Understanding humoral responses to hepatitis C virus (HCV) has proven extremely difficult and B cells have generally been neglected because they do not seem to significantly influence the course and outcome of HCV infection. Despite almost all infected patients are positive for virus-specific antibodies, approximately 80% of these individuals develop chronic and often progressive disease, whose major long-term complications are cirrhosis, end-stage liver disease, and hepatocellular carcinoma (1,2). Mixed cryoglobulinemia (MC) and B cell non-Hodgkin lymphoma (B-NHL) may also occur and often dominate the clinical picture of chronic HCV infection (3). It is then assumed that B cells are basically inefficient in resolving HCV infection while they are responsible for its lymphoproliferative complications.

MC is a chronic immune complex mediated vasculitis with underlying B cell clonal proliferation that occurs in 10–15% of HCV-infected patients (3). MC immune complexes, which contain monoclonal IgM rheumatoid factor (RF), polyclonal IgG, and viral RNA, deposit in small-to-medium vessel walls causing an inflammatory reaction that can lead to skin lesions, peripheral neuropathy, and renal damage (3,4). IgM RF isolated from unrelated individuals typically display cross-reactive idiotypes, suggesting a high grade of conservation of their germline genes (4). Polyclonal IgG are directed to HCV antigens, binding predominantly core protein (3,4). B-NHL may develop in HCV-infected individuals with or without a history of MC (5) and may include three principal histologic types: lymphoplasmacytic, marginal zone, and diffuse large B cell lymphoma (6). The overall prevalence of HCV infection in patients with B-NHL is roughly 15%, higher than that reported in the general population and in patients with other hematologic malignancies (7). In our own experience, the rate of B-NHL was 1% in HCV-infected patients with and 6.2% in those without MC (P=0.003), after a 10-year follow-up (3). Successful antiviral therapy may not only prevent lymphoma development (8) but also result in its complete regression (5), thus strengthening the etiological link between HCV and lymphoproliferative disorders.

HCV-associated B cell proliferation most likely represents a continuum from the relatively benign clonal B cell expansion of MC to overt NHL. Clonal B cells are predominantly IgM RF-bearing cells with a stereotyped B cell receptor (BCR) commonly encoded by rearranged VH1-69 and Vκ3-20 variable region genes (9-14) in both MC and B-NHL, supporting the hypothesis that B cell clones are selected by a limited number of antigens. Unfortunately, these antigens have not been identified so far and the mechanisms by which HCV drives abnormal B cell expansion remain puzzling. A direct transforming role of the virus appears unlikely, considering that B cells are not direct targets for productive virus replication and that viral RNA sequences cannot be integrated in the host genome. Indeed, B cells do not express the full set of known factors that are essential for HCV entry into hepatocytes (15-17) and neither cell culture-produced genotype 2a HCV, nor pseudoparticles containing functional E1/E2 HCV envelope glycoprotein complexes of different genotypes, can infect primary B cells or B cell lines (17,18). Moreover, level of
HCV RNA associated with lymphocytes from patients’ blood samples is very small and far below one copy per cell (19-22), demonstrating that replication is inefficient in human lymphocytes. Activation of B cells via engagement of CD81 by HCV E2 protein has also been proposed (23), but it is in conflict with the observation that activated B cells in MC are not polyclonal (9-14) and that complete circulating lipoviral particles are not able to stimulate the activation described in vitro with high concentrations of recombinant E2 (16).

Tucci et al. (24) provide insight into the BCR gene repertoire and clonality of B cells in HCV-infected patients without MC. They found increased frequency of class-switched memory B cells and decreased frequency of transitional and naïve B cells in these patients compared to healthy subjects. By performing high throughput sequencing of Ig heavy chain (IGHV) VDJ rearrangements, the authors reveal a preferred usage of some IGHV genes, such as IGHV1-69 and IGHV4-59, in IgM+CD27 non-class-switched memory B cells. Within this B cell compartment, they also found large expanded clones, many of whom displayed intra-clonal diversity. This characteristic is indeed an indicator of antibody diversification and affinity maturation occurred in germinal centers, where proliferating B cell clones undergo somatic hypermutation.

The findings add a new piece of information to B cell biology during HCV infection. They are reminiscent of those observed by our group in subjects who had spontaneously resolved an HCV infection (25,26). Few months after viral clearance, CD27+ memory B cells from these subjects showed a preferential occurrence of specific VDJ elements, thus suggesting that B cell clones that were possibly implicated in the virus eradication were also those prone to aberrant proliferation. It is also interesting to note that in a small fraction of patients, clinical and immunological features of MC vasculitis persist in spite of direct-acting antiviral-induced HCV clearance. Lack of removal of RF from serum after HCV eradication has been found to be associated with a delay in the restoration of normal B cell subset representation, but the precise mechanisms underlying these virus-cleared vasculitides remains to be elucidated (27). Work is ongoing to test viral and self-antigens, along with host genetic factors, in experimental systems mimicking HCV-associated B cell activation.

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Footnote

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References


