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Review

Humanized chimeric mouse models of hepatitis B virus infection

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ABSTRACT

Hepatitis B virus (HBV) infection is associated with an increased risk of hepatic cirrhosis, hepatocellular carcinoma, fulminant hepatitis and end-stage hepatic failure. Despite the availability of anti-HBV therapies, HBV infection remains a major global public health problem. Developing an ideal animal model of HBV infection to clarify the details of the HBV replication process, the viral life cycle, the resulting immunoresponse and the precise pathogenesis of HBV is difficult because HBV has an extremely narrow host range and almost exclusively infects humans. In this review, we summarize and evaluate animal models available for studying HBV infection, especially focusing on humanized chimeric mouse models, and we discuss future development trends regarding immunocompetent humanized mouse models that can delineate the natural history and immunopathophysiology of HBV infection.
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Contents

Introduction

Infection with the non-cytopathic hepatitis B virus (HBV) is a major health issue worldwide. Two billion people have been infected with HBV, and approximately 250 million people suffer from evident chronic infection (Billerbeck et al., 2016; Chan et al., 2016). A wide variety of clinical diseases are associated with persistent high levels of serum HBV DNA. Chronic HBV infection contributes to approximately 50% of hepatocellular carcinoma cases, it remains unknown whether HBV induces hepatocarinoma directly or indirectly via chronic liver inflammation. The specific immune response to HBV, particularly the adaptive immune

Abbreviations: HBV, hepatitis B virus; cccDNA, covalently closed circular DNA; SCID, severe combined immunodeficiency; alb-uPA, albumin-promoted urokinase-type plasminogen activator; RAG2, recombinant activation gene 2; RI, repopulation index; FAH, fumarylacetoacetate hydrolase; FRG, FAH$^{-/-}$RAG2$^{-/-}$IL2Rγ$^{-/-}$; NTBC, 2-(2-nitro-4-trifluoro-methylbenzoyl) 1,3-cyclohexedione; TK-NOG, thymidine kinase transgene in NOD/SCID/IL2Rγ$^{-/-}$; HSVtk, herpes simplex virus thymidine kinase; IFN, interferon; HSC, haematapoietic stem cell; FKBP, FK506 binding protein; HPCs, hepatic progenitor cells; A2/NSG, NOD/SCID/IL2Rγ$^{-/-}$ with HLA-A2 transgene; HLCs, hepatocyte-like cells; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stem cells; hBMSCs, human bone marrow-derived mesenchymal stem cells; FHF, fulminant hepatic failure.

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response, plays a great role in the persistent liver injury that leads to hepatic cirrhosis and fulminant hepatitis. The pre-existing treatments for HBV infection, including antiviral nucleos(t)ides and interferons, can suppress viral replication but cannot completely clear the virus; in addition, these treatments can be hampered by drug resistance and viral mutation. Moreover, viral rebound will unavoidably occur upon treatment interruption. Vaccination is an efficient strategy for controlling HBV epidemics, and the side effects are largely negligible; however, its development has been hampered by the lack of a robust model. Thus, we emphasize the need for establishing a promising HBV model to elucidate the complex molecular mechanism of HBV infection, illustrate the precise HBV pathogenesis and improve the pre-existing treatment strategies for HBV infection.

Establishing such a suitable model is an arduous task because of the extremely narrow host range of HBV, which mostly infects humans. Chimpanzees and tupaias are the only nonhuman primates fully sensitive to human HBV (Allweiss and Dandri, 2016; Wieland, 2015), which enables the development of acute HBV infection and continuous hepatitis. As an immunocompetent host, chimpanzees are used to study the natural course of HBV infection and to evaluate the efficiency of innovative immunotherapeutic approaches. The use of chimpanzees is severely limited by many factors, including strong ethical constraints, economical restrictions, few available animals and the large size of the operation (Wieland, 2015). Surrogate animal models for studying HBV, such as the woodchuck and duck models, are not widely accepted because their hepadnaviruses are somewhat different from HBV. In HBV transgenic mice (Figure 1A), the virus particles cannot enter the liver cells due to the negative expression of the HBV-specific receptor, and detectable liver injury cannot be induced due to the central immune tolerance. Transfection mouse models (Figure 1B) will inevitably cause injury in the liver and heart by adenoviral vectors and high-dose viral injections (von Schaewen et al., 2016).

The various restrictions of the above models hamper the study of HBV. Recently, human liver chimeric mouse models established by transplanting human hepatocytes into immunodeficient mice have been attracting an increasing amount of attention (Figure 1C). The chimeric mice harbouring human hepatocytes are not only sensitive to HBV infection but are also capable of forming nuclear HBV covalently closed circular DNA (cccDNA) (Lai et al., 2016; Lucifora and Protzer, 2016). As such, this is a promising model for studying the complete viral life cycle and developing potentially useful antiviral drugs. This review will briefly evaluate current chimeric mouse models and discuss future development directions.

Chimeric mouse models

HBV-trimera mouse model

The first reported human-mouse chimera system was the HBV-trimera mouse model (Ilan et al., 1999). HBV-infected human liver fragments were transplanted beneath the kidney capsule in lethally irradiated severe combined immunodeficiency (SCID) mice after bone marrow cells transplantation. Previously, this model was applied to simulate human HBV infection because of the short effective infection and to assess potential anti-HBV therapeutic strategies, such as lamivudine, beta-L-5-fluoro-2',3'-dideoxycytidine and plasma-derived polyclonal antibodies, because human peripheral blood mononuclear cells were allowed to engraft. Currently, the model is seldom used because of its serious limitations: although approximately 80% of the mice had viremia at 2-3 weeks after infection, the positive rate of infection dropped to 20% at 6 weeks after infection, as determined by testing HBV DNA samples extracted from calibrated human serum. The donor liver tissue suffered histological changes, including ischaemia and fibrosis, after heterotopic transplantation, indicating that it is difficult to maintain the specific function of implanted human hepatocytes for a long time, particularly a long enough time to assess the appearance of escape mutants. Research efforts should be directed towards creating mouse models harbouring human hepatocytes stably integrated in the liver parenchyma.

Alb-uPA/SCID chimeric mouse model

The urokinase-type plasminogen activator (uPA) transgenic mouse model was available in the early 1990s (Heckel et al., 1990). Furthermore, uPA transgenic mice with severe immunodeficiency were established in 2001 by Dandri et al. and Mercer et al. as ideal recipients of human hepatocytes (Mercer et al., 2001). The model offers a precious opportunity for studying the early kinetics of HBV infection.

The expression of a liver-toxic albumin-promoted urokinase-type plasminogen activator (alb-uPA) controlled by the mouse albumin promoter causes subacute liver failure in newborn animals. *uPA* gene overexpression in the liver leads to very high plasma uPA levels and hypofibrinogenemia, which can result in severe or fatal intestinal and abdominal bleeding soon after birth. To restructure the liver of mice with xenogeneic hepatocytes, the uPA mice were associated with genetically immunodeficient mouse strains, such as SCID or recombinant activation gene 2 (RAG2) mice. Homozygous alb-uPA/SCID mice are difficult to acquire since their hereditary immunodeficiency and bleeding tendency increases the risk of serious infection and perinatal traumatic death; however, they are also necessary because they produce a higher human hepatocyte repopulation index (RI). To improve the survival of uPA homozygous mice, the strategy of achieving human hepatocyte transplantation within the 2nd week after birth is necessary.

An immunodeficient state and severely damaged endogenous murine hepatocytes create favourable conditions for human hepatocyte proliferation. Millions of freshly isolated or cryopreserved and thawed human hepatocytes can be intrasplenically injected into mice, subsequently flowing through the spleen and portal veins into the liver parenchyma, where they ultimately reside and function (Allweiss and Dandri, 2016; DebRoy et al., 2016). At several weeks after transplantation, a variety of human hepatic proteins (including albumin, apolipoprotein Eα-1 antitrypsin, apolipoprotein A, and several clotting factors and complements) in the plasma can be detected. The chimerism rate in alb-uPA/SCID mice reached up to 70% assessed by above biomarkers.

Currently, this model is applied to evaluate genotype-dependent differences in the expression of HBV DNA and antigens, to study the pharmacological responses of human hepatocytes and to exploit viral interference mechanisms in human hepatocytes, among others. However, haematological disorders, a poor breeding efficiency, a narrow time window for transplantation and kidney disorders hamper the development of the alb-uPA/SCID chimeric mouse model.

FRG chimeric mouse model

To overcome most limitations of the uPA mouse model, Grompe and coworkers first successfully transplanted human hepatocytes into triple-mutant mice (FRG mice). These mice were established by crossing fumarylacetoacetate hydrolase $(FAH)^{-/-}$ mice with mice having a $RAG2^{-/-}$ interleukin 2 receptor gamma $(IL2R\gamma)^{-/-}$ immunodeficient background (Azuma et al., 2007).

FAH is the last enzyme in the tyrosine catabolic pathway, and its deficiency leads to the accumulation of the toxic metabolite

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