COMMENTARY

Redemption of autoreactive B cells

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Autoreactive antibodies can be pathogenic in a myriad of diseases. Consequently, the adaptive immune system actively removes or inactivates self-reactive B cells, while promoting the survival of B cells that recognize exogenous antigens, including microbial pathogens (1, 2). These physiological mechanisms of immune tolerance are often defective in autoimmune diseases (3, 4), and much effort is currently being expended learning how to mitigate autoreactive B-cell responses in the setting of autoimmune diseases. An unwelcome consequence of tolerizing selection is reduction in the potential diversity of the primary B-cell repertoire that limits the availability of B cells capable

of generating protective responses against pathogens (5). An example of immunological censoring by tolerance is apparent in the protective antibodies elicited by HIV-1 infection, called broadly reactive neutralizing antibodies (bnAbs) (6). The majority of bnAbs are either polyreactive (reactive with many unrelated molecules), autoreactive (reactive with one specific self-antigen), or both (7), and in some cases, reactivity with host antigens is tightly linked to HIV-1–neutralizing activity (8, 9). Thus, in contrast to autoimmunity where the goal is to reduce autoreactive B-cell responses, vaccinologists are trying to activate and expand disfavored bnAb B-cell clonal

lineages subject to control by immune tolerance (6–13).

In PNAS, Sabouri et al. (14) outline a surprising pathway for the utilization or "redemption" of autoreactive anergic B cells. The authors demonstrate that B cells that recognize both foreign and self-antigens can be activated by immunization and recruited into germinal centers (GC) where hypermutation of the B-cell antigen receptor (BCR) can reduce self-reactivity while maintaining the capacity of the redeemed B cells to recognize an exogenous antigen (14).

This is a surprising finding, not only because anergic B cells are refractory to most activating stimuli (1, 15, 16), but also because this finding emphasizes the poorly understood capacity of GC to select BCR mutants with lowered affinity for abundant, soluble antigen (17). Anergic B cells, it now seems, are capable of making substantial contributions to humoral immunity. An important and exciting corollary of this work is the potential elucidation of novel cellular pathways for vaccines to target anergic B cells for the induction of antibody to microbial epitopes that mimic host antigens (e.g., HIV-1 bnAbs).

B cells develop from progenitors that generate functional BCR by genomic rearrangements of V (variable), D (diversity), and J (joining) gene segments (18). This process results in a highly diverse set of BCR capable of reacting with virtually any antigen but also produces autoreactive B cells (19, 20). Indeed, some 70% of newly generated ("late pre-B") human BCR are autoreactive (19, 21); the majority of these self-reactive BCR are eliminated or inactivated by immune tolerance mechanisms (19), including the induction of anergy or B-cell unresponsiveness (16, 22–24).

In GC, antigen-specific B cells recruited to follicular dendritic cells respond to follicular dendritic cell-associated antigen by proliferation and the accumulation of V(D)J mutations introduced by activation-induced cytidine deaminase. GC mutant B cells are selected for increasing BCR affinity to antigen in a Darwinian process mediated by competition
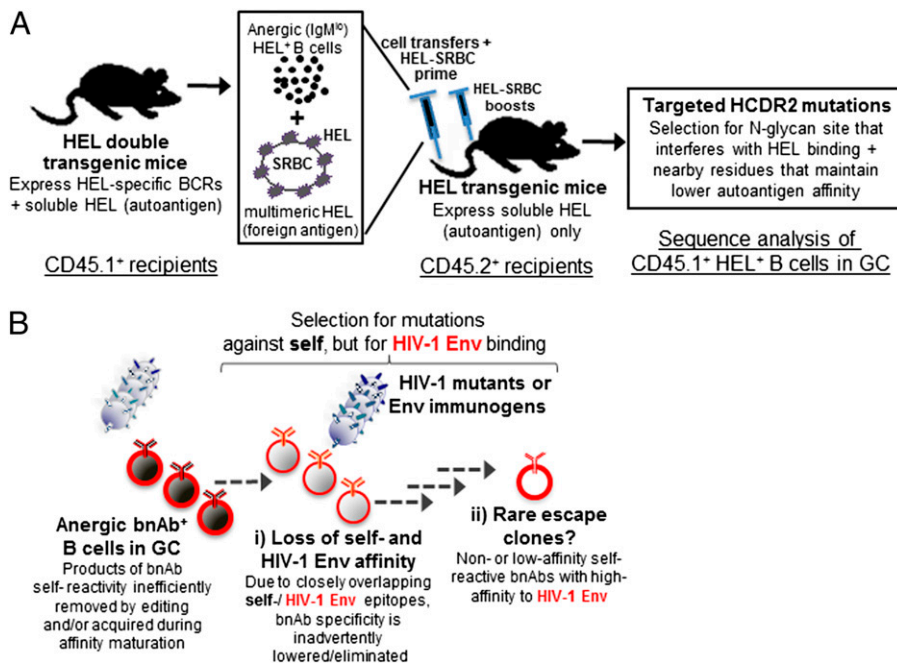

Fig. 1. Experimental demonstration of autoantibody redemption in the HEL transgenic mouse system. (A) The immunization schema that allowed detection of rescued anergic autoreactive B cells following HEL-RBC immunization. HEL-specific B cells from double-transgenic mice, rendered anergic because of their prior encounter with soluble-expressed HEL, were injected into HEL transgenic mice, together with a HEL-SRBC immunogen. Immunized mice driven to generate anergic HEL-specific GC B cells were induced to acquire mutations in the HEL antibody HCDR2 region that resulted in decreased affinity for HEL and increased B-cell survival. (B) An illustration of how such a mechanism may contribute to bnAb responses during HIV-1 infection, and how B-cell populations generated by this process could be harnessed in the setting of HIV-1 vaccination. Vaccination with HIV-1 Env may result in either a population of anergic GC B cells, which have accumulated somatic mutations that generate bnAb specifcity (red) and self-reactivity (black), but may also generate rare B cells with BCR that harbor decreased self-reactivity, while retaining bnAb HIV-1 Env affinity. The hypothesis is that Env vaccination targeted at disfavored bnAb B-cell clonal lineages could drive otherwise unfavored and rare HIV-1–specific B-cell clones in GC to survive and proliferate.

for T-follicular helper cell (T$_{FH}$) survival/proliferation signals (2). Dominance and persistence of GC B-cell clonal lineages is determined by mutant BCR avidity, but these mutations also generate BCR with affinity for self-antigens (25, 26). For this reason, it has long been thought that the GC should be capable of tolerizing autoreactive mutants that arise during affinity maturation (17, 27).

Although the mechanisms that ensure self-tolerance in GC are not well understood, the work of Sabouri et al. (14) calls attention to the potential of V(D)J hypermutation not only to generate autoreactivity but also to silence it, and to redeem autoreactive B cells. Sabouri et al. infer clonal redemption by the analysis of BCR mutations in human B cells that abrogate the intrinsic autoreactivity of VDJ rearrangements containing the IGHV4-34*01 gene segment (28), and by study of transgenic mice that constitutively express soluble hen egg lysozyme (HEL) and the high affinity, HEL-specific Hy10 BCR. In the latter model, mutations in the VH gene segment were found to suppress binding to an HEL self-epitope and, in contrast to experiments demonstrating apoptosis by Hy10 GC B-cell exposed to soluble HEL (27), Sabouri et al. (14) demonstrate that a subset of HEL-reactive Hy10 GC B cells do not die, but proliferate and diversify following immunization with HEL. This expansion of Hy10 B cells depends on mutations in the complementarity determining regions of the Hy10 heavy chain (HCDR2) that lower affinity for HEL (14).

These HCDR2 mutations relax the autoreactivity of Hy10 B cells but not the ability to respond to exogenous antigen ligands, leading to their "redemption" (14). Paradoxically, anergic B cells are able to generate more progeny in GC than do nonanergic, naïve B cells (14), an observation seemingly in tension with previous studies (27, 29) but consistent with reports indicating that GC B cells loaded with antigen expand extensively in the GC dark zone (23, 30). These findings are of interest for those trying to develop vaccines against pathogens bearing neutralizing epitopes that cross-react with self, with HIV-1 as a prominent example (6, 10, 12). Only a subset of HIV-1–infected individuals (~20%) make high levels of HIV-1 bnAbs, and Env vaccination does not induce bnAbs. Knock-in mice that express bnAb BCR exhibit blockade of B-cell development at the first tolerance checkpoint with deletion of >90% of B cells; however, deletion is not complete, with a minority of anergic bnAb B cells

surviving (11, 12, 31). These anergic bnAb B cells can be triggered by vaccine antigens to generate high titers of bnAb and, similar to the findings of Sabouri et al. (14), a fraction of bnAb B cells acquired T-cell–dependent BCR mutations that decreased both

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autoreactivity and binding to the HIV-1 Env, a process termed affinity reversion (Fig. 1) (12, 32). The similarities and differences between autoantibody redemption and affinity reversion merit additional investigation.

Finally, the important findings of Sabouri et al. (14) raise significant questions. Is the

phenomenon of autoantibody redemption generalizable to naturally found human autoantigens to impact microbe vaccine development? To what degree is autoantibody redemption able to patch "holes" in the primary BCR repertoire created by immune tolerance? Can vaccination strategies be devised to harness autoantibody redemption to drive the expansion and persistence of normally disfavored, autoreactive B cells with BCR that recognize microbes? Answers to these questions will be crucial to understanding how microbial pathogens avoid robust immunity and to defining the role of BCR mutation in controlling pathogenic B cells in autoimmune diseases.

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