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Susan M. Kaech

A major conceptual framework for the orchestration of our immune responses against pathogens is the division of labor. Conventionally, the labor is segregated temporally and anatomically with the innate immune cells acting immediately and locally at the site of infection as the first line of defense. Then, several days after B and T cell activation in the distal lymph nodes, Abs and expanded effector T cells recirculate back to the site of infection, as well as systemically, as a second and more potent line of defense. Following successful clearance of the pathogen, populations of long-lived memory T and B cells and plasma cells form that help protect against re-infection in the weeks, months, or years to come. Thus, effective immune responses are multilayered, based on distinct groups of cells that, through their respective functions, complement and reinforce one another over time and space.

The exciting conceptual ramification of the work described in this month’s Pillars of Immunology articles from Sallusto et al. (1) and Masopust et al. (2) is that a similar temporal and spatial division of labor exists within the pool of memory T cells. Rather than being a monolithic cell population, as most memory T cell models suggested until this time, these studies gave new faces to memory T cells, highlighting and providing relevance for their phenotypic, functional, and anatomical diversity. This ultimately led to a deeper understanding of how memory T cell responses are coordinated during reinfection.

Sallusto et al. (1) subdivided human memory T cells from the peripheral blood into multiple cell subsets based on their expression of different homing and chemokine receptors. They found that similar to naive T cells, a large portion of the memory T cells expressed the lymph node– and T cell zone–homing receptors CD62L and CCR7. These CCR7+/CD62L+ memory T cells were referred to as central memory (TCM) cells because they had lymph node–homing potential, longer telomeres, and produced substantial amounts of IL-2, but lower levels of effector cytokines (e.g., IL-4, IL-5, and IFN-γ) and cytotoxic molecules (e.g., perforin) in comparison with the CCR7+CD62L− memory T cells. As a consequence of their heightened effector functions, the CCR7−CD62L+ memory T cells were referred to as effector memory (TEM) cells. Whereas some of the TCM cells also expressed other chemokine receptors such as CXCR4 and CCR4, the TEM cells expressed larger amounts of CXCR3 and CCR5, presumably endowing them with greater potential to migrate into inflamed tissues. Subsequent work found that compared with TEM cells, TCM cells have an increased proliferative capacity in response to Ag and ability to self-renew (i.e., homeostatically proliferate) in response to IL-15 and IL-7 (3–5), suggesting that the less differentiated TCM cells contain more stem-like qualities that enhance their longevity and maintenance of memory T cell pools.

Two years later, two separate studies on memory CD8+ and CD4+ T cells, by the laboratories of Drs. Leo Lefrançois and Marc Jenkins, respectively, provided further evidence that functionally and anatomically distinct memory T cell subsets exist following infection or immunization.

Masopust et al. (2) demonstrated that following systemic vesicular stomatitis virus or oral Listeria infection in mice, Ag-specific memory CD8+ T cells could be found in virtually every tissue analyzed and that their frequencies in nonlymphoid tissues (such as kidney, intestine, liver, lung, and fat pad) tended to be higher than those in lymphoid tissues. Although there was no significant difference in the ability of the memory CD8+ T cells to produce IFN-γ based on their tissue residence, the memory T cells located in nonlymphoid tissues had more immediate and robust cytotoxic activity compared with those in the spleen. These results indicated that memory T cells residing in peripheral tissues had stronger “killer instincts” than those located in secondary lymphoid organs, and directly supported the finding of Sallusto et al. (1) that TCM cells, which lacked lymph node–homing receptors, expressed more perforin than did TEM cells.

Similarly, Reinhardt et al. (6) found that systemic injection of OVA peptide plus LPS into mice containing OT-II CD4+ T cells resulted in memory OT-II T cells localized to both lymphoid and nonlymphoid tissues. These data were visually stunning as the authors used whole-body imaging to track the locations of Ag-specific CD4+ T cells in situ. Moreover, similar to those observed in the blood of humans, the memory OT-II CD4+ T cells in the nonlymphoid tissues, such as the lung, produced more IFN-γ relative to IL-2 than did the cells in secondary lymphoid organs. Taken together, these three studies founded the notion that a division of labor exists among functionally and anatomically distinct memory T cell subsets.

More importantly, however, these studies provided a new vision for how memory T cell responses could be organized into different modules during a secondary infection. The underlying hypothesis quickly became that TEM cells could provide the first line of attack with immediate effector functions at peripheral sites of infection and the TCM cells, displaying a greater capacity to proliferate and produce IL-2, could provide a second line of defense by producing secondary effector cells to bolster the ongoing attack (4, 7–9). In this light, the division of labor among the various memory T cell subsets mirrored the conventional distinction of the fast-acting “innate” and reinforcing...
“adaptive” immune responses. As conceptually appealing as this model stands, it has been more difficult to ascertain experimentally because the results of experiments comparing the protective qualities of T EM and T CM cells have been mixed (3, 5, 10–13). The differences between these studies may reflect greater heterogeneity that actually exists in these memory T cell populations or complications associated with adoptive cell transfers. Alternatively, the differences may reveal that the type of protection afforded by particular subsets of memory T cells may depend on the route of infection, pathogen dose, or tropism, in which case, identifying these features becomes relevant for vaccine development. However, coming back to the tiered and overlapping layers of defense that have evolved in our immune system, it is unlikely that optimal protection to particular pathogens will depend on just one type of memory T cell population or another. Rather, the different memory T cell populations likely function cooperatively with one another and, hence, developing and sustaining phenotypically diverse populations of long-lived memory T cells may be most ideal for host defense.

Since the phenotypic sampling of memory T cells by Sallusto et al. 15 y ago, the field has celebrated the profound diversity of memory T cells. With the technological advances in multiparameter flow cytometry, the expression patterns of numerous proteins and transcription factors in effector and memory T cells have revealed that these populations are highly heterogeneous, more so than perhaps we will ever fully comprehend, containing dozens of additional subsets (14–21). This work has greatly enhanced our knowledge of how various cytokines, signals, and transcription factors regulate the formation of T EM and T CM cells. Moreover, we have greatly refined our ability to distinguish different subsets of effector CD4+ T cells (e.g., Th1, Th2, Th17, and T follicular helper cells) (19, 20, 22, 23) and CD8+ T cells (e.g., terminal effector and memory precursor cells) (16, 24, 25) that give rise to different types of memory CD4+ and CD8+ T cells. Although this work illustrates that the division of labor and long-term cell fates of various effector and memory T cell subsets are certainly more complex than originally put forth, one cannot underestimate the utility of the simple, yet elegant, T EM/T CM conceptual paradigm. Not only has it placed functional value on distinguishing different types of memory T cells that reside in different locations, but it also provided new nomenclature that fostered communication of our ideas and results. Indeed, the recent recognition of tissue-resident memory T cells (T RE) (26–29), which can be distinguished apart from circulating T EM and T CM cells at mucosal borders and appear to operate as sentinel cells at the portals of pathogen entry, has advanced considerably in part because the T CM/T EM paradigm was already established to allow further functional and anatomical refinement of memory T cell populations. As vaccine studies progress, particularly for HIV, malaria, and tuberculosis, the T EM/T CM/T RE memory T cell paradigm will help investigators in their search for correlates of protection mediated by memory T cells. Additionally, as more is learned about the signals that induce the development of different types of memory T cells, new methods may arise for enhancing or tailoring the types of memory T cells generated during vaccination. Likely, we have not yet realized the full impact of these original findings.

Lastly, one cannot discuss the topic of memory T cells without feeling the great loss of Dr. Leo Lefrançois and recognizing his numerous contributions to the field. He was a pioneer and pillar of our immunological community, and his passion for elucidating how T cells form and function in different anatomical compartments has been pivotal to our understanding of host defense. For me personally, he was a welcoming colleague and neighbor when I started my laboratory just a few miles down the road from his. His fun-loving outlook on life and science was inspirational to me. It is a great honor to recognize his work as a Pillar of Immunology article and to help pass on Leo’s legacy to the newer generations of immunologists as we teach them about his discoveries, many of which are already considered “textbook.”

Disclosures
The author has no financial conflicts of interest.

References


