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Review

Barriers of hepatitis C virus interspecies transmission

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ABSTRACT

Hepatitis C virus (HCV) is a major causative agent of severe liver disease including fibrosis, cirrhosis and liver cancer. Therapy has improved over the years, but continues to be associated with adverse side effects and variable success rates. Furthermore, a vaccine protecting against HCV infection remains elusive. Development of more effective intervention measures has been delayed by the lack of a suitable animal model. Naturally, HCV infects only humans and chimpanzees. The determinants of this limited host range are poorly understood in part due to difficulties of studying HCV in cell culture. Some progress has been made elucidating the barriers for the HCV lifecycle in non-permissive species which will help in the future to construct animal models for HCV infection, immunity and pathogenesis.

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Introduction

Hepatitis C virus (HCV) is a positive-sense, single stranded RNA virus classified within hepacivirus genus of the Flaviviridae family. HCV has a high propensity for establishing lifelong persistent infections, which are associated with a significant risk of progressive liver fibrosis and hepatocellular carcinoma. Worldwide at least 130 million people are chronically infected resulting in an estimated 366,000 deaths due to cirrhosis and cancer annually (Perz et al., 2006). Epidemiological data is incomplete and in the United States alone the frequency of chronic carriers may be twice as high (Edlin, 2011). Thus, HCV poses a major public health threat. Treatment options have improved but are still limited. Furthermore, the current standard of care, consisting of a combination of pegylated interferon (IFN) alpha, the nucleoside analog, ribavirin (RBV), and one of two HCV NS3–4A protease inhibitors, boceprevir or telaprevir, is not well tolerated. Prior to the approval of these directly acting antivirals (DAAs) roughly 50% of genotype 1 infected patients – clinically, the hardest HCV substrain to treat – who underwent treatment, cleared the infection.

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Inclusion of a HCV protease inhibitor to the peg-IFN/RBV regiment has increased sustained virological response (SVR) rates in certain clinical trial cohorts to 60–70% (Jacobson et al., 2011; Kwo et al., 2010; McHutchison et al., 2009; Poordad et al., 2011). Currently, numerous viral and host proteins are being pursued as antiviral drug targets. Second-generation protease inhibitors and several compounds interfering with the functions of the NS5A phosphoprotein and the RNA-dependent RNA polymerase, NS5B, are already being tested in clinical trials (Yang et al., 2011). A combination of orally administered DAAs with distinct mechanisms of action holds promise to boost SVR rates across all HCV patient cohorts. Despite these successes unexpected toxicity in late-stage clinical trials has led to the discontinuation or delays in development of some very potent compounds, including the protease inhibitor BILN2061 (Lamarre et al., 2003), the nucleotide polymerase inhibitor BMS-986094(Vernachio et al., 2011), and the cyclophilin A antagonist, alisporivir (Coelmont et al., 2009). These challenges highlight the need for thorough pre-clinical testing in predictive animal models. Likewise, the development of pan-genotypic prophylactic or therapeutic vaccines instrumental in containing the HCV epidemic in resource-poor communities would be greatly accelerated by a tractable animal model.

Chimpanzees are the only available immunocompetent *in vivo* experimental system, but their use is limited by ethical concerns, restricted availability and prohibitively high costs. Undoubtedly, more tangible animal models are needed not only to prioritize clinical development of vaccine and drug candidates, but also to gain deeper insights into virus–host biology. The study of HCV in conventional cell culture systems, i.e. human hepatoma cells, may not accurately reflect host responses to infection. With the advent of more sensitive detection methods for viral infection and improved technical ability to culture primary hepatocytes it is now possible to dissect HCV infection in a physiological-relevant environment (Jones et al., 2010a; Ploss et al., 2010). However, even in the most advanced tissue culture platforms, including micropatterned primary hepatocyte co-cultures (MPCCs; Jones et al., 2010a; Khetani and Bhatia, 2008; Ploss et al., 2010), cultures of human fetal hepatocytes (Andrus et al., 2011; Marukian et al., 2011), or hepatocyte-like cells derived from induced pluripotent-stem cells (iPSCs; Roelandt et al., 2012; Schwartz et al., 2012; Wu et al., 2012), important features of liver biology as yet cannot be adequately recapitulated. Within the liver, numerous cell types, including hepatocytes and various non-parenchymal cell subsets (i.e. liver sinusoidal endothelial cells, stellate cells, and oval cells), are arranged in an intricate three-dimensional architecture. Nutrient and oxygen gradients within the liver result in a compartmentalization of the liver, referred to as zonation, affecting metabolism, detoxification and response to injury. Whether those specific microenvironments impact HCV infection is not understood and may only be adequately modeled within the three-dimensional context of the liver. Furthermore, a tractable animal model may be suitable to decipher mechanisms of viral persistence and pathogenesis and assess disease states and co-morbidities, such as HIV, alcohol or nutritionally exacerbated viral hepatitis, or extrahepatic manifestations associated with HCV infection.

The chimpanzee model

The only hosts known to be naturally permissive to HCV infection are humans and chimpanzees (Table 1). The basis for this limited species tropism is incompletely understood and the topic of this review. The chimpanzee model played an instrumental role in early characterization of non-A, non-B hepatitis (Houghton, 2009) which ultimately led to the discovery of HCV as the etiologic agent for the classically defined non-A non-B hepatitis by Michael Houghton and his team in 1989 (Choo et al., 1989). Subsequently, many important discoveries were facilitated by their use; for example it was first demonstrated in chimpanzees that *in vitro* transcribed RNA from a HCV cDNA clone was infectious (Kolykhalov et al., 1997). Furthermore, experimental infection of chimpanzees with HCV helped to define the nature of protective immunity (Farci et al., 1992; Prince et al., 1992) and to demonstrate the significance of cellular subsets, most stringently the role of CD4 and CD8 T cells in controlling chronic HCV infection (Grakoui et al., 2003; Shoukry et al., 2003). Chimpanzees remain the only fully immunocompetent animal model for HCV infection and consequently, have and continue to play an important role in evaluating the preclinical efficacy of vaccine candidates (reviewed in Houghton, 2011). Precedence for the efficacy of new treatment modalities, such as the IFN-free control of HCV infection with DAAs (Olsen et al., 2011) or interference with the liver specific microRNA (miR) 122 (Lanford et al., 2010) was first shown in chimpanzees. Despite their utility, the use of large apes in biomedical research has raised ethical concerns, which culminated in the ban of experiments conducted in chimpanzees in many countries. An NIH moratorium on 'non-essential' chimpanzee research (NIH, 2011) is likely to constrain HCV research in the future and has made the need for alternative animal models even more pressing.

HCV infection in other primate species

The natural host reservoir of HCV remains poorly defined. While chimpanzees can be experimentally infected with HCV, the prevalence in chimpanzees or other great apes, gorillas and orangutans in the wild is not known. In search of alternative, more readily accessible experimental models for HCV numerous species have been tested for their susceptibility to HCV. Woodchucks, old- and new-world monkeys, including Cynomolgus, Rhesus, Japanese, Green monkeys, Doguera (Abe et al., 1993), Chacma Baboons (Sithebe et al., 2002), Cottontop tamarins (Garson et al., 1997) and marmosets appear to be mostly resistant

Table 1
HCV susceptibility of selected species.

	Human	Great ape(s) (chimpanzee)	Tree shrew	Monkeys (rhesus macaque)	Mice
HCV susceptibility	yes	yes	yes	yes	no
Entry	yes	yes	yes	yes	no
Replication	yes	yes	yes	no	no
Assembly	yes	yes	yes	?	yes

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