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VIRAL DISEASE

Steps towards an HCV vaccine

Results from a clinical study (ClinicalTrials.gov identifier: NCT01070407) of an investigational adenovirus-based vaccine against hepatitis C virus (HCV) suggest that inducing host T cell responses might be an effective strategy to provide protective immunity against HCV.

HCV infection can be spontaneously controlled in a proportion of infected individuals, and studies of host genetics and immunology suggest that T cells have an important role in protective immunity against HCV. So a vaccine that induces T cell responses might stimulate immune-mediated control of HCV infection. Indeed, in a previous study, a vaccine based on a segment of DNA coding for the nonstructural region (from NS3 to NS5B) of HCV genotype 1b that was delivered using adenovirus constructs induced T cell responses and suppressed acute viraemia in chimpanzees.

In the current study, published in *Science Translational Medicine*, Barnes and colleagues investigated whether such an approach might also induce T cell responses in healthy volunteers. To do this, they used two replication-defective vectors based on rare adenoviral serotypes (to try and overcome the formation of neutralizing antibodies in the volunteers): chimpanzee adenovirus 3 (ChAd3) and human adenovirus 6 (Ad6) vectors, both of which were engineered to express the HCV proteins NS3, NS4 and NS5 of HCV genotype 1b.

After first determining that the vaccine was safe and well tolerated, the authors showed that priming doses of the vaccine induced immune responses (assessed by increases in interferon-γ production) that peaked at 2–6 weeks and were detectable for 24 weeks after vaccination. Moreover, vaccination induced long-lived central and effector memory T cells that could be detected for 6 months after a boosting dose of the vaccine.

Because a broad T cell response (that is, one that is directed against several target antigens) correlates with better control of the virus, it was encouraging to note that at the highest dose of the vaccine, reactivity against the peptides NS3, NS4A/B, NS5A and NS5B was observed.

The authors next analysed the T cell responses that were induced by vaccine administration. Both vectors induced HCV-specific $CD4^+$ and $CD8^+$ T cells that secreted multiple pro-inflammatory and antiviral cytokines, including interferon-γ, tumour necrosis factor and interleukin-2, although the response of $CD4^+$ T cells (which have a key role in defence) was much lower than that of the $CD8^+$ cells.

Next, the authors tested whether the T cell responses induced by genotype 1b were cross-reactive against other HCV genotypes. Overall, cross-genotype recognition occurred but it was of a lower magnitude; the response to genotype 1a was about half of the response to genotype 1b, and that of genotype 3a was about a fifth of the response to genotype 1b.

Following this, they assessed whether the response induced by a priming dose of the ChAd3 vaccine could be boosted by a dose of the Ad6 vaccine, and vice versa. Although there was some boosting of T cell responses, the overall magnitude did not exceed that elicited by the priming vaccine; the boosting effect was greatest when ChAd3 was used as the priming vaccine. This suggested that the priming vector induced cross-neutralizing adenovirus antibodies.

ImageSource

The authors note that although priming the T cell response using chimpanzee adenoviral vectors appears to be robust, the use of alternative vectors to boost the response might avoid potential cross-neutralization and so maximize long-term memory responses; trials of such a strategy are underway (EudraCT identifier: 2009-018260-10).

Charlotte Harrison

ORIGINAL RESEARCH PAPER Barnes, E. *et al.* Novel adenovirus-based vaccines induce broad and sustained T cell responses to HCV in man. *Sci. Transl. Med.* **4**, 115ra1 (2012)