LIVER TRANSPLANTATION

Immune responses to HCV infection linked to liver transplant tolerance

A new study has investigated the mechanisms involved in immune-mediated tolerance of liver transplant tissue in patients with chronic HCV infection undergoing immunosuppressant withdrawal. Tolerance was found to be associated with HCV-specific immune responses: the upregulation of type 1 interferon (IFN1) and IFN1 signalling pathways and increased numbers of exhausted CD8⁺ T cells. Furthermore, inflammation did not correlate with an inability to establish tolerance.

“The existence of liver recipients with persistent HCV infection who nevertheless develop operational tolerance challenges the notion that immunological memory and inflammation constitute major barriers for the achievement of allograft tolerance in the clinic,” comments corresponding author Alberto Sánchez-Fueyo.

The prospective, phase II, immunosuppressant withdrawal clinical trial included 34 patients with HCV infection, who received a liver transplant at least 3 years prior. Half of the patients developed operational tolerance, which was defined as stable liver function and biopsy results excluding subclinical rejection 12 months after immunosuppressant withdrawal.

Gene expression analysis of liver biopsy tissue identified a substantial increase in the expression of *IFN1* and *IFN1*-stimulated genes in allograft-tolerant patients (so-called tolerant patients) compared with nontolerant patients. Genetic alterations remained stable before and after immunosuppressant withdrawal.

In addition, tolerant patients had a greater number of exhausted CD8⁺ T cells than nontolerant patients during immunosuppressant withdrawal. T-cell exhaustion is a feature of chronic viral infections (positively correlating with *IFN1* expression) in which T-cell effector function is reduced and the expression of inhibitory receptors (which dampen T-cell responses) is increased. The authors hypothesize that HCV-induced IFN1 signalling enables viral immune evasion and establishes a “tolerogenic liver microenvironment” by promoting CD8⁺ T-cell exhaustion and inhibiting HCV-specific CD8⁺ T-cell function.

Intriguingly, the mechanisms by which HCV avoids immune surveillance, which seem to aid the development of graft tolerance, are distinct from the development of tolerance in uninfected patients who have received a liver transplant. The increased expression of immunoregulatory genes seen in HCV-positive tolerant patients was not found in HCV-negative tolerant patients. The genetic and lymphocyte profile of HCV-infected tolerant patients indicates that aspects of immune tolerance are unique to chronic HCV infection.

Whether the new generation of direct-acting antiviral agents will affect tolerance in the event of HCV elimination will be the focus of future studies for the group.

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Original article Bohne, F. *et al.* HCV-induced immune responses influence the development of operational tolerance after liver transplantation in humans. *Sci. Transl. Med.* 6, 242ra81 (2014)