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Rodent Models with Humanized Liver: A Tool to Study Human Pathogens

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1. Introduction

The recent development of small animal models for experimental hepatotropic infection has opened new perspectives for the evaluation of novel therapeutic and/or prophylactic compounds against hepatitis B virus (HBV), hepatitis C virus (HCV) and Plasmodium falciparum, three major hepatic pathogens responsible for millions of deaths each year. Indeed, till now in vitro and in vivo models have their limitations. As example, primary human hepatocytes (PHH) are susceptible to infection by HBV (Gripon et al 1988), HCV (Fournier et al 1998) and by sporozoites (the hepatic stage of Plasmodium falciparum) (Mazier et al 1985), but are hampered by a rapid dedifferentiation of the PHH (the loss of differentiation leads to a loss of susceptibility to infection) and the difficulties of obtaining fresh cells. In vivo, the chimpanzee constitutes the best non-human primate which can be used for studies of HBV, HCV and Plasmodium falciparum (Dandri et al 2005b; Kremsdorf & Brezillon 2007; Moreno et al 2007), but multiple drawbacks, including ethical issues, the inability to produce numerous progeny in a short time (long gestation periods) and exorbitant housing and breeding costs render difficult the accessibility.

For a long time, liver cell transplantation was just a dream; fortunately, experimental biology as led researchers to create new challenging mouse models. Indeed, generation of new mouse models for human hepatocyte transplantation have permitted, for the first time, experimental manipulations of human hepatotropic pathogens of man which are immediate problems of human health, as well as the study of cell transplantation in a regenerative medicine perspective. Here, we will focus on the development of humanized mice models using hepatocyte transplantation to study the three major hepatic pathogens.

2. Transplanted hepatic cells can replace a diseased liver in mice

Few papers laid the foundations for the entire field of liver cell transplantation in mouse. They described and applied a genetic-based animal model for competitive liver regeneration where exogenous transplanted hepatocytes have a selective advantage and can replace the diseased tissue. Two mice models were described: transgenic mice expressing high levels of uPA (urokinase-Plasminogen Activator) (Rhim et al 1994) and mice deficient for the fumaryl acetoacetate hydrolase (FAH) (Grompe et al 1993) (Fig. 1).

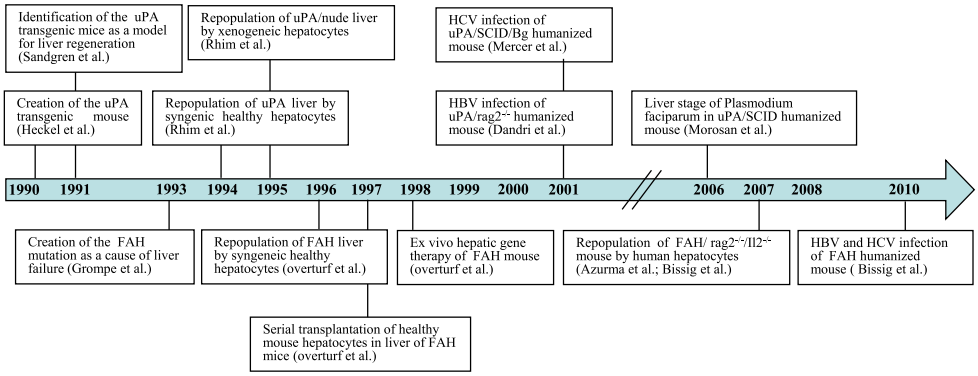

Fig. 1. Steps in the creation mouse models for liver cell transplantation and for infection by liver pathogens. The arrow represents a timeline. Each box represents an independent and initial study describing a mouse model to study liver cell transplantation and the infection of a humanized model by a hepatotropic pathogen. If a group of boxes are connected through the same line to the timeline this means that these studies were published the same year.

2.1 uPA mouse model

The initial observation that opened up the field of liver cell transplantation was serendipitous. With the goal of establishing an *in vivo* system to analyze the coagulation and fibrinolytic systems, Heckel et al. produced transgenic mice expressing high levels of uPA (urokinase-Plasminogen Activator) under control of the albumin enhancer/promoter for liver specific expression (Heckel et al 1990) (Fig.2).

As expected, the transgenic animals showed elevated plasma uPA levels, which often provoked a lethal syndrome of neonatal bleeding, causing the death of numerous transgenic founders. Sandgren et al. observed that some transgenic animals were characterized by a gradual normalization of the liver function over the first weeks (Sandgren et al 1991). The authors concluded that transgene expression was toxic to hepatocytes, and that the surviving animals were viable because deletion of the transgene was occurring, followed by clonal expansion of the rare cells that had lost the deleterious gene. Indeed, even in animals with only a few red spots, the existence of only a few "cured" cells was sufficient to ensure replacement of the diseased liver, providing an in vivo demonstration of the unexpectedly high proliferative potential of adult liver cells.

The same team then demonstrated the ability of a small number of "normal" hepatocytes to repopulate ad-integrum the liver of transgenic uPA mice (Sandgren et al 1991). Indeed, the overexpression of uPA protein in hepatocytes is cytotoxic, giving rise to a continuous liver regeneration process. Under these conditions, hepatocytes which lose the transgene by somatic reversion, as well as healthy transplanted hepatocytes, have a strong survival advantage over resident cells (Rhim et al 1994; Sandgren et al 1991). Throughout the regenerative process, the liver size remained normal, and blood chemistry analyses were used to demonstrate that the engrafted cells were functionally competent. Finally, the authors included an important control to demonstrate that the transplanted liver cells

underwent expansion only in the Alb-uPA transgenic and not in normal livers, leading to the critical deduction that a regenerative stimulus, that persists in the transgenic mice from birth until 6 to 8 weeks, when the transgene expressing liver has been replaced by donor cells, or endogenous hepatocytes deleted for the transgene, was necessary to obtain clonal expansion of the transplanted cells. To complete the picture, Rhim et al. introduced the nude gene into the Alb-uPA mice, and used homozygous as well as hemizygous transgenics to demonstrate that xenogenic hepatocytes from rats could reconstitute the diseased livers (Rhim et al 1995).

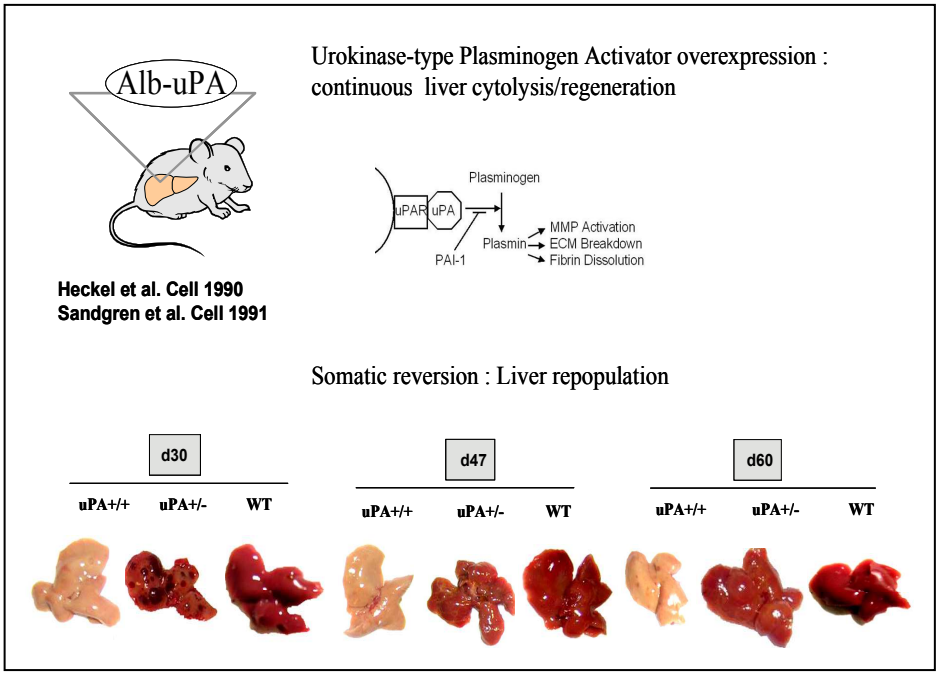

Fig. 2. The Alb-uPA model. Urokinase-type Plasminogen Activator overexpression induces continuous liver cytolysis and regeneration. Gross appearance of liver of Alb-uPA transgenic mice at different time after birth demonstrating somatic reversion of the transgene. Left, homozygous transgenic liver displaying a uniformly white color; center, hemizygous transgenic liver with regeneration nodules, right, non transgenic control.

Based on their proven utility as hosts for liver repopulation, Alb-uPA transgenic mice were backcrossed onto an immunodeficient background (SCID, Rag2$^{-/-}$ or Rag2$^{-/-}$/Pfp$^{-/-}$) to obtain a mouse model which tolerated the xenotransplantation of Human, Woodchuck and Tupaia hepatocytes (Dandri et al 2001a; Dandri et al 2001b; Dandri et al 2005a; Meuleman et al 2005; Petersen et al 1998; Rhim et al 1994; Tateno et al 2004). Because of the reversion process occurring in heterozygous mice for the Alb-uPA transgene, optimum liver repopulation requires intrasplenic transplantation of high quality adult hepatocytes into mice that are homozygous for both the SCID trait and the Alb-uPA transgene, and within one or four weeks of birth. In these conditions, human hepatocytes engrafted and repopulated the mouse parenchyma. Resulting chimeric liver showed satisfactory hepatic architecture and

intermingling of the mouse and human subcellular structures, indicating a physiological integration of transplanted cells (Meuleman et al 2005; Tateno et al 2004).

2.2 FAH mouse model

Fumaryl acetoacetate hydrolase (FAH) deficiency causes the human disease hereditary tyrosinaemia type I, an enzyme implicated in the degradation pathway of tyrosine, leading to the accumulation in the liver of toxic metabolites. The inhibitor 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione (NTBC) blocks this pathway at the beginning preventing the generation of these metabolites (Lindstedt et al 1992). Grompe et al. constructed mice with FAH deficiency and described that the NTBC, with treatment begun in utero and maintained thereafter, permitted not only survival of the animal, but also normalized the liver function of the deficient mice (Grompe et al 1993; Grompe et al 1995) (Fig. 3).

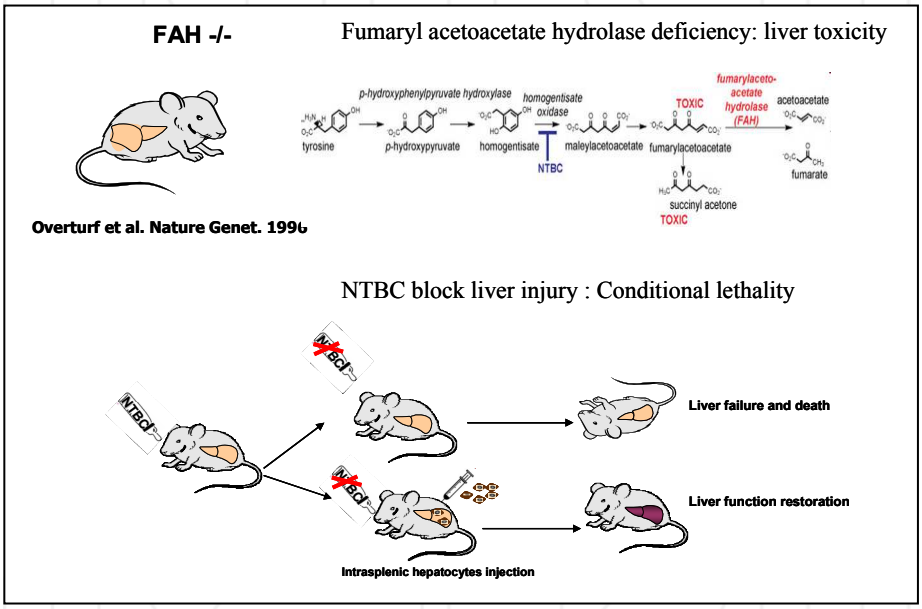

Fig. 3. The FAH model. Fumaryl acetoacetate hydrolase deficiency induces liver toxicity which is blocked by NTBC administration. Mice are submitted to intrasplenic injection of hepatocytes and NTBC drug is withdrawn.

The FAH model was then used for liver transplantation freshly isolated hepatocytes from wild type congenic animals; as in the experiments using the Alb-uPA model, data reported by Overturf et al. demonstrate that a selective advantage of transplanted cells is necessary to obtain repopulation (Overturf et al 1996).

Until recently the transplantation of human hepatocytes into this mouse was not successful: FAH/nude, FAH/NOD/SCID or FAH/Rag1$^{-/-}$ mice appeared to be unable to allow persistence and repopulation by human hepatocytes (Azuma et al 2007). Recently, two different groups have used nearly the same strategy to create a novel mouse model to study

human liver cell transplantation. They backcrossed the Rag2$^{-/-}$/il2$^{-/-}$ mouse with an FAH$^{-/-}$ mouse to give rise to a new mouse model which could be effectively transplanted and repopulated by human hepatocytes, presumably because they lacked not only B and T but also NK cells (Azuma et al 2007; Bissig et al 2007). Differences in methods to obtain satisfactory repopulation have emerged. One group specified the necessity of treating the mice by pre-injection of an adenovirus encoding the uPA protein (Azuma et al 2007) to allow engraftment of human cells, and they found that treatment with an anti human complement agent (Futan) to control the bleeding associated with uPA was not necessary. The second group did not need to use adenovirus encoding the uPA expression, but found that the Futan treatment was necessary (Bissig et al 2007). In both cases, the FAH/Rag2$^{-/-}$/il2$^{-/-}$ mouse model was successfully transplanted and repopulated (up to 90% of the mouse liver was repopulated by human hepatocytes 3 months post transplantation). Interestingly, it was shown by histological staining that human hepatocytes were interspersed among mouse hepatocytes and did not form individualized clones. Moreover, highly humanized mice permitted long term expansion and maintenance of human cells, and could be used to perform serial transplantation of human hepatocytes from one humanized mouse to a second generation without requiring a new batch of human cells. Finally the humanized livers of the mice expressed a broad range of human markers, including detoxification enzymes (Azuma et al 2007; He et al 2010), and thus, should be useful for pharmacological studies.

3. Mice with chimeric liver: An efficient tool to study hepatotropic pathogens

It was subsequently shown that both humanized mouse models could be infected by HBV and HCV (Fig.1). The uPA/SCID model has already allowed studying HBV or HCV viral life cycle and direct pathogenesis independently to an immune response. In both models, human hepatocytes, maintain their ability to express numerous enzymes implicated in the metabolism and detoxification (p450 family) pathways (Katoh et al 2007; Strom et al 2010) and are suitable to evaluate both the antiviral potential of drugs and the potential toxicity of antiviral compounds. Moreover, the uPA/SCID mice were used to study hepatic stage of Plasmodium falciparum infection.

It is known that distinct HBV genotypes could participate to the severity of liver disease. In order to improve the definition of virological differences among HBV genotypes, Sugiyama and colleagues used the Alb-uPA/SCID mice as a tool to evaluate HBV replication according to viral genotype and confirmed their in vitro previous results, showing a higher replication of genotype C compared to genotype A (Sugiyama et al 2006). Moreover, in a more recent study they have shown that genotype G, which is not detectable in mono-infection, has a higher level of replication in co-infection with HBV genotype H; and that co-infection may cause fibrosis (Tanaka et al 2008).

Another group has taken advantage of immune suppression of the xenograft mouse model to demonstrate that liver disease induced by HBV is not only the result of activation of the immune system, but can be, at least in part, directly mediated by the virus (Meuleman et al 2006). However, it should be noted that the drastic cytopathic effect was observed using a highly pathogenic strain (HBV genotype E) isolated from a patient with fulminant hepatitis. In a recent study, Lutgehetmann et al demonstrated that, as in vitro and in patients,

interferon alpha failed to induce ISGs (MxA, OAS, TAP-1) in HBV infected hepatocytes, validating the model for the study of direct interaction between virus and host cells (Lutgehetmann et al 2011)

Petersen et al., using the flexibility of the uPA mouse model, which could be repopulated either by Tupaia belangeri or human hepatocytes and infected by Wooly Monkey HBV or HBV respectively, have tested inhibitors of viral entry (Petersen et al 2008). In both systems, the authors showed that the treatment of repopulated mice with acylated HBV preS-derived lipopeptides prevented viral infection. This alternative approach could benefit patients undergoing liver transplantation to prevent vertical transmission as well as reinfection.

This model can establish long lasting chronic infections and constitute a perfect model to study anti-retroviral treatments. Indeed, it has been validated in different reports showing a good responsiveness to several reverse transcriptase inhibitors (lamivudine, adefovil dipivoxil) (Dandri et al 2005; Tsuge et al 2005). Others steps of viral replication can be targeted, it has been demonstrated that in infected mice HAP BAY 41-4109 (inhibition of capsid formation) was able to diminish HBV viremia (Brezillon et al 2011). Finally, the presence of HBV cccDNA in nucleus of infected human hepatocytes will allow testing new therapeutic approaches to clear hepatocytes or to control transcription from cccDNA (Lutgehetmann et al 2010).

Concerning HCV, infected humanized mice have been used to demonstrate antiviral activity of several molecules, (IFNα2b, BILN2061, Telaprevir, HCV-796) that were already used in clinic, or in pre-clinical trials (Kamiya et al 2010; Kneteman et al 2006; Kneteman et al 2009; Vanwolleghem et al 2007). All these molecules have demonstrated antiviral effect against HCV. Moreover the model has permitted to describe cardio-toxicity of BILN2061, confirming the perfect suitability of humanized mice for antiviral therapy evaluation. This model can also been used to study susceptibility of different viral recombinant strains to actual treatments. This will allow strategies from "bench to bedside" to design specific treatment for each patient (Kurbanov et al 2008).

As for HBV, the design of inhibitors targeting several steps of HCV replication is the key to treat patients. In addition to protease and polymerase inhibitors, some groups tried to target viral entry. Meuleman et al have demonstrated the ability of antibodies directed against cellular surface molecules (CD81 and SR-B1) involved in virus entry to protect human hepatocytes from HCV infection (Meuleman et al 2008; Meuleman et al 2011a; Meuleman et al 2011b). Matsumura et al have shown that amphipatic DNA polymers inhibited HCV post-binding stage and thus blocked de novo infection (Matsumura et al 2009)

It is clear that the immune response to viral infection plays a major role in the outcome of liver disease during HCV infection. To study the involvement of the innate immune system against viral infection, Walters et al., used the immunotolerant Alb-uPA/SCID mouse model to analyze transcriptome profiles of HCV infected versus non infected mice (Walters et al 2006). Globally, in the Alb-uPA/SCID mouse model, HCV infection activates the transcription of interferon-stimulated genes which are in particular implicated in establishing the innate immune response, and thus active in the inhibition of HCV replication. Moreover, and as previously shown in HCV-infected patients and HCV transgenic mice, these authors confirmed in the Alb-uPA/SCID mouse model the relationship between severe HCV infection and perturbation of lipid metabolism (Joyce et al

2009). These observations strongly suggest that liver disease may not be mediated exclusively by an HCV-specific adaptive immune response. Thus, the innate immune response may play a fundamental role in the pathogenesis of HBV and HCV infection.

Infection by the Plasmodium falciparum parasite is restricted to human and closely related species. As for the HBV and HCV viruses, ethical and financial reasons limit the use of non human primates to study this pathogen. Numerous studies have used a humanized mouse that carries human erythrocytes (Moreno et al 2007). Sporozoites, the hepatic stage of the pathogen [for review in the viral cycle of Plasmodium falciparum see (Greenwood et al 2008)] were used to infect chimeric liver of humanized Alb-uPA/SCID mice. The authors demonstrated that the reduction of the innate immune response by anti-macrophage and anti-NK cell treatments both enhance the humanization of Alb-uPA/SCID mice and allowed the infection of human hepatocytes by sporozoites as well as the maturation of the pathogen (Morosan et al 2006). This new model should permit the evaluation of drugs directed specifically against the hepatic stage of the infection. This model has also been used to study biology of P. falciparum, using genetically knock out for Liver-stage antigen-1 parasite, that could show that LSA-1 plays a critical role during late liver-stage schizogony and is thus important in the parasite transition from the liver to blood (Mikolajczak et al 2011). Moreover, this constitutes a starting point to create a future humanized model allowing study of the entire parasite cycle.

4. Concluding remarks

The recent development of small mouse models for experimental HBV, HCV or Plasmodium falciparum infection has opened new perspectives for the evaluation of novel therapeutic and/or prophylactic compounds against these pathogens. These models are physiologically relevant, in that they are based on the transplantation of primary hepatocytes. However, to integrate humanized mouse technology into development process, the technology must be accessible, reproducible and at a reasonable cost. Indeed, both mouse models are relatively complicated to use, but they present the unquestionable advantage of being much less expensive and easier to maintain and breed than primates.

The present challenge is the construction of mice combining human immune and liver cells. Mice with humanized immune systems already represent the model of choice for various lymphotropic pathogens. The addition of human hepatic tissue holds promise for the study of hepatotropic pathogens. Indeed, this will help to understand how hepatotropic pathogens are detected by the immune system, why the majority of individuals fail to mount an effective response, the factors involved in chronic viral persistence versus resolution of infection. A recent report Washburn et al have developed a specific mouse model, humanized with human immune system and liver tissues (Washburn et al 2011). These mice generate a specific immune response against the HCV and seem to develop liver diseases.

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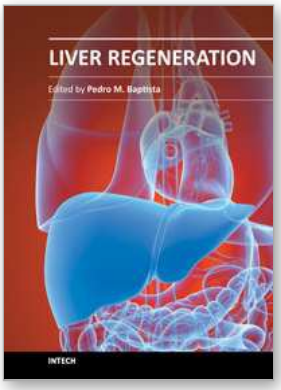

Liver Regeneration

Edited by PhD. Pedro Baptista

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Doctors and scientists have been aware of the "phenomenom" of liver regeneration since the time of the ancient Greeks, illustrated by the mythic tale of Prometheus' punishment. Nevertheless, true insight into its intricate mechanisms have only become available in the 20th century. Since then, the pathways and mechanisms involved in restoring the liver to its normal function after injury have been resolutely described and characterized, from the hepatic stem/progenitor cell activation and expansion to the more systemic mechanisms involving other tissues and organs like bone-marrow progenitor cell mobilization. This book describes some of the complex mechanisms involved in liver regeneration and provides examples of the most up-to-date strategies used to induce liver regeneration, both in the clinic and in the laboratory. The information presented will hopefully benefit not only professionals in the liver field, but also people in other areas of science (pharmacology, toxicology, etc) that wish to expand their knowledge of the fundamental biology that orchestrates liver injury and regeneration.

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