupling of signaling pathways from the TCR to the nucleus that operates in both naïve and memory CD4+ T cells. This type of approach that is both open-ended with respect to the biochemical and molecular species studied yet focused on a discrete functional response has proven to be very powerful in elucidating relevant pathways, and is certain to be applied to the study of distinct phenotypes in T cell biology.

Completing this volume is the article by D'Cruz et al, which addresses the molecular regulation of survival and self-renewal that is established during the critical effector to memory transition phase through which the majority of CD8+ T cells die by apoptosis, leaving a small (5–10% of peak numbers) cohort of long-lived memory cells. These authors offer a insightful perspective on the cell intrinsic proteins and transcription factors that regulate the key functional capacities required for the expression of the memory phenotype by a given cell, as well as the environmental/extrinsic signals through which these are induced and maintained. Taken together, these six articles will provide the interested reader with a timely and insightful survey of key aspects relevant to the field of T cell memory, and a clear indication of the fruitful areas of current and future investigations.