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REVIEW

Human genetic basis of fulminant viral hepatitis

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Abstract

In rare cases, hepatitis A virus (HAV) and hepatitis B virus (HBV) can cause fulminant viral hepatitis (FVH), characterized by massive hepatocyte necrosis and an inflammatory infiltrate. Other viral etiologies of FVH are rarer. FVH is life-threatening, but the patients are typically otherwise healthy, and normally resistant to other microbes. Only a small minority of infected individuals develop FVH, and this is the key issue to be addressed for this disease. In mice, mouse hepatitis virus 3 (MHV3) infection is the main model for dissecting FVH pathogenesis. Susceptibility to MHV3 differs between genetic backgrounds, with high and low mortality in C57BL6 and A/J mice, respectively. FVH pathogenesis in mice is related to uncontrolled inflammation and fibrinogen deposition. In humans, FVH is typically sporadic, but rare familial forms also exist, suggesting that there may be causal monogenic inborn errors. A recent study reported a single-gene inborn error of human immunity underlying FVH. A patient with autosomal recessive complete IL-18BP deficiency was shown to have FVH following HAV infection. The mechanism probably involves enhanced IL-18- and IFN-γ-dependent killing of hepatocytes by NK and CD8 T cytotoxic cells. Proof-of-principle that FVH can be genetic is important clinically, for the affected patients and their families, and immunologically, for the study of immunity to viruses in the liver. Moreover, the FVH-causing *IL18BP* genotype suggests that excessive IL-18 immunity may be a general mechanism underlying FVH, perhaps through the enhancement of IFN-γ immunity.

Introduction

Acute liver failure (ALF) is a life-threatening condition characterized by massive necrosis of the liver in humans. Clinical manifestations include a severe impairment of hepatic function, with progressive jaundice, disturbed coagulation, and encephalopathy developing within 8 weeks of the onset of the first symptoms and signs, at least in individuals without preexisting liver disease. The main causes of ALF are diverse and include paracetamol toxicity, metabolic disorders (such as Wilson's disease), autoimmune diseases, and infection with liver-tropic viruses, also known as fulminant viral hepatitis (FVH) (Stravitz and Lee 2019; Bernal and Wendon 2013; Bernal et al. 2010; Ganger et al. 2018; Kathemann et al. 2015; Ichai and Samuel 2008). Around 5% of all cases of ALF remain unexplained (Ganger et al. 2018). The percentage of ALF due to viral infections ranges from 10 to 45% depending on geographic area (Stravitz and Lee 2019; Colleti Junior et al. 2019). Hepatitis A virus (HAV) and hepatitis B virus (HBV) are the liver-tropic viruses most frequently implicated in FVH (Liu et al. 2001; European Association for the Study of the Liver 2017). Other viruses, such as herpes viruses, may be involved to a lesser extent. The current prevalence and incidence of FVH worldwide are not precisely known, but previous studies have suggested that FVH develops in no more than 0.5% and 0.1% of individuals with symptomatic HAV (Lemon et al. 2018) and HBV (Asgari et al. 2019) infections, respectively. The outcome is poor, with fewer than 20% of patients surviving in the absence of liver transplantation. By contrast, survival rates may reach 80% after liver transplantation (Lemon et al. 2018; Bernal et al. 2015). Very little is known about the pathogenesis of FVH. Its rarity and typically sporadic nature suggested that the causal viruses were unlikely to be abnormally virulent (Ajmera et al. 2011; Fujiwara et al. 2001; Sato

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et al. 2003). Several groups have reported the more frequent occurrence of some HBV mutations in patients with FVH than in patients with other forms of HBV infection (Sainokami et al. 2007; Ozasa et al. 2006; Friedt et al. 1999). Conversely, reports of rare multiplex and/or consanguineous families have suggested a possible contribution of inborn errors of immunity (IEI) (Durst et al. 2001; Yalniz et al. 2005; Yoshida et al. 2017). Moreover, single-gene IEI have been found to underlie other severe, isolated viral infections, such as herpes simplex virus encephalitis, attenuated live measles and yellow fever vaccine diseases, Kaposi sarcoma, severe influenza pneumonitis, epidermodysplasia verruciformis, and fulminant EBV disease (Byun et al. 2013; Ciancanelli et al. 2015, 2016; Jong et al. 2018a, b; Hernandez et al. 2018, 2019; Jackson et al. 2016; Tangye and Latour 2020; Zhang and Casanova 2015; Zhang et al. 2018, 2019; Lafaille et al. 2012, 2015; Latour and Fischer 2019). These observations suggest that FVH may be caused by a liver IEI to viruses. Here, we review the mouse and human genetic studies leading to the recent discovery of the first inborn error of liver immunity to viruses.

Genetic studies in mice

Human hepatitis viruses are not natural pathogens of mice. Alternative infectious and non-infectious mouse models have, therefore, been developed, for dissection of the pathogenesis of FVH. The most common infectious model of hepatitis is based on viruses from the mouse hepatitis virus (MHV) family. These viruses are coronaviruses, which resemble HAV in being single-stranded (+) RNA viruses, but differ from HAV in having an envelope. MHVs differ in tissue tropism and virulence, with the hepatotropic viruses MHV3 and MHVA59 having high and low virulence, respectively (Le Prevost et al. 1975a; Wijburg et al. 1997). In mice, MHV3 infection leads to a spectrum of hepatic phenotypes, ranging from high susceptibility to complete resistance, depending on genetic background. The BALB/c and C57BL6 strains are both highly susceptible to MHV3 infection, whereas the A/J strain is resistant, except during the neonatal period (Le Prevost et al. 1975b; Tardieu et al. 1980; Levy et al. 1981). A cytopathic effect of the virus is not the only explanation for this, as viral replication in hepatocytes is similar in susceptible and resistant mice (Taguchi et al. 1983; Levy et al. 1983). Hepatic failure is the major disorder observed in susceptible mice, but hepatocytes are not the only cells targeted by MHV3. This virus also replicates in endothelial (sinusoidal and vascular) and immunological cells (hepatic macrophages, also known as Kupffer cells, and natural killer (NK) cells) (Pereira et al. 1984). MHV3 infection has been studied for decades, both genetically and immunologically, to decipher the spectrum of infectious phenotypes (Le Prevost et al. 1975a).

In the 1970s, macrophages and lymphocytes (Tardieu et al. 1980) were reported to be involved in the anti-MHV3 immune response, together with type I (in vivo) and type II (in vitro) interferons (IFNs) (Virelizier et al. 1976; 1977; Virelizier and Gresser 1978). In 1979, Levy-Leblond et al. showed, by crossing MHV3-resistant and MHV3-susceptible mouse strains, that acute liver disease was determined by one or two genes unrelated to the H-2 complex with a recessive mode of inheritance (Levy-Leblond et al. 1979). A few years later, another group published results confirming the model of two recessive genes unrelated to the H-2 locus (Dindzans et al. 1986). They also established a link between susceptibility to MHV3 infection and the level of macrophage procoagulant activity (PCA) (Dindzans et al. 1986). This link was confirmed by the treatment of susceptible mice with a neutralizing antibody against MHV3-induced PCA, which rendered these mice resistant, and by the induction of PCA in resistant mice, which rendered them susceptible (Li et al. 1992; Fingerote et al. 1996). Following molecular cloning, the *Fgl2* gene was identified as encoding an interferon (IFN)γ-inducible fibrinogen-like protein, responsible for macrophage PCA (Levy et al. 1981; Qureshi et al. 1995; Parr et al. 1995a, b). Its expression promotes fibrinogen deposition, leading to the activation of coagulation cascades and PCA. By contrast to the nucleocapsid proteins of non-hepatotropic MVHs, the nucleocapsid (N) protein of MHV3 and MHVA59 is required for the induction of *Fgl2* expression, through the binding of the transcription factor hepatic nuclear factor 4 to the *Fgl2* promoter (Ning et al. 1999; 2003) Finally, following MHV3 infection, *Fgl2*-knockout (KO) mice display milder disease and lower mortality than wild-type mice, suggesting a key role for FGL2 in the pathogenesis of MHV3-induced FVH (Marsden et al. 2003).

Reverse genetics techniques have been used to dissect out the mechanism of MHV3-induced FVH in greater detail. A few KO mice have been tested, some of which were more susceptible than WT mice, with earlier and higher mortality. These models included knockouts of programmed death (PD)-1, IL-33 and V-set immunoglobulin domain-containing 4 (VSIG4) (Carriere et al. 2017; Chen et al. 2011; Li et al. 2017). PD-1 modulates the balance between the antimicrobial immune response and immune system-mediated tissue damage. IFNγ and TNFα are more strongly induced in PD-1-KO mice than in WT mice, leading to higher levels of FGL2 secretion and greater tissue damage. Treatments blocking IFNγ and TNFα decrease mortality in PD-1-KO mice, suggesting a role for these two cytokines in the pathogenesis of MHV3-induced FVH (Chen et al. 2011). IL-33 is a ubiquitously and constitutively expressed cytokine. It

belongs to the IL-1 family and has pleiotropic functions, including IFNγ induction and inflammatory effects (Carriere et al. 2017). MHV3 infection in IL-33-KO mice is associated with an increase in neutrophil recruitment and a lack of infiltrating NK cells, T cells, and macrophages (Carriere et al. 2017). These mice display lower levels of IFNγ induction, but much higher levels of TNFα and IL-6 induction than WT mice during infection. Finally, VSIG4 is a complement receptor of the immunoglobulin superfamily. It is expressed exclusively in tissue macrophages, including Kupffer cells. Inflammatory cytokines, not only such as IFNγ and TNFγ but also FGL2, are strongly induced in VSIG4-KO mice, leading to uncontrolled macrophage-mediated inflammation and tissue damage (Li et al. 2017).

By contrast, other KO mice become resistant to MHV3-induced FVH. For example, mortality was shown to be much lower in B- and T-lymphocyte attenuator (BTLA)-KO mice than in their WT littermates (Yang et al. 2013). This resistant phenotype is related to a lack of FGL2 induction, resulting in lower levels of fibrinogen deposition and tissue damage. Despite similar levels of IFNγ and TNFα production in WT and BLTA-KO mice, macrophage apoptosis rates were higher in BTLA-KO mice, and a smaller number of these macrophages infiltrated the liver (Yang et al. 2013). TNFα-KO mice were also found to have a resistant phenotype, due to lower levels of FGL2 induction (Yang et al. 2013). In another study, C5aR-KO mice were found to be resistant to MHV3-induced FVH, with lower mortality, reflecting lower levels of TNFα, IL6 and FGL2 induction, whereas IFNγ production was similar to that in WT mice (Liu et al. 2015). Interestingly, macrophage scavenger receptor 1 (MSR1)-KO mice were less susceptible to MHVA59-induced FVH. The authors reported a lower induction of inflammatory cytokines (TNFα, IL-6 and IFNγ) and lower levels of FGL2 and C5a secretion (Tang et al. 2018). FLG2- and TNFα-KO mice were confirmed to be resistant to infection, whereas IL-6-KO mice have a phenotype similar to that of WT mice (Liu et al. 2015). Finally, TLR2 is strongly induced during MHV3 infection, as are IL6, IL33 and TNFα (Li et al. 1992). TLR2-KO mice are less susceptible to MHV3 infection than WT mice, with lower levels of viral replication and liver damage, and delayed mortality. These findings reflect lower levels of inflammatory cytokine production, but not of FGL2 production, together with a delayed recruitment of neutrophils, macrophages and NK cells (Bleau et al. 2016). Overall, they suggest that, in the mouse model, MHVA59- or MHV3-induced FHV results from uncontrolled PCA due to high levels of inflammation and macrophage activation, leading to high levels of fibrinogen deposition and tissue damage.

Genetic studies in humans

Very little is known about the pathogenesis of human FVH. The human *FGL2* gene was identified following studies in mice (Levy et al. 2000). In patients with FVH due to HBV, FGL2 is strongly expressed in macrophages in liver tissue, as observed in the mouse model. Plasma concentrations of FGL2, IFNγ, IL-1β, and IL-18 are higher in patients with FVH than in healthy or chronically infected individuals without FVH (Liu et al. 2015; Shinoda et al. 2006; Yumoto et al. 2002; Zhu et al. 2005). Activated $CD68^+$ macrophages have been detected in areas of active necrosis (Levy et al. 2000). The serum viral load in patients with FVH due to HAV or HBV is similar to or lower than that in patients with acute benign HAV or HBV hepatitis (Sainokami et al. 2007; Ozasa et al. 2006; Rezende et al. 2003). These observations suggest that the clinical phenotype is probably due more to a lack of inflammation regulation than to a lack of control over viral replication. Interestingly, three multiplex families with FVH due to HAV have been described: an Iranian family with three previously healthy siblings (17, 19 and 24 years old), a Turkish family including an affected brother and sister (16 and 18 years old), and a Japanese family with two affected brothers (59 and 63 years old) (Durst et al. 2001; Yalniz et al. 2005; Yoshida et al. 2017), consistent with genetic predisposition. Despite these findings, little is known about the pathogenesis of FVH in humans. Genetic studies have recently been performed on large cohorts of FVH patients, with either a candidate gene approach or a genome-wide approach. These studies yielded suggestive, but not conclusive findings.

A first human genetic study was published in 2011 by Kim et al. (2011). In this paper, the authors reported a case–control study on children from Argentina (30 children with FVH due to HAV and 102 controls) and one candidate gene *TIM1*, also known as *HAVCR1*, encoding the HAV receptor. They found a difference of borderline significance in the distribution of the 157insMTTTVP insertion between patients and controls (p value 0.037), with an allelic frequency of the insertion of 37% in patients and 28% in controls. This insertion leads to the production of an elongated form of the receptor. HAV infects hepatocytes expressing the short and long forms of this receptor with equal efficiency. However, NKT cells expressing the long form of TIM1 are more cytotoxic, potentially accounting for the rapid destruction of hepatocytes. This study was the first to investigate why only some HAV-infected individuals develop FVH. However, given the incidence of the disease, the allele frequency in the general population is too high to be compatible with the hypothesis of single-gene IEI, as previously reported in other severe viral

diseases (Byun et al. 2013; Ciancanelli et al. 2015, 2016; Jong et al. 2018a, b; Hernandez et al. 2018, 2019; Jackson et al. 2016; Tangye and Latour 2020; Zhang and Casanova 2015; Zhang et al. 2018, 2019; Lafaille et al. 2012, 2015; Latour and Fischer 2019). In 2014, a second study was performed on a cohort of ten adult patients with acute liver injury or failure due to HAV. This study made use of a "hypothesis-free" strategy based on whole-genome sequencing. The authors initially analyzed their data under a hypothesis of genetic homogeneity, implying that one or several mutations of the same gene were common to most patients. No rare mutation meeting this criterion was detected under either the autosomal recessive (AR) or the autosomal dominant (AD) genetic model. Under a hypothesis of genetic heterogeneity, implying that each patient has a mutation of a different gene, the authors identified eight candidate genes, four under the AR model and four under the AD model, but no further functional investigations were performed to establish a genotype–phenotype correlation (Long et al. 2014).

More recently, two other genetic studies have been performed on cohorts of patients with FVH due to HBV. In 2018, Ajmera et al. compared exome data from 14 patients with FVH, and 50 patients with chronic or acute (non-FVH) hepatitis to exome data for 2963 controls, all of European ancestry (Ajmera et al. 2019). They identified one single-nucleotide polymorphism (SNP), a missense mutation (rs2277680, A181V) in *CXCL16*, which was underrepresented in the FVH cohort relative to the others (only 9% of patients in the FVH cohort had a valine residue at position 181 (V181) vs. 43–50% in the others), including the controls, with a p value of 8.8×10^{-5}. CXCL16 is a chemokine highly expressed in liver, especially on cholangiocytes, hepatocytes and hepatic endothelial cells, and it interacts with the CXCR6 receptor expressed on NKT cells. Functional studies have shown that the V181 allele cannot mediate monocyte adhesion ex vivo (Petit et al. 2011). Ajmera et al. hypothesized that the overrepresented A181 allele has a deleterious impact due to greater NKT cell adhesion, which may mediate hepatic inflammation, leading to massive destruction of the liver in FVH patients. In 2019, an association study on exome data compared 21 cases of FVH in adult patients to 172 HBV^+ controls (Asgari et al. 2019). At the single-variant and gene-based levels, the analyses found no significant association. These results suggest various possibilities: predisposition to FVH may not be inherited, or may be caused by monogenic lesions in some patients, and perhaps digenic or oligogenic lesions in others, with a high degree of genetic heterogeneity (with patients carrying FVH-causing variants of different genes).

In this context, we recently reported a child who died from FVH following infection with HAV who was homozygous for a private 40-nucleotide deletion in *IL18BP*, which encodes the IL-18-binding protein (IL-18BP) (Belkaya et al. 2019). Unlike the four non-synonymous variants of this gene found in the homozygous state in public databases, this variant is loss-of-function. IL18BP is a soluble antagonist of IL18, an inflammatory IFNγ-inducing cytokine that activates NK and T-cell cytotoxicity. IL18BP has a high affinity for IL18 and blocks the binding of this cytokine to its membrane-bound receptor, IL18R. IL-18 is hepatotoxic and was initially identified as the cytokine responsible for liver failure in the mouse model (Okamura et al. 1995; Tsutsui et al. 1992). Human IL-18 and IL-18BP are both produced by hepatocytes and macrophages, which are destroyed and highly activated, respectively, during FVH. We have shown that, in the absence of IL-18BP, excessive NK cell activation by IL-18 results in the uncontrolled killing of human hepatocytes in vitro. We suggest that the lack of negative regulation of IL-18 by IL-18BP in vivo leads to the enhanced activation and production of IFN-γ by NK and T lymphocytes in patients, resulting in the activation of macrophages and hepatocyte killing (Fig. 1). Inherited human IL-18BP deficiency thus underlies fulminant HAV hepatitis by unleashing IL-18, and possibly IFN-γ. These findings suggest that human IL-18 is toxic to the liver and that IL-18BP is its antidote.

Conclusion

In conclusion, the discovery of IL-18BP deficiency as a genetic etiology of FVH provided proof-of-principle that FVH can be caused by single-gene inborn errors selectively disrupting liver-specific immunity to viruses. It also points to IL-18 as an anchor molecule in the pathogenesis of FVH. The massive killing of hepatocytes due to uncontrolled inflammation seems to be the mechanism underlying the pathogenesis of FVH. However, the genetic and mechanistic dissection of FVH pathogenesis remains in its infancy. Further studies are required to determine, in more detail, the roles of hematopoietic cells (cytotoxic lymphocytes, macrophages) and non-hematopoietic cells (hepatocytes) in the establishment of FVH. The discovery of an IEI underlying FVH is important from a clinical standpoint, as it makes it possible to deliver a diagnosis to patients and their families, and from an immunological standpoint, as it will facilitate the deciphering of liver-intrinsic immunity. These studies may pave the way for the development of novel preventive or therapeutic interventions. Recombinant human IL-18BP (Tadekinig Alfa; AB2 Bio) has been proposed as a treatment for preventing acetaminophen hepatotoxicity (Bachmann et al. 2018). There may be other ways to manage patients who would die from infection without liver transplantation, a procedure that remains associated with heavy short- and long-term morbidity and mortality. The discovery of novel genetic etiologies of FVH may also pave the

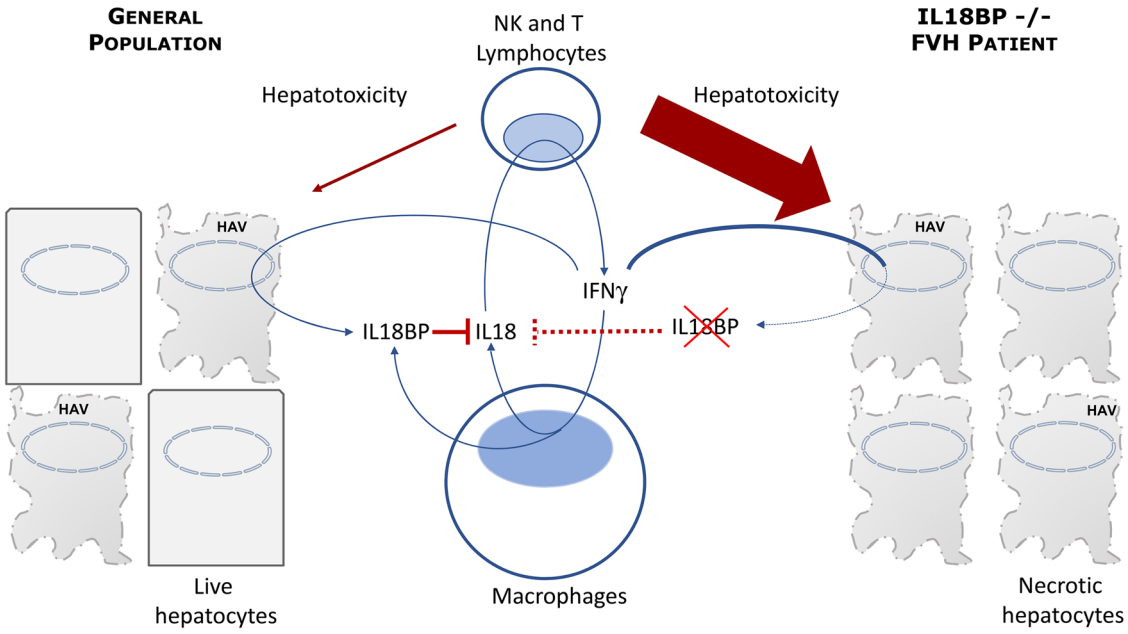

Fig. 1 Schematic model of FVH pathogenesis in IL18BP deficiency. Following HAV infection in a healthy individual, IL-18 is secreted by macrophages in the liver. This cytokine activates NK and T lymphocytes, inducing IFN-γ production and cytotoxicity to eliminate HAV-infected cells. IFN-γ also induces IL-18BP secretion by hepatocytes and macrophages to antagonize IL-18 activity. However, in the absence of IL-18BP, excessive IL-18 activity leads to uncontrolled, massive immune-mediated hepatotoxicity and severe liver injury

way for the development of a new treatment for other forms of fulminant hepatitis, such as acetaminophen-induced hepatitis, and, perhaps, chronic hepatitis.

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