ANTIVIRAL IMMUNITY

IL-21 comes with age

Depending on the age at which an individual becomes infected with human hepatitis B virus (HBV) there are two different immune response patterns. Infection during infancy often results in chronic disease, whereas infection during adulthood usually leads to an acute response and viral clearance. A recent study provides new insights into how age can influence the immune response to HBV infection.

Lymphopenic transgenic mice expressing the HBV envelope or the intact HBV virus in the liver (referred to here as HBV-transgenic mice) were used to model HBV infection at different ages. Adoptive transfer of adult naive splenocytes into these mice mimicked the initiation of a primary infection. This resulted in a potent inflammatory response in adult HBV-transgenic mice, but induced minimal hepatic inflammation in young HBV-transgenic mice, despite the fact that the HBV-dependent production of interleukin-12 (IL-12), interferon-γ (IFNγ) and IL-4 was comparable.

Similar to what has been described in humans, Publicover *et al.* showed that adult but not young HBV-transgenic mice expressed antibodies specific for HBV surface antigen and cleared HBV surface antigen from the circulation. Moreover, hepatic T cells from adult but not young HBV-transgenic mice generated potent and polyclonal immune responses against HBV. Thus, the authors concluded that some of the main components of acute and chronic HBV infection are reproduced in the HBV-transgenic mouse model.

So which parameters determine the effectiveness of the immune response in early or late HBV-infected individuals? To answer this, the authors analyzed the hepatic lymphocyte repertoire of early- and late-reconstituted HBV-transgenic mice. Interestingly, the numbers and proportions of $CD8^+$ T cells and T follicular helper (T_{FH}) cells were elevated in adult mice compared with young mice. Moreover, adult HBV-transgenic mice exhibited a significant increase in the number of IgG^+ plasma cells.

Finally, IL-21 — a T_{FH} cell-derived cytokine that helps plasma cell generation and antibody isotype switching, and promotes $CD8^+$ T cell expansion — was shown to be involved in acute but not chronic HBV-associated inflammation. IL-21 was expressed by liver-derived $CD4^+$ T cells (mainly hepatic T_{FH} cells) from adult HBV-transgenic mice, whereas it was not expressed by hepatic $CD4^+$ T cells from young HBV-transgenic mice. Furthermore, IL-21 receptor-deficient splenocytes mediated an impaired immune response to HBV in adult HBV-transgenic mice that resembled the response of young HBV-transgenic mice. In humans, IL-21 expression was found to be elevated during acute HBV infection but low in patients with chronic HBV infection, even during actively flaring disease.

Based on their findings, the authors suggest that ineffective hepatic T_{FH} cell priming during early HBV infection can lead to decreased IL-21 production and, thus, to the suboptimal B cell and $CD8^+$ T cell responses that are responsible for the viral persistence in chronic HBV infection.

Maria Papatriantafyllou

ORIGINAL RESEARCH PAPER Publicover, J. *et al.* IL-21 is pivotal in determining age-dependent effectiveness of immune responses in a mouse model of human hepatitis B. *J. Clin. Invest.* **121**, 1154–1162 (2011)