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Reply to Sayed

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To the Editor—

We appreciate the comments made by Sayed [1] regarding our article [2]. We found that rhesus macaques with experimental hepatitis E virus (HEV) infection demonstrated clinical signs consistent with acute viral hepatitis, viral shedding in feces and serum, and development of antiviral antibody responses that are similar to the natural history of HEV infection in humans [3, 4]. Rhesus macaques are susceptible to infection by HEV genotypes 1–4 and have proved to be a reliable experimental model for studying HEV genotype 1 primary infection and reinfection [2, 5, 6]. As with 2 human volunteer inoculation studies [7, 8], HEV RNA was found in the serum and feces of infected rhesus macaques before the elevation of serum alanine transaminase (ALT) activity [3]. The onset of ALT elevation in the serum and histopathological changes in the liver correlated with immune responses marked by anti-HEV antibody responses and viral clearance from the stool of infected rhesus macaques [3, 5]. Other than nonhuman primates, the experimental studies of HEV infection in pigs, rabbits, and human liver chimeric mice showed no elevation in serum ALT activity [9–11].

Cytotoxic T cells, natural killer (NK) cells, and NK T cells were found to be involved in liver injury by HEV infection [12, 13]. Host factors interacting with various immune cells and cytokines such as type I interferons (IFNs) are also associated with liver injury [14, 15]. We found that acute HEV genotype 1 infection induced up-regulation of type I IFN response genes at the peak and decline of HEV replication [3]. A study in Ifnar1$^{/-I}$ mice lacking receptors for both type I and type II IFNs with hepatitis A virus infection showed that hepatocellular apoptosis and hepatic inflammation resulted from MAVS and

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IRF3/7 signaling [16]. Superoxide dismutase 1 (SOD1) protects hepatocytes against type I IFN–driven oxidative damage in viral hepatitis. A study using SOD1 knockout mice found that IFN-I signaling was a key inducer of virusmediated oxidative liver damage by viral hepatitis [17]. These studies demonstrated that liver injury could occur in the absence of $CD4^+$ or $CD8^+$ T cells or NK cells.

In our studies, rhesus macaques with primary HEV genotype 1 infection had ALT activity elevated from 1.8- to 7.8-fold (94 IU/mL, 231 IU/mL, and 288 IU/mL, respectively) above cutoff values (60 IU/mL, 46 IU/mL, and 38 IU/mL, respectively) [3]. Elevation of ALT activity in chimpanzees experimentally infected with HEV genotype 1 infection was shown to be lower [18]. A previous study also reported that the same dose of HEV genotype 1 virus inoculation to rhesus monkeys, cynomolgus monkeys, and chimpanzees resulted in the highest mean peak of ALT value in the cynomolgus monkeys, followed by the rhesus monkeys and the chimpanzees [5]. However, ALT activity was not elevated in humanized mice [10]. These observations suggest that levels of the liver injury and innate immune responses against HEV infection such as IRF7 gene expression could express differently in each experimental infection system, as Sayed has commented. IRF7 gene expression was upregulated at the peak of HEV RNA replication in the HEV-infected rhesus macaques and in the first week of viremia in chimpanzees, but not in the humanized mice [3, 10, 18]. All HEV genotype 1–reinfected animals in our study showed down-regulation of IRF7 gene expression and no elevation of ALT activity [10]. Observations from our study and references cited by Sayed suggest that the type I IFN signaling mechanism could be an inducer of HEV infection–mediated liver injury and that the innate immune response gene, IRF7, may have an important role in liver pathology during acute HEV infection.

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