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VIRAL HEPATITIS

SUBINFECTIOUS HCV EXPOSURE

Clearance of acute HCV infection with systemic viraemia can result in T-cell-based immune protection upon reinfection. HCV-specific T-cell responses have also been detected in some individuals without any history of acute HCV infection despite frequent exposure; it has been suggested that these low-level exposures confer T-cell-mediated resistance to infection. Barbara Rehermann and colleagues thus set out to study this hypothesis.

The researchers used chimpanzees in their investigation as this *in vivo* model most closely represents HCV infection in humans. "We repeatedly exposed chimpanzees to human plasma with trace amounts of HCV," explains Rehermann. "The chimpanzees developed HCV-specific T-cell responses but no quantifiable viraemia or seroconversion." These chimpanzees were then exposed to a standard HCV challenge to examine whether these T-cell responses conferred immune protection. Interestingly, the opposite was found. The chimpanzees did not mount a memory response and *de novo* T-cell responses were suppressed both in the blood and in the liver. Moreover, an expansion in the number of regulatory T cells (T_{REG} cells) was observed. By contrast, chimpanzees that had previously cleared an acute HCV infection were able to rapidly clear a second HCV challenge.

"We refute the notion that individuals who are frequently exposed to low-dose HCV and remain negative for HCV and for antibody to HCV may have T-cell mediated protective immunity upon HCV infection," says Rehermann. Instead the researchers suggest that clearance of a previous acute infection (with systemic viraemia) might be required to confer this protective immunity.

The number of chimpanzees included in the study was small, which precluded a statistical comparison of outcomes of HCV challenge between HCV pre-exposed and naive animals. The researchers now plan to study T_{REG}-cell responses in humans who are frequently exposed to HCV. "Our findings might be relevant for vaccine research and for epidemiological studies because an increased T_{REG} cell number in frequently exposed individuals and in endemic areas might reduce the response to vaccines," concludes Rehermann. Strategies to reverse this immune suppression should be examined.

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Original article Park, S.-H. *et al*. Subinfectious hepatitis C virus exposures suppress T cell responses against subsequent acute infection. *Nat. Med*. doi:10.1038/nm.3408