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Persistence of exhaustion in cured hep C

David E. Kaplan UNIVERSITY OF PENNSYLVANIA; CORPORAL MICHAEL J. CRESCENZ VA MEDICAL CENTER

In this issue of *Blood*, Del Padre et al[1] evaluated the impact of eliminating chronic antigen exposure on B-cell exhaustion in the human therapeutic setting of direct-acting antiviral therapy for chronic hepatitis C virus infection (HCV) complicated by mixed cryoglobulinemia (MC). The phenotype of hepatitis C–related MC B cells has been previously demonstrated by this group and others[2] to include low-level CD21 expression ($CD21^{low}$) and hypoproliferation in response to stimulation either through the B-cell receptor or Toll-like receptor 9, imperfectly termed "exhausted" or "anergic." At baseline, $CD21^{low}$ B cells from HCV-infected patients expressed markers of chronic activation, with elevated and near-maximal basal levels of phosphorylated extracellular signal–regulated kinase, and were also predisposed to apoptosis. During oral direct-acting antiviral therapy, the authors observed that by 4 weeks (at which point, most patients have no circulating HCV RNA), these basal abnormalities at least partially normalized. During longitudinal follow-up after patients were documented as cured, the overall frequency of $CD21^{low}$ cells progressively declined from 50% to 30% of circulating B cells. However, the frequency of $V_H1\text{-}69^+$ B cells specific for HCV-related MC generally remained stable, although some regained CD21 expression. Despite partial resolution of the exhaustion phenotype, surviving $V_H1\text{-}69^+$ B cells remained hypoproliferative upon Toll-like receptor 9 ligation, suggesting that the B-cell exhaustion phenotype is durably programmed into antigen-specific B cells during long-term extracellular antigen exposure.

Mixed cryoglobulinemia is one of several B-cell proliferative disorders that may result from chronic hepatitis C infection, and it is thought to be driven by expansion of HCV envelope-specific B cells that preferentially use immunoglobulin gene segments $V_H1\text{-}69$ and $V_k3\text{-}20$,[3] and to evolve rheumatoid factor activity through somatic hypermutation.[4] Although MC is an infrequent complication of chronic hepatitis C infection, the technological ability to identify and isolate HCV-specific B cells via an anti-idiotype $V_H1\text{-}69$–specific antibody (G6) has made this condition an important model for studying humoral immune dysfunction during human chronic viral infection. Prior studies have identified that $V_H1\text{-}69^+$ B cells manifest genetic signatures of enhanced interferon-mediated responsiveness, apoptosis, and B-cell anergy; are phenotypically most commonly $CD27^+/IgM^+/CD11c^+/CD21^{low}$; are prone to apoptosis; and are hyporesponsive to B-cell receptor crosslinking.[2,5]

B-cell anergy, an adaptive response to chronic antigen exposure for autoreactive B cells, has been postulated to be a vulnerability exploited by pathogens to evade humoral sterilization and enhance permissiveness for chronic bloodborne infections. Recent data suggest that the T-box expressed in T cells (T-bet) transcription factor, critical for inducing sterilizing humoral immunity in acute infections,[6] may also regulate the exhausted state in both autoreactive[7] and antigen-induced anergic B cells.[8,9] No data to date specifically link the anergy properties observed in cryoglobulin-producing B cells and T-bet, but there are phenotypic similarities ($CD11c^+/CD21^{low}$) that suggest a possible relationship that should be explored; rapid upregulation of T-bet in convalescent $CD21^{low}$ B cells upon reexposure to autologous HCV strains ex vivo has been observed,[8] suggesting a link between B-cell receptor ligation, T-bet, and the $CD21^{low}$ exhaustion phenotype.

How are these data clinically relevant? The persistence of $V_H1\text{-}69$ B cells after sustained virological response clearly explains the persistence of symptomatic cryoglobulinemic vasculitis observed in some HCV-cured patients.[10] However, these data may have broader implications on the early and late immunopathogenesis of chronic infection. That antigen-specific B-cell anergy is durably programmed suggests that B-cell exhaustion might rapidly redevelop in the setting of reinfection, potentially contributing to the lack of protective immunity observed in many resolved chronic infections. The current study creates the context for further exploration of the mechanisms associated with induction of B-cell exhaustion in vivo. Once the regulation of B-cell anergy in chronic infection is better understood, therapeutic manipulation could significantly affect the outcomes not only of chronic hepatitis C, but also of other chronic viral and parasitic infections.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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