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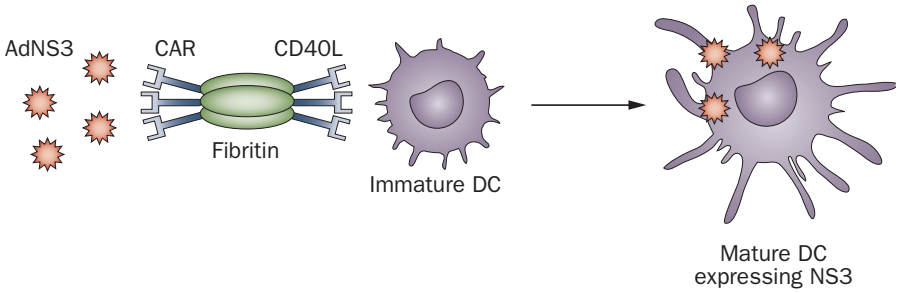
HEPATITIS C

Induction of immune responses against HCV

A new strategy to enhance immune responses against HCV has been reported. This technique could have important therapeutic implications—new treatment options for chronic HCV infection are needed as the rate of response to current therapy is low.

Evidence suggests that T-cell immunity is important in the clearance of HCV; inducing T-cell responses is, therefore, an interesting treatment approach.To date, results from studies using various HCV antigens to illicit a T-cell response have demonstrated some potential, but with a limited effect on viral load.

There has been a growing interest in using dendritic cells (DCs) to stimulate T-cell immunity. Previous work has shown that mouse DCs transduced with a recombinant adenovirus encoding HCV NS3 protein (AdNS3) are able to induce T-cell responses against NS3. "Although adenoviruses have been widely used to introduce *ex-vivo* foreign antigens into DCs, there are two important drawbacks to this approach: the low transduction efficiency of DCs ... and the poor DC maturation induced by adenoviruses..." explains Pablo Sarobe, one of the authors of the current study. "Thus, we looked for a strategy able to improve DC transduction and induce their complete maturation."



Adaptor molecules targeting CD40 enhance adenoviral transduction and DC maturation, leading to the induction of T-cell responses against HCV. Abbreviations: AdNS3, adenovirus encoding HCV NS3 protein; CAR, coxackie adenovirus receptor; DC, dendritic cell. Image created in consulation with P. Sarobe.

The authors investigated the use of adaptor molecules for targeting AdNS3 to DCs. These adaptor molecules contain a CAR (coxackie adenovirus receptor) domain fused to either mouse or human ectodomains of CD40L through a fibritin moiety. "These molecules ... not only facilitate viral transduction, but also induce potent DC maturation, due to the CD40/CD40L interaction," says Sarobe.

In vivo and *in vitro* mouse models demonstrated that the adaptor molecules were indeed able to enhance DC transduction efficiency and maturation, and, consequently, T-cell responses against HCV. In addition, the human version of the adaptor molecule lead to efficient transduction and maturation of DCs not only in healthy individuals, but also in patients with chronic HCV infection.

"We are currently preparing a clinical trial involving 15–20 noncirrhotic patients chronically infected with HCV genotype 1b previously resistant to conventional therapy. Patients will receive three subcutaneous injections of DCs transduced with AdNS3 targeted with the human version of the adaptor molecules," concludes Sarobe. "This study will help us to analyze the effect of our strategy in chronic HCV infection."

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Original article Echeverria, I. *et al.* Enhanced T-cell responses against hepatitic C virus by *ex vivo* targeting of adenoviral particles to dendritic cells. *Hepatology* doi:10.1002/hep.24325