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HEPATITIS C VIRUS INFECTION, IgM MONOCLONAL GAMMOPATHY AND WALDENSTRÖM'S MACROGLOBULINEMIA

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The relevance of viral infection to the pathogenesis of Waldenström's macroglobulinemia (WM) remains to be established. Infection with hepatitis C virus (HCV) has been strongly suggested to play a primary role in mixed cryoglobulinemia, a lymphoproliferative disorder characterized by bone marrow multifocal lymphoid infiltrates of oligo or/and monoclonal B cells. These findings have triggered the search for a link between HCV and malignant lymphoproliferation, including non-Hodgkin's lymphoma and WM. A key consideration in HCV pathobiology is that antigen-activated B cells undergo massive clonal expansion. Interestingly, a disproportionate distribution of expanded B cell clones is found in different biologic compartments, suggesting that IgH VDJ mutational activity is differentially regulated. The over-representation of B cell clonal expansions in the liver strongly emphasizes that microenvironment factors play a major role in their emergence and persistence. Though the basic processes of Ig V gene recombination are mostly thought to take place in the bone marrow, there is evidence that immature B cells outside the bone marrow retain recombination gene activating activity. It was recently reported that specific B cell clonotypes in HCV chronic carriers are mainly located in the portal tracts of liver tissue. Though the highly diverse CDRH3 sequences of B cell clonalities suggest that they are the result of an antigen-driven response, identity of the antigen(s) is unknown. It can be speculated that both selection and expansion of B cell clonotypes are the result of an increased affinity process following VDJ rearrangements with functional substitutions in CDRH3 region. It can be suggested that HCV induces a "mutator" phenotype and activates the machinery of somatic hypermutation in B cells, possibly by inducing error-prone DNA polymerases and by activation-induced cytidine deaminase. Somatic hypermutation introduces point-missense mutations in immunoglobulin V genes and their flanking regions. This step precedes the positive selection of B cells expressing a receptor with high affinity for an antigen. This raises the possibility that B cells proliferate and undergo active somatic hypermutation outside the germinal centers. Many IgM-expressing B cells located in secondary lymphoid tissues resemble IgM-expressing memory cells which are likely to represent the non-malignant counterpart of IgM-expressing tumor cells. A role for HCV in transforming IgM-expressing cells may be proposed.