Natural History, Clinical Manifestations, and Pathogenesis of Hepatitis A

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Hepatitis A virus (HAV) is transmitted by the fecal–oral route and is a major cause of acute viral hepatitis. The clinical manifestations of HAV infection range from asymptomatic infection to acute liver failure (ALF), but do not include progression to chronic hepatitis. Risk factors for severe acute hepatitis A are older age (>40 years) and preexisting liver disease. Some patients may show atypical clinical features such as relapsing hepatitis, prolonged cholestasis, or extrahepatic manifestations. Almost all hepatitis A patients spontaneously recover with supportive care. However, in the case of ALF (<1%), intensive care and urgent decision on liver transplantation are required. Liver injury during hepatitis A is not directly caused by HAV but is known to be caused by immune-mediated mechanisms. In this review, the natural history and clinical manifestations of hepatitis A are described. In addition, mechanisms of immunopathogenesis in hepatitis A are discussed.

Hepatitis A virus (HAV) is transmitted by the fecal–oral route and is a major cause of acute viral hepatitis, which can lead to acute liver failure (ALF) and mortality in severe cases. The number of global hepatitis A cases was ~1.4 million with 27,731 deaths in 2010 (Havelaar et al. 2015). HAV infection often causes symptomatic hepatitis in adults, whereas it tends to result in an asymptomatic subclinical infection in children. Following socioeconomic development and public health improvement, the global incidence of HAV infection has been decreasing. However, an increasing number of individuals are infected at older ages, leading to more severe clinical manifestations and greater disease bur-

den (Murphy et al. 2016). The clinical manifestations of HAV infection range from asymptomatic infection to ALF, and some patients show atypical features such as relapsing hepatitis or prolonged cholestatic hepatitis, as well as extrahepatic manifestations. In this review, we consider pitfalls in the diagnosis of hepatitis A, therapeutic considerations including predictors for urgent liver transplantation, and mechanisms of pathogenesis.

NATURAL HISTORY OF HEPATITIS A

HAV is highly stable in ambient temperatures and can withstand low pH, drying, and deter-

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Figure 1. A typical course of hepatitis A. After a 3- to 5-week incubation period following hepatitis A virus (HAV) infection, patients develop symptoms of hepatitis with elevation of serum alanine aminotransferase (ALT) levels. Fecal virus shedding and viremia are present and peak during the incubation period. Anti-HAV antibodies appear in serum first as immunoglobulin (Ig)M and subsequently as IgG. Virus-specific T-cell responses coincide with the elevation of serum ALT levels.

gents. HAV inactivation requires heating foods ($>85^{\circ}\text{C}$) for 1 min or disinfecting surfaces with a 1:100 dilution of sodium hypochlorite (household bleach) for 1 min (Nainan et al. 2006). After ingestion of HAV through the fecal–oral route, HAV survives the acidic stomach environment and is ultimately delivered to the liver. Whether it first replicates at a primary site within the gastrointestinal tract is uncertain. HAV replicates in hepatocytes and is then secreted into bile and thus back into the gastrointestinal tract. It is finally excreted via feces or transferred to the liver through an enterohepatic cycle until virus neutralization (Cuthbert 2001).

Following an incubation period of 15–50 days (mean, 30 days) after HAV infection, patients develop symptoms of acute hepatitis with elevated levels of serum aspartate/alanine aminotransferases (AST/ALTs) (Fig. 1). Before symptoms, there are waves of viremia and copious amounts of fecal viral shedding. Feces are the primary source of HAV transmission because of their high viral load. In comparison, serum HAV concentrations are two or three $\log_{10}$ units lower than in the feces (Martin and Lemon 2006). Therefore, risk of transmission is highest during the prodromal phase before symptoms or biochemical manifestations. The virus is also shed in the saliva at even lower concentrations (Amado Leon et al. 2015). Con-

cordant with clinical hepatitis, anti-HAV immunoglobulin M (Ig)M and subsequently anti-HAV IgG appear in the serum and saliva, accompanied by a marked reduction of fecal virus shedding and viremia (Fig. 1). Although anti-HAV IgM is detectable for up to 6 months, anti-HAV IgG persists, conferring lifelong immunity (Normann et al. 2004).

CLINICAL MANIFESTATIONS OF HEPATITIS A

Clinical Signs and Symptoms of Acute Hepatitis A

The clinical manifestations of HAV infection range from asymptomatic infection to ALE, but it does not progress to chronic hepatitis. Development of symptomatic hepatitis is associated with patient age. Relatively few children under 6 years of age ($<30\%$) manifest hepatitis symptoms, whereas the majority of adults ($>70\%$) develop symptoms that persist for 2–8 weeks (Fig. 2) (Armstrong and Bell 2002). The onset of hepatitis A is often abrupt with fever (18%–75%), malaise (52%–91%), nausea or vomiting (26%–87%), abdominal discomfort (37%–65%), and then dark urine (28%–94%) and jaundice. Less commonly, pruritus, diarrhea, arthralgia, or skin rash develop. When

Clinical Manifestations and Pathogenesis of Hepatitis A

Figure 2. The clinical outcomes of hepatitis A virus (HAV) infection. Clinical manifestations of HAV infection depend on the age of patients. Most adult patients develop symptomatic hepatitis, whereas most young children do not. Common hepatitis symptoms are fever, malaise, nausea or vomiting, abdominal discomfort, and dark urine and jaundice. Reported extrahepatic complications include acute kidney injury, acalculous cholecystitis, pancreatitis, pleural or pericardial effusion, hemolysis, hemophagocytosis, pure red-cell aplasia, acute reactive arthritis, skin rash, and neurological manifestations such as mononeuritis, Guillain–Barré syndrome, and transverse myelitis.

the patient seeks medical advice, the fever has usually disappeared. On physical examination, hepatomegaly (78%) and jaundice (40%–80%) are frequently detected (Koff 1992; Khan et al. 2012).

Laboratory Findings and Diagnosis

Laboratory results show elevated levels of total bilirubin (mean peak level of 7–13 mg/dL), alkaline phosphatase (mean peak level of 319–335 IU/L), and ALT (mean peak level of 1952–3628 IU/L). Sometimes, very high levels of ALT (~10,000 IU/L) are observed, but this is not a poor prognostic indicator (Tong et al. 1995; Jung et al. 2010b). Prolonged prothrombin time ([PT] <40%) and high bilirubin levels in the absence of hemolysis indicate severe hepatitis with a potential risk for ALF. Radiological findings of hepatitis A include hepatomegaly, gallbladder wall thickening more than 3 mm (80%) with arterial heterogeneity, periportal tracking, and perihepatic lymph node enlargement (>7 mm in diameter) (Fig. 3) (Park et al. 2013). Gallbladder wall thickening is associated with high bilirubin levels and may be an independent factor of severe hepatitis, which is defined as PT ≤ 40% or bilirubin ≥ 10 mg/dL (Suk et al. 2009).

Because symptoms or biochemical laboratory findings are nonspecific for HAV infection,

serological confirmation is essential for diagnosis. Detection of serum anti-HAV IgM via commercially available assays is the primary diagnostic method in clinical settings. However, 6%–11% of symptomatic patients do not show a detectable anti-HAV IgM at clinical onset, especially during the early symptomatic phase (Jung et al. 2010b; Lee et al. 2013). Therefore, repeated examination of anti-HAV IgM 2 to 5 days after the first examination should be performed if there is clinical suspicion. Seroconversion to anti-HAV IgM positivity on the second examination leads to the correct hepatitis A diagnosis. Rarely (8%–20%), anti-HAV IgM can be transiently detected in persons who have recently received an HAV vaccine (Nainan et al. 2006). Previous HAV infection is diagnosed by a positive serum anti-HAV test in the absence of IgM anti-HAV. Although saliva anti-HAV IgM testing can be used as a screening test in the setting of outbreak investigations, its sensitivity is lower than serum testing (Amado Leon et al. 2015).

Complications of Acute Hepatitis A

HAV infection is self-limited and does not progress to chronic hepatitis. However, 10%–20% of patients develop relapsing hepatitis or prolonged cholestasis lasting for more than 6

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Figure 3. Radiological findings of hepatitis A. (A) Transabdominal ultrasonography shows diffuse wall thickening of the gallbladder (arrows) measuring ~10 mm. (B) Transverse computed tomography (CT) scan depicts low attenuating halo around the right portal vein indicating periportal tracking (arrowheads). Perihepatic lymph node enlargement is also noted (arrow).

months (Fig. 2). Relapsing hepatitis develops in up to 12% of patients after initial hepatitis resolution but is mostly a milder form of hepatitis compared with the initial one. Viremia and fecal viral shedding reappear with relapsing hepatitis (Glikson et al. 1992). A study using a chimpanzee model suggested that relapsing hepatitis might be associated with rapid contraction of or failure to maintain virus-specific CD4⁺ T-cell responses (Zhou et al. 2012).

Prolonged cholestasis (total bilirubin level >5 mg/dL lasting for >4 weeks) is observed in 5%–7% of patients and presents with pruritus and fatigue. It is related to preexisting chronic

hepatitis B, prolonged PT, and high total bilirubin at initial examination (Jung et al. 2010b). Although these patients show severe cholestasis with total bilirubin levels of up to 40 mg/dL, patients are generally in good condition with nearly normal levels of AST/ALT and PT and finally recover.

Acute Liver Failure in the Setting of HAV Infection

Hepatitis A severity is related to age at infection and preexisting liver diseases. ALF, which develops in 0.015%–0.5% of hepatitis A patients, has

the highest rates in older adults (>40–50 years of age) and patients with underlying chronic liver diseases with limited hepatic functional reserve (Chen et al. 2016; Murphy et al. 2016). In a prospective, multicenter study in South Korea of 595 adult hepatitis A cases (mean age of 31 years), 99.5% of patients spontaneously recovered, 0.5% developed ALF, and 0.2% experienced ALF-related mortality (Jung et al. 2010b). The 1988 Shanghai hepatitis A epidemic, which affected >300,000 people mostly in their 20s to 40s, showed a similar case fatality rate (0.015%). In that study, the case fatality rate of hepatitis A with underlying chronic hepatitis B (0.05%) was 5.6 times higher than in those without hepatitis B virus infection (0.009%) (Keeffe 1995; Cooksley 2000).

The effect of HAV viral load on the ALF risk is controversial. One study reported that lower serum HAV viral load was associated with a higher risk of ALF (Rezende et al. 2003). However, more recent studies have shown that a higher viral load is related to ALF (Lee et al. 2015). Variable blood sampling times and the fluctuating nature of viremia during the acute phase may be related to this discrepancy. Likewise, although nucleotide sequence variation in the 5' nontranslated segment of the HAV genome has been associated with severe acute hepatitis A, this has not been confirmed (Fujiwara et al. 2002; Kanda et al. 2010; Ajmera et al. 2011). A human genetic polymorphism, 157insMTTVP, in the gene encoding T-cell immunoglobulin and mucin domain-1 (TIM1)/HAVCR1 was associated with ALF in Argentinean patients (Kim et al. 2011). TIM1 is a phosphatidylserine receptor that facilitates cellular entry of many enveloped viruses. Recent studies show that it does not play an essential role in HAV entry, but TIM1 does enhance uptake of quasi-enveloped “eHAV” virions (Das et al. 2017).

HAV-related ALF outcomes from a U.S. study ($n = 29$) and a South Korean study ($n = 35$) similarly showed that 55%–57% of patients spontaneously recovered, 31%–38% underwent liver transplantation, and 6%–14% died without transplantation (Fig. 2). A prognostic model incorporating serum ALT <2600 IU/L, creatinine >2.0 mg/dL, intubation, and pressor use was

proposed for predicting transplantation or death (Taylor et al. 2006). An independent factor for spontaneous survival was degree of hepatic encephalopathy in the Korean study (Kim et al. 2008).

Extrahepatic Manifestations

Reported extrahepatic manifestations include acute kidney injury, acalculous cholecystitis, pancreatitis, pleural or pericardial effusion, hemolysis, hemophagocytosis, pure red-cell aplasia, acute reactive arthritis, skin rash, and neurological manifestations such as mononeuritis, Guillain-Barré syndrome, and transverse myelitis (Jeong and Lee 2010). Acute kidney injury (AKI), defined by serum creatinine level >2.0 mg/dL or at least a 1.5-fold increase from baseline serum creatinine level, develops in 1.5%–7.6% of hepatitis A patients (Jung et al. 2010b; Choi et al. 2011). Prerenal azotemia, interstitial nephritis, and acute tubular necrosis predominantly contribute to AKI in hepatitis A along with intravascular hemolysis, direct hepatotoxicity of hyperbilirubinemia, or immune complex-associated glomerulopathy. It is associated with older age (>40 years), male sex, diabetes, high alcohol intake, leukocytosis, elevated C reactive protein (CRP) level, higher bilirubin level, higher AST/ALT level, or low albumin level. In nonfulminant hepatitis A, 10%–50% of AKI cases require renal replacement therapy (Jung et al. 2010a). Rare cases of autoimmune hepatitis following hepatitis A have been reported. However, prior HAV infection has been associated with a lower probability of having hay fever and asthma (Matricardi et al. 2002).

Hepatitis A during pregnancy is generally benign. However, preterm uterine contraction is commonly associated with HAV infection, especially during the second and third trimester. This may be associated with proinflammatory cytokines or hyperbilirubinemia. In Israel, 13 pregnant cases showed a high rate (9/13, 69%) of gestational complications such as premature contraction, placental separation, premature rupture of membranes, and vaginal bleeding (Elinav et al. 2006). In 12 South Korean pregnancy cases, there were two preterm labors, one

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premature rupture of membranes, and one fetal ascites and intraabdominal calcification, which spontaneously resolved (Cho et al. 2013). Fetal meconium peritonitis may be related to intra-uterine HAV infection, which in two reported cases led to neonatal small bowel perforation (Leikin et al. 1996; McDuffie and Bader 1999). However, fetal outcome is generally benign and mother-to-child transmission is very rare. Although HAV RNA may be detected in breast milk, breastfeeding is not contraindicated.

Management

There is no specific antiviral therapy for hepatitis A. Supportive care such as adequate hydration and symptomatic control of fever or vomiting with antipyretics or antiemetics is generally performed. Extrahepatic complications must be monitored, and renal function support via hemodialysis may be required. In the case of prolonged cholestasis, a few studies have reported response to corticosteroid therapy. However, corticosteroid treatment should be used with caution, considering the prolonged presence of HAV RNA (up to 12 months) in the liver (Lanford et al. 2011) and potentially harmful effects of corticosteroids on the immune control of HAV. Administration of ursodeoxycholic acid or cholestyramine may be considered for pruritus control (Jeong and Lee 2010). Furthermore, hepatitis A-associated ALF may rapidly progress within a week. Thus, intensive, multidisciplinary care and recognition of poor prognostic factors are needed to facilitate urgent decision-making situations regarding liver transplantation.

PATHOGENESIS

Viral Replication in the Host

According to a recent study, a quasi-enveloped form of HAV (eHAV) is detected in the serum and plasma of infected hosts, whereas a non-enveloped, naked form of HAV is shed through feces (Fig. 4) (Feng et al. 2013). eHAV is released from hepatocytes and subsequently loses its lipid envelope following exposure to high concen-

trations of bile salts in the biliary canaliculus (Walker et al. 2015; Hirai-Yuki et al. 2016b). HAV can take advantage of the specific characteristics of eHAV and nonenveloped HAV for immune evasion and efficient viral transmission, respectively. Within infected hosts, the quasi-envelope of eHAV cloaks the capsid, sequestering it from neutralizing antibodies that target capsid proteins (Feng et al. 2013). Non-enveloped, naked HAV is very stable and is shed in feces via the intestinal tract while preserving its infectivity. Moreover, in the environment, nonenveloped, naked HAV is highly transmissible to other hosts because of its high physico-chemical stability (Walker et al. 2015).

During acute hepatitis A, peaks of fecal shedding of the virus and viremia are followed by hepatocellular injury, which is manifested by elevation of liver enzymes in the serum such as ALT (Fig. 1) (Shin et al. 2016a). After the first increase in serum ALT levels, viral shedding in feces usually continues for ~2 to 3 weeks, although sensitive reverse transcription polymerase chain reaction methods may detect it for longer periods (Martin and Lemon 2006). Clinical relapse with fecal viral shedding can occur following the resolution of hepatitis A (Sjogren et al. 1987), and prolonged viremia has also been reported in some adult patients with hepatitis A (Normann et al. 2004). A chimpanzee study reported the persistence of hepatitis C virus (HCV) RNA in the liver for months after cessation of fecal virus excretion (Lanford et al. 2011). Meanwhile, protracted forms of HAV infection were strongly associated with a specific HLA-DR allele, HLA-DRB1*1301 (Fainboim et al. 2001).

Extrahepatic sites of HAV replication have been suggested. In fact, HAV antigens can be detected in not only hepatocytes but also in the spleen, lymph nodes, and kidneys of infected nonhuman primates (Mathiesen et al. 1978). HAV antigens have also been detected in small intestine crypt cells in owl monkeys (*Aotus trivirgatus*) orally inoculated with HAV (Asher et al. 1995); this has not been confirmed in humans. In addition, HAV has been detected in the tonsils and saliva shortly after viremia (Cohen et al. 1989) although the viral titer in saliva is very low.

Figure 4. Two different forms of infectious hepatitis A virus (HAV) virions. Quasi-enveloped HAV (eHAV) is detected in serum and plasma of the infected host, whereas nonenveloped, naked HAV is shed in feces. New replicated progeny virus is released from hepatocytes in the quasi-enveloped form and subsequently loses its lipid envelope following exposure to bile salts in the biliary canalculus. The viral capsid within the quasi-enveloped eHAV virion is protected from neutralizing antibodies. Nonenveloped, naked HAV is highly stable. It is shed in feces via the intestinal tract and maintains infectivity in the environment. LSECs, Liver sinusoidal endothelial cells.

Liver Injury

As described above, acute HAV infection often causes severe liver injury in adults, whereas it tends to result in a subclinical, asymptomatic infection in children (Shin et al. 2016a). ALF develops in extreme cases. In the liver with hepatitis A, hepatocyte degeneration and infiltration by mononuclear inflammatory cells are observed. Activation of Kupffer cells and disruption of bile canaliculi may also be observed.

The mechanism for liver injury during hepatitis A has not yet been clearly elucidated. Moreover, the reason why adults tend to experience symptomatic liver injury after HAV infection is poorly understood. However, it is known that the liver injury is not caused by

direct cytopathic effect of HAV (Siegl and Weitz 1993). This is indirectly supported by the fact that viral replication and fecal excretion both peak before serum ALT level elevation. Moreover, HAV-infected cells do not show cytopathic effects, and their metabolism is not impacted when infected by HAV in vitro (Gauss-Muller and Deinhardt 1984), further indicating that hepatitis A liver injury is not caused by virus-induced cytopathology. Instead, liver injury in hepatitis A is caused by immune-mediated mechanisms involving both innate and adaptive immune responses to the virus (Shin et al. 2016a). Indeed, patient studies indicate possible roles for T cells, cytokines, and chemokines in liver injury during hepatitis A, as described below.

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**MECHANISMS OF
IMMUNOPATHOGENESIS****T Cells**

During hepatitis A, the appearance of T cells in the liver temporally coincides with an increase in serum ALT levels (Fig. 1), suggesting an important role for T cells in liver injury (Shin et al. 2016a). At the same time, viral titers in feces and serum start to decrease. Virus-specific CD8⁺ T cells may contribute to both viral control and liver injury in HAV-infected hosts. Early studies reported that peripheral blood lymphocytes or liver-derived CD8⁺ T-cell clones from hepatitis A patients exert cytotoxicity against HAV-infected cells (Kurane et al. 1985; Vallbracht et al. 1986, 1989) and produce IFN- γ (Kurane et al. 1985; Maier et al. 1988; Fleischer et al. 1990), which can amplify inflammation at the infection site. Following on these early reports, other studies suggest a role for HAV-specific CD8⁺ T cells in the induction of liver injury in hepatitis A. A recent study described CD8⁺ T-cell responses targeting multiple epitopes of HAV and observed an activated phenotype of HAV-specific CD8⁺ T cells in the blood of patients with acute HAV infection (Schulte et al. 2011). On the contrary, a chimpanzee study showed that HAV-specific CD8⁺ T cells were undetectable in the blood during acute HAV infection or were nonfunctional if detected (Zhou et al. 2012). Instead, HAV-specific CD4⁺ T cells were detected and polyfunctional. In summary, how T cells contribute to liver injury in hepatitis A has yet to be fully elucidated, including antigen specificity, subsets, activating signals, and effector molecules, all of which need to be further clarified.

A role for natural killer T (NKT) cells was suggested in relation to the 157insMTTTP polymorphism described above in the gene encoding TIM-1/HAVCR1 (Kim et al. 2011). TIM1 was previously considered to be an essential cellular receptor for HAV, but is now known to contribute only to the cellular entry of quasi-enveloped virions (Das et al. 2017). Severe HAV-induced liver injury was associated with the six amino acid insertion in TIM-1 (Kim et al. 2011). Moreover, NKT cells expressing the long form

of TIM-1 exerted stronger cytolytic activity against HAV-infected cells than those expressing the short form (Kim et al. 2011).

Antibodies and Immune Complexes

Early clinical studies showed immune complex deposition in the liver and reduced levels of serum complement in hepatitis A patients (Inman et al. 1986; Margolis et al. 1988). These immune complexes contained IgM and IgG antibodies, HAV capsid proteins, and C3 complement cleavage products (Margolis et al. 1988). However, it is not clear whether immune complexes and complement activation contribute to liver inflammation and injury during hepatitis A.

A recent study with peripheral blood from hepatitis A patients showed that a substantial number of antibody-secreting cells (ASCs) have specificities to antigens unrelated to HAV, a bone marrow plasma cell-like phenotype, and dominantly secrete IgM during acute HAV infection (Hong et al. 2013). These data suggest that pre-existing plasma cells are mobilized and released into the circulation and contribute to antigen-nonspecific IgM secretion during acute HAV infection. However, the role of the antigen-nonspecific IgM response in the immunopathogenesis of HAV infection has not yet been clarified.

Cytokines and Chemokines

Diverse cytokines and chemokines play a role in immune-mediated host injury by their effector and immunomodulatory functions. In hepatitis A patients, serum levels of several cytokines and chemokines are increased compared with healthy controls, including interleukin (IL)-6, IL-8, IL-18, IL-22, CXC-chemokine ligand (CXCL)9, and CXCL10, although the cells that produce them have not been identified (Shin et al. 2016b). In addition, serum levels of granzyme B and soluble Fas ligand, which are molecules involved in T-cell cytotoxicity, are also increased in hepatitis A patients. Among them, serum levels of Fas ligand and IL-18 significantly correlate with serum ALT levels and total bilirubin levels, respectively, in hepatitis A patients (Shin et al. 2016b), suggesting that differ-

ent immune mechanisms may contribute to hepatocellular injury and cholestatic injury during hepatitis A. Moreover, serum levels of CXCL9 and CXCL10 significantly correlate with serum ALT levels (Shin et al. 2016b). CXCL9 and CXCL10 are chemokines that recruit effector T cells to peripheral inflammatory sites by binding to CXCR3, which is typically expressed by effector helper 1 CD4⁺ T cells and cytotoxic CD8⁺ T cells. Amplification of liver injury by antigen-nonspecific mononuclear cells, which are recruited to the liver by CXCL9 and CXCL10, is well known, although studied in a murine model of hepatitis B (Iannacone et al. 2007).

Very recently, a unique mechanism for CXCL10 production in HAV-infected cells was elucidated. HAV RNA is sensed by pathogen-associated molecular pattern receptors such as MDA5 in the cytosol or TLR3 in the endosome (Fig. 5). However, downstream signals are interrupted by HAV proteins. An intermediate product of HAV polyprotein processing, 3ABC, cleaves MAVS (Yang et al. 2007), and another precursor, 3CD, cleaves TRIF (Qu et al. 2011). In addition, the HAV 3C^{pro} protease cleaves NEMO (Wang et al. 2014). Although HAV blocks signals downstream from MDA5 and TLR3 by such mechanisms, type III interferon (IFN)- λ s and CXCL10 are produced by HAV-infected cells, particularly at an early stage of HAV infection (Sung et al. 2017). CXCL10 is produced in HAV-infected cells in a MAVS and IRF3-dependent manner (Fig. 5) (Sung et al. 2017). However, secreted type I or III IFNs are not required for CXCL10 production. This finding corresponds to the fact that CXCL10 expression is increased in the liver and blood of HAV-infected chimpanzees, whereas IFN responses are minimally induced in the infected liver (Lanford et al. 2011). This mechanism may be pivotal for liver inflammation during HAV infection, as it induces the production of CXCL10 even without IFNs. Similar findings have been reported in a murine model of hepatitis A (see below) (Hirai-Yuki et al. 2016a).

Regulatory T Cells

In immune-mediated host injury, regulatory T (Treg) cells can modulate effector T-cell activity.

Treg cells have been shown to play a role in liver injury regulation during acute HAV infections. The number of circulating CD4⁺CD25⁺Foxp3⁺ Treg cells is diminished by Fas-mediated apoptosis during hepatitis A (Choi et al. 2015). In addition, the suppressive function of Treg cells can be directly inhibited by the binding of HAV particles to TIM-1 expressed by Treg cells (Manangeeswaran et al. 2012). Furthermore, the number of Treg cells in the blood and the suppressive activity of the total Treg cell population are inversely correlated with serum ALT levels (Choi et al. 2015). These data indicate that decreased CD4⁺CD25⁺Foxp3⁺ Treg cell population activity is associated with severe liver injury during hepatitis A. However, the frequency of circulating Treg cells does not correlate with the frequency of HAV-specific, IFN- γ -producing CD8⁺ T cells in the blood (Choi et al. 2015). Further studies are required to identify the effector cells mainly targeted by the suppressive activity of Treg cells during hepatitis A and to clarify how reduced Treg cell population frequencies and activities are related to liver injury.

A Murine Model of HAV Infection

As described above, the mechanisms responsible for immune-mediated liver injury have not yet been clearly elucidated. This is in part attributed to the absence of a small animal model for HAV infection and hepatitis A. Recently, a murine model of HAV infection with human hepatitis A features was described (Hirai-Yuki et al. 2016a). In this study, mice lacking the type I IFN receptor or both type I and II IFN receptors were inoculated intravenously with HAV, resulting in the development of features typifying human hepatitis A, including fecal virus shedding, viremia, increased serum ALT levels, necrosis or apoptosis of hepatocytes, and infiltration of the liver by inflammatory cells, including macrophages, natural killer cells, and CD4⁺ and CD8⁺ T cells (Hirai-Yuki et al. 2016a). Further analyses with this model revealed that hepatocellular apoptosis and hepatic inflammation occurs by a MAVS and IRF3/7-dependent, but IFN-independent mechanism (Hirai-Yuki et al. 2016a). In this model, multiple cytokines

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Figure 5. Mechanism of CXC-chemokine ligand (CXCL)10 expression in Hepatitis A virus (HAV)-infected hepatocytes. HAV RNA is sensed by MDA5 in the cytosol or TLR3 in the endosome. However, downstream signaling is interrupted by HAV proteins as described in the text. Nonetheless, interferon λ (IFN- λ) and CXCL10 are produced from HAV-infected cells, particularly at an early stage of HAV infection. CXCL10 is produced in HAV-infected cells in a MAVS- and IRF3-dependent but IFN-independent manner. CXCL10 can contribute to liver inflammation and hepatocyte injury by recruiting CXCR3⁺ immune cells to the HAV-infected liver.

and chemokines were expressed in the liver by the same mechanism (Hirai-Yuki et al. 2016a), corresponding with the recent finding in human cells described above (Sung et al. 2017). This study revealed the critical role of MAVS signal-

ing in liver injury induced by HAV infection using a unique murine model. However, it remains to be confirmed whether this model exactly recapitulates the mechanisms of pathogenesis of hepatitis A in humans.

CONCLUDING REMARKS

In regions with inadequate levels of sanitation, HAV is readily propagated among children and often results in a self-limited, asymptomatic, and subclinical infection, which induces neutralizing antibodies that confer lifelong protective immunity. Thus, improvements in sanitation increase the size of the HAV-naïve adult population susceptible to HAV infection. In this situation, increasing numbers of individuals can be infected at older ages, leading to more severe clinical manifestations and greater disease burden. Currently, inactivated HAV vaccines that elicit neutralizing antibodies are available, and vaccination will largely reduce the incidence of HAV infection and symptomatic hepatitis.

Although liver injury in hepatitis A is known to be caused by immune-mediated events, the exact pathogenesis mechanisms have not yet been clarified. Immune-mediated mechanisms of liver injury are common to the pathogenesis of hepatitis A, hepatitis B, and hepatitis C (Shin et al. 2016a). Elucidating the immunopathogenesis of hepatitis A will not only lead to better clinical management of hepatitis A patients, but could also facilitate the development of novel therapeutic approaches reducing liver injury in patients with hepatitis B or C.

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