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Generation of polyfunctional T cells against HCV by T cell redirection and vaccination

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Abstract

The hepatitis C virus (HCV) is the major cause of liver disease and it is estimated that around 170 millions of people are infected worldwide. The available therapy is a combination of pegylated-interferon-alpha, ribavirin and since 2011, also NS3/4A protease inhibitors boceprevir and telaprevir. The standard treatment is associated with considerable side effects and does not cure all patients. Several vaccine candidates, prophylactic and therapeutic, are in the developing phase, but none of them so far have proven to be able to prevent or clear the HCV infection. Thus there is a vital need for an alternative approach for chronically infected HCV patients who do not respond to the standard treatment. Chronic HCV infection leads to severe liver inflammation and subsequent cirrhosis and hepatocarcinoma. T cell failure has been indicated as the main reason of viral persistence. On the contrary, an efficient T cell response has been suggested to hold the key to HCV resolution. In particular, antiviral T cells that are polyfunctional are associated with effective control of HCV replication. The present thesis investigated two different approaches to generate HCV-specific polyfunctional T cells and their potential to reduce HCV RNA+ hepatoma cells and to reduce HCV antigen+ tumor growth was assessed subsequently. Here the two approaches are based on the idea on T cell receptor (TCR) transfer that enables introduction of HCV-antigen specificity from one T cell to another, and DNA vaccination that is enhanced by electroporation. Paper I and II demonstrated that HCV NS3 (NS31073-1081) and NS5A (NS5A1992-2000)-specific TCR isolated from HLA-A2 transgenic mice can be transferred to human T cells. Such HCV-specific redirected human T cells demonstrate a different mechanism of action associated with their antigen specificity. NS3-specific TCRs were polyfunctional with potent lytic activity capable to eliminate human hepatoma HCV replicon cells replicating HCV subgenomic RNA, whilst the NS5A-specific TCRs instead ware mainly IFN-gamma producers and less cytolytic. This has an interesting implication as the latter may spare the host from unwanted cell injury during elimination of HCV-infected cells. Paper III explored the potential of the NS5A DNA vaccine used in paper II. This pre-clinical study showed that one single injection of the vaccine followed by electroporation could give rise to a polyfunctional T cell response in both wild-type and NS5A-transgenic mice, thought the latter group showed signs of tolerance. A series of truncated NS5A vaccine constructs revealed the locations of the protective antigen that gives the protective immunity. In this study, new murine MHC-I restricted CTL epitope were also identified, which enables immunological studies in HCV transgenic mouse models. These findings provide evidence that high-magnitude and high-quality T cell response able to assist the immune control of HCV can be engineered in vitro and by therapeutic vaccination. It has implications for development of HCV treatments for patients who cannot be cured by antiviral therapy. The TCR-reagents may also serve as tools to gain better understanding of HCV immunology.

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