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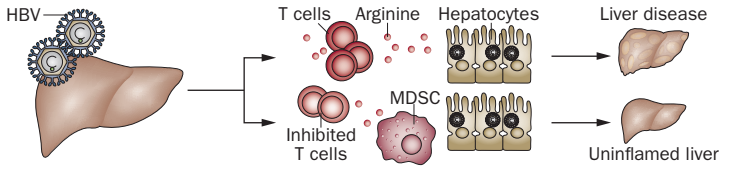
HEPATITIS

Myeloid-derived suppressor cells in HBV infection

New research published in *Nature Medicine* presents a mechanism involving myeloid-derived suppressor cells (MDSCs) that regulates liver immunopathology in HBV infection.

In hepatitis B, liver damage is not caused by the virus itself but by the immune response it elicits (active liver disease). However, in many cases the virus replicates for decades without triggering a cytopathic inflammatory reaction (immunotolerant phase). When analysing blood and liver samples from patients with chronic hepatitis B (CHB), Mala Maini and colleagues made a discovery that could explain these contrasting outcomes. "We were really struck by the finding that granulocytic MDSCs (gMDSCs) were only expanded in patients with replicating HBV without immunopathology [as opposed to patients with HBV and active liver disease]," notes Maini. "This gave us the first hint that they could be downmodulating inflammation in the liver of HBV-infected patients."

A dynamic change of gMDSC counts during varying disease activity was also evident: repeated sampling of patients in the acute stages of the infection showed a correlation between gMDSC frequency and viral load increases.



Arginine deprivation by gMDSCs inhibits T cells. Image produced in consultation with M. Maini.

Prior to hepatic flares, which are characterized by T-cell responses that damage surrounding tissue, the number of gMDSCs declined, whereas the count was highest during virus replication without liver damage. The authors postulate that the protective effect of gMDSCs might be the result of metabolic manipulation. They demonstrated that gMDSCs in CHB without immunopathology produce arginase-1, an enzyme that catabolizes L-arginine. T cells require this amino acid for normal function; a gMDSC-mediated decrease in L-arginine availability can therefore inhibit T-cell responses. Study results indicated that L-arginine serum levels were lower in patients with CHB without liver inflammation than healthy individuals. Also, gMDSCs suppressed HBV-related T-cell responses and proliferation when co-culturing them *in vitro*. L-arginine deprivation further induced the upregulation of L amino acid reporters in HBV-specific T cells isolated from the liver of individuals with CHB. This compensatory response to L-arginine starvation was reproduced *in vitro* and implies that T cells reprogramme their metabolic response.

"From a clinical standpoint, it will be important to investigate whether the regulation of immunity in HBV by gMDSC and/or arginine supply constitutes a tractable therapeutic target, particularly for younger patients in the immunotolerant, highly infectious phase who are not currently amenable to antiviral suppressive therapy," concludes Maini. The authors also plan to examine whether the immunosuppressive effect of MDSCs can be harnessed in other clinical settings, for example liver transplantation.

Christine Weber

Original article Pallett, L. J. *et al*. Metabolic regulation of hepatitis B immunopathology by myeloid-derived suppressor cells. *Nat. Med.* doi:10.1038/nm.3856