The persistence of memory: A unique niche for IgG memory B cells

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The concept of immunologic memory has been documented since ancient times. Indeed, in 450 BC, the Greek historian Thucydides observed that those who had survived a disease were most apt to visit the newly stricken, because “[they] knew it was from experience, and had now no fear for themselves, for the same man was never attacked twice.” Despite this long-standing appreciation, the mechanisms responsible for immunologic memory have proven elusive. This is particularly true for the mediators of humoral immunity, B lymphocytes.

Germinal Centers Generate IgG Memory B Cells

Within the prevailing paradigm of clonal selection, antigen-specific B-cell clones within preimmune pools expand and differentiate to generate memory B cells after occupation of their IgM antigen receptors. However, in even the most exuberant humoral immune responses, the activated B-cell clones represent a small proportion of total B cells. Consequently, both during activation and as the response wanes, the exact sources, identity, and anatomic localization of memory B cells are increasingly difficult to trace. Accordingly, fundamental questions about the nature and positioning of memory B cells remain. For example, do memory B cells preferentially occupy particular anatomic sites, and do these localization properties influence their behavior on subsequent antigen challenges? Moreover, what underlies the relatively rapid kinetics of memory antibody responses: are memory B-cell activation requisites less stringent than those of primary B cells or are they uniquely positioned to respond more swiftly than their preimmune counterparts? In PNAS, Aiba et al. (1) use powerful *in vivo* tools to provide several important clues for solving these puzzles.

Although some level of immunologic memory can be derived from expanded primary clones, whose affinity for antigen and IgM heavy-chain characteristics remain unchanged, strong protective humoral immunity originates from germinal centers (GCs). These characteristic structures wax and wane during the 3- to 4-wk duration of an immune response and are initiated through bidirectional communication between responding T and B cells

(2–4). Early in this scenario, antigens bound by the B cell's IgM receptors are ingested, degraded, and presented to CD4⁺ T cells. These, in turn, direct the further activation and differentiation of the B cell and in concert with activities of follicular dendritic cells, initiate the GC reaction. Within the GCs, rapidly dividing primary B cells continue to interact with T helper cells and follicular dendritic cells. These ongoing interactions foster the selection of B cells whose antibody products acquire higher antigen affinity through mutations introduced by the enzyme AICD. They also direct the genetic processes associated with class-switch recombination, whereby the genes used for the constant regions of the Ig

been activated. Importantly, using their cell-cycle-dependent fluorescent genetic constructs, they find that these IgG memory B cells proliferated on secondary antigen challenge.

Interestingly, these cells are found adjacent to CD4⁺ T cells, suggesting an organized niche in which antigen-experienced B cells may be positioned to rapidly engage in the interactions required to initiate responses on subsequent antigen challenges. Indeed, in a final series of experiments, the authors show that these IgG memory cells remain capable of antigen presentation and themselves depend on cognate interactions with helper T cells for their reactivation (1).

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heavy chain are changed from IgM to one of the IgG isotypes. An overall result of the GC reaction is, thus, the formation of memory B cells bearing these class-switched, high-affinity IgG receptors, which are believed to mediate the most efficacious protective humoral immunity.

A Splenic Niche for IgG Memory Cells

Aiba et al. (1) use a combination of sophisticated approaches to track memory B cells. Their primary observation is that, although IgM memory B cells were found scattered throughout the spleen—consistent with prior reports that some memory cells are recirculating—class-switched IgG memory B cells are sessile and preferentially localized to regions adjacent to vestigial splenic GC-like structures. In a powerful series of experiments, the authors use adoptive transfer of antigen-receptor transgenic B cells, coupled with a reversible fluorescent marker of cell-cycle activity, to identify these memory B cells. With this combined armamentarium, they are able to show that antigen-specific IgG memory cells are largely nondividing. Furthermore, they likely represent somatically mutated, affinity matured cells, because an inducible marker linked to AICD expression had

Implications and Questions

These findings *in toto* are important from several standpoints and raise several additional intriguing mechanistic and conceptual questions. Foremost, they identify a previously unappreciated anatomic niche for class-switched high-affinity memory B cells. The apparent predilection of IgG memory cells to form these structures suggests that they differ fundamentally from IgM memory cells in their homing and lodging characteristics. This observation strengthens the emerging notion that multiple memory B-cell subsets with different functional properties exist (5). Accordingly, determining the genetic program that underlies these unique functional properties as well as the timing and signaling involved in initiating a particular memory subset program should afford both basic and translational insights.

It is likely that additional structural aspects of this niche are important to understanding memory responses. For example, further investigation of the adjacent T cells is particularly alluring. Although most of these T cells lack Programmed Death Ligand-1, a marker of the activated T-cell subset that populates GCs, it is tempting to speculate that they are, nonetheless, antigen-specific memory T cells. If so, these peri-GC memory niches may provide a focus of organization that enables

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appropriate interactions on subsequent antigen exposure. This is particularly attractive given the finding that the IgG memory cells both present antigen and continue to require cognate help for their activation. Indeed, squaring the rapid kinetics of memory responses with a cognate-help requirement has been difficult, because if the cells continued to recirculate as primary cells, interactions between antigen-specific memory T- and B-cell clones would be relatively rare, predicting kinetics similar to primary responses. In contrast, if cells of appropriate specificity remain sessile and juxtaposed, these events will occur nearly simultaneously with the introduction of antigen, thus reconciling this conundrum. In a similar vein, these structures may be positioned in a manner that affords earlier or more effective antigen capture, further enhancing their ability to mount exceptionally rapid responses on rechallenge. The purposeful trafficking of antigen in secondary lymphoid structures is only now becoming fully appreciated, and ad-

ressing this in the context of these IgG memory B cell structures may prove fruitful.

Another outcome of segregating IgG memory B cells with their associated CD4 T cells may guarantee that GCs formed in secondary responses are predestined to be populated by B cells that have already undergone affinity maturation. This might avoid the relatively redundant exercise of recruiting cells with a broad range of affinities and repeating a protracted competitive affinity maturation process—perhaps allowing a nearly immediate wave of long-lived plasma-cell formation. Indeed, secondary responses are known for their great expansion of affinity-matured antigen-specific plasma-cell pools.

Finally, it will be of substantial conceptual importance to understand how these niches are maintained. Memory cells by definition are exceptionally long lived compared with preimmune naïve B cells. How memory cells are freed of competition with their primary counterparts has proven a difficult question. However, the estab-

lishment of specialized niches may in itself allow supporting stromal interactions that can sustain these cells in a quiescent state indefinitely. Determining the survival requirements of these cells and the means through which these are supplied within the peri-GC niches will thus be important. In this regard, it is enticing to imagine that the IgG memory B cells may themselves engender formation of these structures. In this case, unlike primary cells that are subject to exogenous homeostatic controls to determine their longevity, these highly selected antigen-experienced cells may instead instruct the establishment and maintenance of their own niche. This implies an essentially open-ended increase in these structures based on continuing antigenic experiences and raises the question as to whether such self-promoting properties extend to other antigen-experienced niches, such as those for central memory T cells and long-lived plasma cells.

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