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A close view of the Hepatitis C virus vaccines with further perspective

Dear Editor

Hepatitis C virus (HCV) is a serious international health threat that persistently infects around 170 million individuals worldwide (~2% of the world's population). It is estimated that there are three to four million people are infected with HCV annually; the majority of HCV-infected cases remain undetected as chronic HCV carriers because HCV infection barely presented with clinical manifestation earlier than the onset of advanced liver disease stage [1]. Chronic infection with HCV is associated with end-stage liver disease e.g. fibrosis, cirrhosis, as well as hepatocellular carcinoma (HCC) if left untreated [2]. A recent survey has estimated that up to 30 million HCV asymptomatic carriers will be resurged in China by 2050 with the current trend [3].

Recently, the World Health Organization (WHO) set a target to eliminate the HCV infection by 2030. However, there are serious limitations to achieving this goal. Despite the continuous declining global HCV infection trend, screening protocol for the detection of chronic HCV carriers remains insignificantly underestimated. The current standard therapy using a combination of PEGylated interferon-alpha and ribavirin has limited efficacy around 70% against HCV genotype 1 (the predominant HCV genotype in the world). Furthermore, the cost of therapies, poor compliance with direct-acting antivirals (DAAs) or their adverse events, the emergence of DAA-resistant strains, as well as susceptibility to reinfection after re-exposure following HCV cure in high-risk individuals has proven challenging [5,6]. In addition, the lack of an efficacious vaccine will increase the inconsistency of the global elimination of HCV infections.

There is robust impetus to introduce prophylactic or therapeutic efficient vaccines even with partial protection against HCV. Current evidence suggested that HCV nucleotide sequences are frequently evolving during infection (>30% difference) greater than human immunodeficiency virus (HIV). However, HCV has been categorized into seven distinct genotypes, including several subtypes. HCV carries an error-prone NS5B RNA-dependent RNA polymerase without calibration (estimated 10^{-5} to 10^{-4} nucleotide errors/replication cycle) and mutant strains exhibit robust resistance to neutralizing antibodies, and impressive adaptation with the host that facilitates immune evasion using viral enveloped glycoprotein 2 (gpE2), and high production rate of HCV (~10^{12} virions/day). Genetic variability of E1 and E2 glycoproteins, as well as the NS5A regions between HCV genotypes, or incomprehensive understanding of HCV immune-pathogenesis, and also will disappoint us to develop vaccine studies. Meanwhile, there are numerous opposite findings that significant encouragement for vaccine development, for example, 1) approximately one-quarter of HCV infected individuals will spontaneously eradicate the virus without treatment, 2) intravenous drug users (ivdus) or chimpanzees with re-exposure to HCV with previous cure dose does not develop to chronic or persistent infection due to natural immunity responses, 3) chimpanzee model studies revealed stimulation of a robust immune response against HCV infection following vaccination, convalescent humans chimpanzees are protected against re-exposure to the virus, and HCV vaccine can elicit substantial titers of cross-neutralizing antibodies [7–9].

Previous studies revealed that about 20% of HCV-infected individuals were cleared spontaneously during the natural course of hepatitis C virus infection. However, the primary immune mechanisms have not been fully comprehended. In this regard, the role of interferon-lambda 3, human leukocyte antigen class II, and natural killer cell receptor KIR2DL3, as well as human leukocyte antigen C group 1 ligand have been correlated with spontaneous viral clearance [10]. Ideal HCV vaccines at least should reach virus clearance similar to natural immune response. There are two approaches to HCV vaccine design including 1) the development of an efficient HCV vaccine that elicits virus clearance by neutralizing antibodies. Indeed, Pestka et al., 2007 revealed that patients with complete clearance of HCV infection have higher neutralizing antibodies titers; thus, the introduction of HCV vaccines that stimulate robust neutralizing antibodies could able to achieve complete virus clearance [11]. 2) Provocation of a broad cellular immunity by delivery of the non-structural HCV proteins as another approach. Similar relevant studies were showed the importance of $CD4^+$ T helper or $CD8^+$ cytotoxic T cell responses in successful virus clearance; hence, delivery of immune-dominant non-structural proteins e.g. NS3, NS4a, NS4b, NS5a, or NS5b contains vaccines can be able to suppress the acute viremia by induction of immune response [4]. Currently, two HCV vaccine type that is considered the potential for clinical use. The first candidate is gpE1/gpE2 glycoprotein heterodimer-based vaccine with MF59 adjuvant. The chimpanzees that received this vaccine failed to develop into persistent carriers of the virus [7]. This vaccine induces cross-genotype neutralizing antibodies against seven HCV genotypes in humans [12]. Therefore, HCV structural-based vaccines could reach virus clearance by induction of neutralizing antibodies or ameliorate T-cell responses as a prophylactic vaccine.

Another potential candidate is the adenovirus 3 viral vector expressing the non-structural genes (NS) of HCV (ChAd3 NS), followed by a boost with Modified Vaccinia Ankara (MVA) expressing NS. The heterologous challenge of chimpanzees suggested that this vaccine could provide rapid recall of memory T cell responses in response to re-exposure to hampered acute viremia [13]. Priming and boosting this vaccination could have beneficial effects on the migration of activated T-cells to the infected liver where HCV replication may ameliorate immune response e.g. production of interferon-γ or TNF-α in combination with antiviral drugs [14]. A recent meta-analysis by Dahari et al., 2010 suggested that non-structural proteins significantly decrease viral persistence compared to naïve animals [8]. Therefore, this vaccine can be considered a potential therapeutic vaccine against HCV.

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There are several scrambles regarding the development of an efficient HCV vaccine after the discovery of HCV in the last 30 years ago. However, the introduction of a valuable HCV vaccine to prevent chronic HCV infection is feasible, when our understanding is comprehensive regarding immune-pathogenesis of HCV infection with more details. Involved mechanisms in HCV-specific $CD4^+$ T-cell failure, as well as immune evasion in chronic HCV infection, are considered the largest bans in the development of further therapies. In addition, further large human cohorts at high risk of infection need to be performed for efficacy trials. Nevertheless, it is being hopeful that a partially effective HCV vaccine will become available.

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