Infection, Genetics and Evolution 22 (2014) 120–129

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Review

Therapeutic vaccines against hepatitis C virus

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ARTICLE INFO

Article history:
Received 17 May 2013
Received in revised form 31 December 2013
Accepted 7 January 2014
Available online 23 January 2014

Keywords:
Hepatitis C virus
Immunity
T cells
Therapeutic vaccine
Epitope

ABSTRACT

Hepatitis C virus (HCV) is a blood-borne pathogen which has chronically infected about 130–210 million people worldwide. Current standard-of-care (SoC) therapy is an inadequate and expensive treatment with more side effects. Two direct-acting antiviral agents (DAAs) (telaprevir and boceprevir) in combination with SoC therapy have been used in patients infected with HCV genotype 1. Although these drugs result in a shortening of therapy, they also have additional side effects and are expensive. In their stead, several second-generation DAAs are being investigated. What important is that all-oral, interferon (IFN)- and ribavirin-free regimens for the treatment of HCV-infected patients are now being investigated, and will be applied in the next year. Preventive measures against HCV, including vaccine development, are also now in progress. However, no therapeutic vaccine against HCV has been produced to date. An effective vaccine should induce robust and broadly cross-reactive $CD4^+$, $CD8^+$T-cell and neutralising antibody (NAb) responses. Current data indicate that vaccines can usually not completely prevent HCV infection but rather prevent the progression of HCV infection to chronic and persistent infection, which may be a realistic goal. This review discusses the important roles of NAbs and $CD8^+$T-cells in the development of therapeutic vaccines, and summarizes some important epitopes of HCV recognized by $CD8^+$T-cells and some prospective therapeutic vaccine approaches.

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Abbreviations: HCV, hepatitis C virus; SoC, standard-of-care; DAAs, direct-acting antiviral agents; NAb, neutralising antibody; UTRs, untranslated regions; SR-BI, scavenger receptor class B type I; OCLN, tight-junction proteins occludin; CLDN-1, claudin-1; LDL-R, low density lipoprotein receptor; GAGs, glycosaminoglycans; NPC1L1, Niemann-Pick C1-like 1; SVR, sustained virological response; IFN, interferon; PEG-IFN, pegylated interferon; RdRp, RNA-dependent RNA polymerase; VLDL, very low-density lipoprotein; GWAS, genome-wide association studies; SNP, single nucleotide polymorphisms; DCs, Dendritic cells.

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http://dx.doi.org/10.1016/j.meegid.2014.01.008
1567-1348/

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1. Introduction

Hepatitis C virus (HCV) has led to chronic infection in approximately 3% of the world population (Ascione et al., 2007; Lavanchy, 2009; Shepard et al., 2005). Each year, 3–4 million people are newly infected with HCV and 476,000 patients die from HCV-associated end-stage liver disease and its complications (Shepard et al., 2005). Among all HCV infected individuals, 20% of them eradicate the virus over weeks or months and are often asymptomatic. The remaining 80% of them will develop chronic disease, of whom about 20% and 1–5% will eventually develop liver cirrhosis and liver cancer, respectively (Afdhal, 2004; Lauer and Walker, 2001). Currently, it was reported that HCV infection was a leading cause of death in human immunodeficiency virus (HIV)-coinfected patients (Salmon-Ceron et al., 2005). HCV-related end-stage liver disease is the most common reason for liver transplantation today in the US and Western Europe (Tang and Grise, 2009). No vaccine is now available to prevent hepatitis C infection (Houghton and Abrignani, 2005). Therefore, previous incidence as well as new incidence all account for future disease burdens.

The 9.6 kb viral RNA genome is composed of an open reading frame flanked by 5′- and 3′-untranslated regions (UTRs). When HCV enters into the cytoplasm, the viral RNA genome is translated to a polyprotein (approximately 3,000 amino acids in length) that is post-translationally cleaved into three major structural viral proteins (core, envelope (E) 1 and 2), a small membrane polypeptide p7 and six non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) (Grakoui et al., 1993; Reed and Rice, 2000; Tang and Grise, 2009). HCV enters cells through receptor-mediated endocytosis. Several cellular receptor proteins including the tetraspanin CD81 (Lindenbach et al., 2005; Pileri et al., 1998), scavenger receptor class B type I (SR-BI) (Scarselli et al., 2002), tight-junction proteins occludin (OCLN) (Benedicto et al., 2009; Liu et al., 2009; Ploss et al., 2009) and claudin-1 (CLDN-1) (Evans et al., 2007; Liu et al., 2009), low density lipoprotein receptor (LDL-R) (Agnello et al., 1999; Molina et al., 2007), and glycosaminoglycans (GAGs) (Barth et al., 2003; Germi et al., 2002) have been shown to be the receptors for HCV. Recently, Sainz and coworkers demonstrated that the Niemann-Pick C1-like 1 (NPC1L1) cholesterol adsorption receptor is also involved in HCV entry (Sainz et al., 2012).

In this review, the important roles of NAbs and $CD8^+$T-cells in vaccine development are discussed. And then some important epitopes of HCV recognized by $CD8^+$T-cells and several prospective therapeutic vaccine approaches are overviewed. After introduction of the current treatment and future treatment options for HCV patients, the problems and challenges associated with the development of therapeutic HCV vaccines will be described.

2. Current treatment and future treatment strategies for HCV

According to the EASL and APASL guidelines (European Association for the Study of the Liver Collaboration., 2011; Omata et al., 2012), the combination of pegylated interferon (PEG-IFN)-a and ribavirin is the approved and well accepted therapy for chronic hepatitis C. However, this therapy is long, expensive, toxic, and only effective in around 50% of patients infected with the most common genotype (Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001, 2006). Moreover, telaprevir and boceprevir were recommended to be used in combination with PEG-IFN-a plus ribavirin in HCV 1-infected patients according to the AASLD (Ghany et al., 2011) and APASL guidelines. This new treatment regimen clearly demonstrated a 20–30% increase for the SVR rate of genotype 1-infected patients. And treatment can be significantly shortened in proportion to patients with satisfactory early responses (Bacon et al., 2010; Jacobson et al., 2010; Poordad et al., 2010; Sherman et al., 2010). However, use of triple therapy is limited only to genotype 1-infected patients, the cost of treatment rises further and around 40% of the treated patients have the additional side effects such as cutaneous rash and anemia (Bacon et al., 2011; Jacobson et al., 2011; Poordad et al., 2011). Moreover, the triple therapy is associated with the rapid onset of drug resistance (Kwo et al., 2010; McHutchison et al., 2010).

In the future, an IFN-free, ribavirin-free regimen with improved tolerability, less frequent dosing for improved adherence and high SVR rates is desirable. In a phase 2a study, the all-oral, IFN- and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 was well tolerated and achieved high SVR rates in patients with HCV genotype 1 infection. Further studies of this regimen are warranted (Everson et al., 2013).

3. Therapeutic HCV vaccine

New therapies with higher efficacy, lower adverse effects and improved tolerability are urgently required due to the limitations of the current therapies. The development of safe, effective and affordable vaccines for treatment of HCV remains the best choice for controlling the global epidemic. And a balanced T-cell response and broad spectrum NAb activity is ideal for HCV vaccine development. However, a significant challenge for vaccine development is to identify protective epitopes conserved in the majority of viral genotypes and subtypes. This problem is compounded by the fact that the envelope E1E2 proteins, the targets for NAb response, are two of the most variable proteins of the virus.

3.1. Challenges to HCV vaccine development

3.1.1. HCV diversity

Due to the high production rate and the short half-life of HCV and the low-fidelity of the NS5B RNA-dependent RNA polymerase (RdRp), HCV mutates at nearly one nucleotide per replication cycle. These frequent mutations result in the presence of many distinct but closely related HCV variants (known as quasispecies) typically in one infected individual, which clearly poses a significant challenge to successful vaccine development.

The greatest genetic variability is identified in the E1 and E2 glycoproteins (Simmonds et al., 2005). Thus, the envelope region may causes difficulties in the development of cross-protective vaccines to induce NAbs. However, studies have demonstrated that plasma samples and monoclonal antibodies could cross-neutralize the different genotypes (Kachko et al., 2011; Law et al., 2008; Simmonds et al., 2005; Stamataki et al., 2008; Zhang et al., 2009). Indeed, the phase I trial of the HCV E1E2MF59C.1 vaccine showed that the recombinant E1/E2-puried proteins is safe and induced significant lymphoproliferative and antibody responses in humans (Frey et al., 2010). Therefore, despite the challenges presented by HCV diversity, there are promising indications that cross-protective immune responses exist in natural infection and can be mimicked by vaccination.