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Grand challenges in immunological memory

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The development of immune memory, in response to primary infections with pathogens and to vaccination, is the basis of acquired immunity that protects the individual as well as the population from infection, morbidity, and mortality. Effective immunological memory that includes a faster and bigger response by antigen-specific B and T cells, is the key weapon we have to protect us from recurrent infection with a vast array of deadly pathogens. Yet we know much less about the formation, maintenance, and regulation of T and B memory cells than we do about the primary response of naïve lymphocytes, which is more easily analyzed. We believe that there are additional qualitative differences between memory and naïve lymphocyte responses to be defined soon.

Because immune systems are critical to the survival of all animals, they have co-evolved with pathogens and I believe we are only now starting to appreciate the amazing sophistication and dazzling complexity that memory lymphocytes and also innate cells display. For instance over the last few years it has become clear that T cells can be subdivided into considerably more functional subsets than previously thought. There are of course the subsets defined by cytokine profile and determined by initial exposure to polarizing cytokines. These include Th1, Th2, and Treg cells and more recently Th17 cells of the CD4 lineage, with comparable subsets among CD8 T cells and hints of related B cell subsets and there may be additional cytokine-determined lineages that have not yet been appreciated. But this is only part of the story. Most of the cytokine polarization is achieved during the initial naïve lymphocyte response, but subsequent interactions lead to further specialization, with both the location and type of APC providing further differentiation signals. As an example interaction with B cell APC in follicular sites can drive T cells to become follicular helpers (T_{FH}). In addition it is clear that effectors of the varied subsets described above can individually become terminally differentiated or senescent or can differentiate into both central and effector memory cells. These multiple fates seem to occur concurrently generating further diversity. This multidimensional variation of T cells raises many questions about memory that will be fertile ground for new experimentation and should yield many new insights. Defining memory cells becomes a more complex task as we appreciate the increased range of functional activities that have been and will be identified as characteristics of immune memory.

One key area where we can expect progress in the next few years is in the understanding of the molecular pathways that induce lymphocytes and innate cells of different subsets, and a definition of factors regulating those pathways. These will begin to help us understand how the immune system ensures the concurrent generation of a broad range of effector subsets, but also a tailoring of their distribution to suit the pathogen.

We have much to learn about the nature of the pool of memory cells. First we need to know whether all effector subsets develop a memory counterpart? If so which traits of effector subsets are stable and determined by epigenetic modifications that are passed down to subsequent generations of effector and memory cells? We want to know whether the rules for each subset transitioning to a memory stage are the same and how the rules determine memory? For instance does the apparent different susceptibility to death, shape the make-up of the memory pool? Do the same survival factors support each subset into memory and provide maintenance of the population? What cells in what locations make the factors that regulate memory cell homeostasis and how does location regulate memory? Is the lifespan of all long-lived memory cell subsets the same? Does each of the subsets make short and long-lived memory? Do most or all subsets co-exist once they are in a memory state or can they cross-regulate each other? Determining how each of these impacts the effect of vaccination on future protective immunity will indeed be a challenge!

Another relatively unexplored area relates to the fact that animals are repeatedly exposed to most pathogens, with consequences for memory cells and the pool of memory that are little understood. How does each round of recall responses influence the memory cells that persist? How are naïve responses and generation of new memory cells impacted? Are the properties of secondary, tertiary, etc., memory the same or distinct? If the latter, do they change in a predictable way and what regulates this? How much does previous history of exposure lead to cross-reactions that alter the change or make-up of the response? In particular, what influence does on ongoing secondary response have on a primary response to the same and to different pathogens? How do pathogen-specific factors influence all these processes? Since humans and laboratory mice differ so greatly in their history of exposure, how can we translate the results from studies in the mouse to humans? How much do they differ? Finally how do different host environments that exist because of age or other factors such as metabolic state, inflammation, etc., influence memory T cell generation and maintenance?

This short list of just a few of the questions that come to mind, reveals the need for a forum such as *Frontiers in Immunological Memory*. I hope *Frontiers* will serve as a vehicle for discussion and opinion articles and attempts to synthesize and debate current observations in addition to publishing new original research. It can also be a place where new, well-supported but nonetheless phenomenological findings in areas that are not yet "mature" enough for the definition of molecular pathways, can be made available to point the future experimental endeavors in the right direction. In summary I think the field of immunological memory has the potential to blossom tremendously over the next decade and I think that with the help of my superb Associate Editors and a panel of excellent Review editors, we can foster the publication and integration of new findings that will help this to occur.

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