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ANTIVIRAL IMMUNITY

A 'mature' way of controlling HBV

Successful immunity to hepatitis B virus (HBV) infection depends on age: in most cases, the infection of adults results in viral clearance — which depends on a potent, diverse adaptive immune response — but in infants the virus usually persists. Publicover *et al.* now show that lymphocyte organization and immune priming in the liver, which are influenced by the age-dependent production of CXC-chemokine ligand 13 (CXCL13) by hepatic macrophages, contribute to HBV clearance in adults.

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This group previously developed a transgenic mouse model of HBV infection that mimics key aspects of human HBV clearance or persistence. This model involves the expression of HBV transgenes that encode HBV antigens or intact virus in the livers of mice lacking an adaptive immune system. The transfer of wild-type adult immune cells to adult transgenic mice results in an effective immune response and disease kinetics similar to those observed in humans who clear HBV infection. By contrast, the transfer of adult immune cells to young transgenic mice results in a restricted immune response and disease kinetics similar to those of infants who have persistent HBV infection.

Using this mouse model, the authors showed that priming of an effective HBV-specific adaptive immune response first occurs in the liver, followed by the lymph nodes and the spleen. Thus, is there a defect in priming in the liver of young mice that results in viral persistence? Hepatic clusters of macrophages, dendritic cells, B cells and T cells were shown to form in adult transgenic mice following immune cell transfer. By contrast, the number of such clusters was greatly reduced in the livers of young mice. These mice also had lower numbers of IgG^+ cells and IgG^+ clusters compared with adult mice, which suggests that there is reduced B cell differentiation and antibody class switching in the liver.

Macrophage depletion in adult transgenic mice using clodronate liposomes before immune cell transfer resulted in an altered hepatic lymphocyte organization that was similar to young mice. Furthermore, these adult mice did not develop a robust HBV-specific adaptive immune response. Hepatic macrophages from either transgenic or wild-type mice, but not macrophages from other tissues, were shown to increase their expression of CXCL13 with age. Adult recipients of immune cells that lacked the expression of the CXCL13 receptor, CXC-chemokine receptor 5 (CXCR5), developed an ineffective immune response to HBV, had fewer IgG^+ B cell clusters in the liver and had lower numbers of isotype-switched B cells compared with recipients of wild-type immune cells.

Finally, the authors showed that CXCL13 expression increases in an age-dependent manner in the human liver and is increased in the blood of adults who have cleared HBV infection.

Taken together, these data suggest that the age-dependent increase in CXCL13 production by hepatic macrophages contributes to the liver lymphocyte organization and the immune priming that facilitates effective immunity to HBV in adults.

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ORIGINAL RESEARCH PAPER Publicover, J. *et al.* Age-dependent hepatic lymphoid organization directs successful immunity to hepatitis B. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI68182 (2013)