Review

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Progress in the development of preventive and therapeutic vaccines for hepatitis C virus

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Hepatitis C virus (HCV) is a blood borne disease estimated to chronically infect 3% of the worlds' population causing significant morbidity and mortality. Current medical therapy is curative in approximately 50% of patients. While recent treatment advances of genotype 1 infection using directly acting antiviral agents (DAAs) are encouraging, there is still a need to develop vaccine strategies capable of preventing infection. Moreover, vaccines may also be used in future in combination with DAAs enabling interferon-free treatment regimens.

Viral and host specific factors contribute to viral evasion and present important impediments to vaccine development. Both, innate and adaptive immune responses are of major importance for the control of HCV infection. However, HCV has evolved ways of evading the host's immune response in order to establish persistent infection. For example, HCV inhibits intracellular interferon signalling pathways, impairs the activation of dendritic cells, $CD8^+$ and $CD4^+$ T cell responses, induces a state of T-cell exhaustion and selects escape variants with mutations $CD8^+$ T cell epitopes. An effective vaccine will need to produce strong and broadly cross-reactive $CD4^+$, $CD8^+$ T cell and neutralising antibody (NAb) responses to be successful in preventing or clearing HCV.

Vaccines in clinical trials now include recombinant proteins, synthetic peptides, virosome based vaccines, tarmogens, modified vaccinia Ankara based vaccines, and DNA based vaccines. Several preclinical vaccine strategies are also under development and include recombinant adenoviral vaccines, virus like particles, and synthetic peptide vaccines. This paper will review the vaccines strategies employed, their success to date and future directions of vaccine design.

Keywords: Hepatitis C; Vaccines; Therapeutic vaccines; Preventative vaccines; Antivirals; Cellular immunity; Neutralising antibody.

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Introduction

HCV infects 3% of the world's population (~130 million individuals) and causes an estimated 476,000 deaths per year as a result of HCV-associated end-stage liver disease and its complications [1,26,131]. Significant advances have been made in the treatment of both acute [65,153] and chronic hepatitis C infection [46,55,92,96,158]. With the recent development of directly acting antiviral agents (DAAs) for HCV, significant improvements in sustained virological response rates are now possible for patients infected with HCV genotype 1 [94,141]. However, even during the next many years treatment will still be based on the administration of interferon alpha and ribavirin [98] which is not only expensive but also associated with a substantial number of side effects. Overall, only a small minority of patients with chronic hepatitis C can currently be cured in most real-world settings with interferon-based treatments [40].

An effective preventive vaccine would considerably reduce the number of new infections and thereby reduce the burden on health care systems. However, there are many impediments to the development of a vaccine for HCV including the existence of multiple HCV genotypes, limited availability of animal models and the complex nature of the immunological response to HCV. Clearance of hepatitis C infection requires strong and broadly cross-reactive $CD4^+$, $CD8^+$ T cell [80,130,132] and neutralising antibody (NAb) responses [114].

The development of a multi-specific T cell response during acute HCV infection is associated with the spontaneous clearance of infection [133] and may provide a level of protection against reinfection [51]. It is also apparent that neutralising antibody is protective and associated with the rapid clearance of hepatitis C viraemia [83,114]. Reinfection among individuals who are repeatedly exposed to HCV, such as injecting drug users (IDU), however, raises concerns that the development of long-term protective immunity for HCV may not be possible [147]. However, cohort studies in IDUs are not able to completely assess the number of episodes of viral clearance compared to persistence [52]. We know that spontaneous recovery does occur in the setting of a successful immune response against HCV [80,87,138] and although the correlates of protective immunity are not completely understood the development of an effective vaccine for HCV should be achievable, as supported by vaccination studies performed in chimpanzees [61].

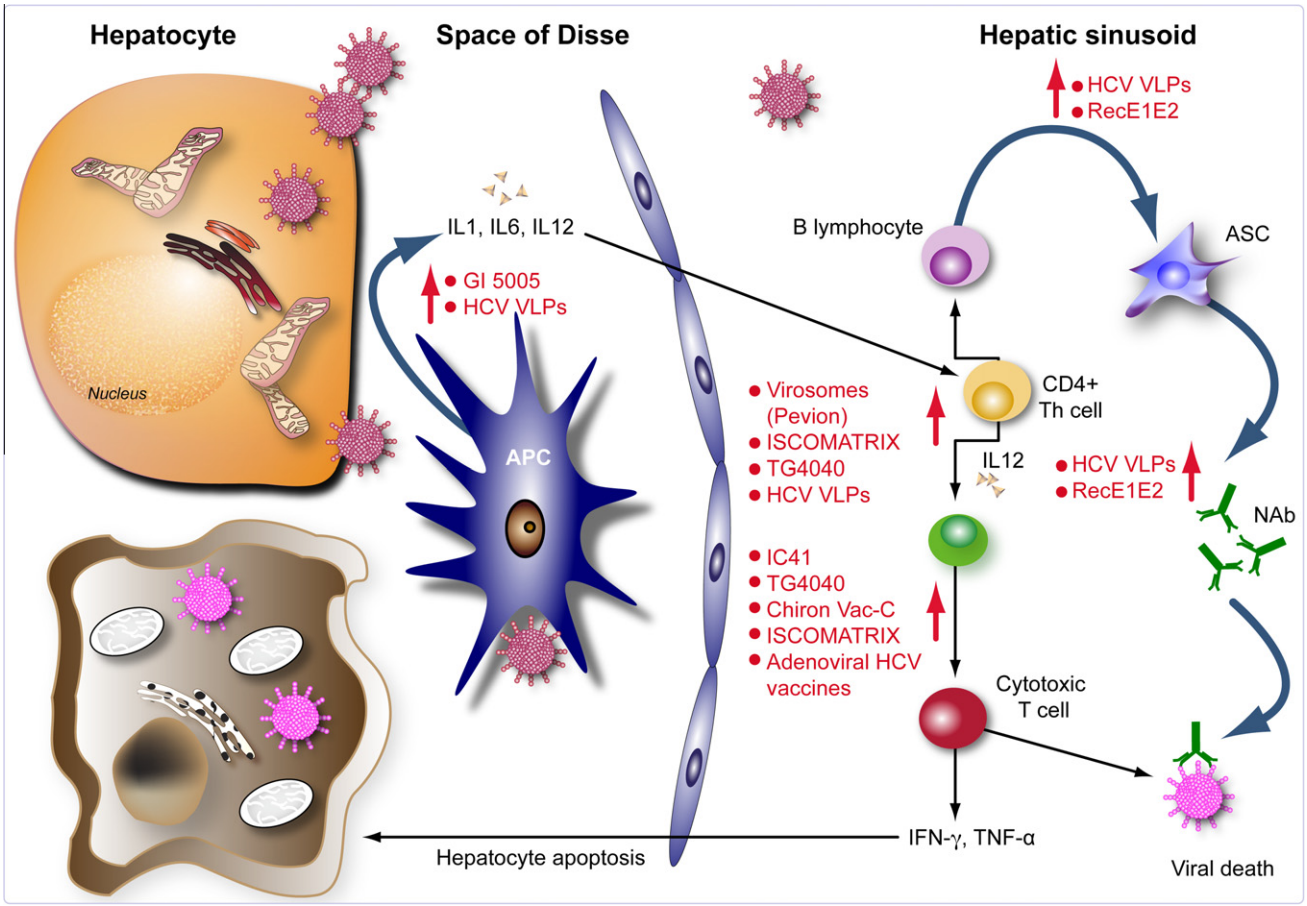

Fig. 1. Summary of the immune responses required to clear HCV and the major sites of action of different HCV preventive and therapeutic vaccines.

Several approaches to HCV vaccine development have now been studied and include recombinant E1 and E2 proteins [22], synthetic peptides [38,72,151], DNA [119], and prime-boost strategies [43] (Fig. 1). Success of these approaches has been limited for a number of reasons including: the delivery of a limited number of protective viral epitopes, the inclusion of incorrectly folded recombinant proteins, the limited humoral and cell mediated responses that are associated with DNA vaccines, and the use of adjuvants with relatively poor potency. It is also now apparent that vaccine inducing strong T cell responses alone may not be sufficient to prevent hepatitis C infection [119]. An effective preventive vaccine against HCV will, therefore, need to induce strong neutralising and cellular immune responses.

Correlates of hepatitis C cell mediated immunity

It is apparent that clearance of hepatitis C infection requires early and multi-specific class 1 restricted $CD8^+$ T cell [28,87,104,132,133,138,142] and class II restricted $CD4^+$ T cell [31,50,77,130] responses to both structural and non-structural HCV proteins (Table 1)(Fig. 1). Clearance of HCV and protection from reinfection is determined not only by the magnitude and/or breadth of multifunctional $CD8^+$ T cells but also by the quality, functional potency, and cytotoxic potential of HCV-specific $CD8^+$ T cells [14,80–82] and the selection of high-avidity $CD8^+$ T cells [110] which respond to a diverse array of HLA-class I restricted HCV-core, E1, NS3, NS4, and NS5 epitopes [14,20,21,80–82,127]. Studies in chimpanzees have also shown that it is possible to induce memory responses that are protective against reinfection [30]. The ability to produce strong HCV specific $CD8^+$ and $CD4^+$ T cell responses are important considerations for effective HCV vaccine design. It may also be important to consider the differences that exist in $CD8^+$ T cell specificities in peripheral compared to intrahepatic $CD8^+$ T cells [45,74,108,154].

The relative contributions of individual viral proteins to the total magnitude of the HCV-specific $CD4^+$ and $CD8^+$ T cell responses also play an important role in determining the outcome of infection. Using various approaches it has been possible to determine a hierarchy of $CD4^+$ and $CD8^+$ T cell responses, particularly to the NS3 protein [80,130,137,152]. It is also possible to elicit strong HCV core specific $CD4^+$ and $CD8^+$ T cell responses in naïve human lymphocytes [89]. These studies argue that the inclusion of $CD8^+$ T cell epitopes representing key viral proteins, like core and NS3, will be essential for the development of a cell mediated vaccine for HCV. However, a recent meta-analysis of the efficacy of HCV vaccines in chimpanzees has shown that the inclusion of structural proteins in vaccines was more significantly associated with protective immune responses compared to vaccines based on non-structural proteins of HCV [30].