Liver disease is one of the most dangerous threats to humans. Some of these patients will eventually develop cirrhosis and hepatocellular carcinoma due to liver inflammation. We focus on finding whether innate recognition of hepatic NK and NKT subsets is involved in liver injury. We established the first murine model of NK cell-dependent acute hepatitis by activating innate Toll-like receptor-3 (TLR-3) by injection with poly I:C, a dsRNA virus mimic. We described for the first time a network among innate immune NK, NKT, and Kupffer cells by using this model, noting that Kupffer cells activated by poly I:C might protect against bacterial toxin (LPS)-induced fulminant hepatitis, while preactivation of NK cells might reduce Con A-induced NKT cell-mediated fulminant hepatitis by blocking NKT cell recruitment to the liver. Moreover, we observed that oversensitivity to injury in HBV-transgenic mice correlated to the over-expression of Rea1, an NKG2D (activating receptor) ligand of NK cells or CD1d, a ligand of TCR-V14 (activating receptor) of NKT cells, on HBV-positive hepatocytes, which leads to an innate immune-induced liver injury or regeneration dysfunction by attacking hepatocytes. Recently, we also observed that innate immune receptors-mediated nonresolving inflammation played critical roles in fibrosis and hepatocellular carcinoma in HBV-tg mice. Additionally, a mouse model of HBV-persistence was established by hydrodynamically injection with HBV genome-containing plasmid, which was tolerant to HBV vaccination. The underlying mechanisms of liver virus-induced systemic immune tolerance was further explored, and the Kupffer cell-Tr1 cell-Tfh cell interplay plays a major role in induction of systemic tolerance. Moreover, these mice were treated with an immunotherapy approach, called vaccine-based IL-12 therapy. The results demonstrated that serum HBsAg decreased dramatically after 3 rounds therapy compared to control HBV carrier mice, and 8 weeks later, almost all treated mice (>90%) became HBsAg negative in sera whereas the spontaneous seroconversion happened very less frequently in control group(<20%). Moreover, anti-NKG2A mAb might reverse the HBV-induced NK cell-tolerance in chronic hepatitis B patients and also HBV-persistent mice. We designed a dual functional small RNA with HBx-RNA silencing and immunostimulatory effects for reversing HBV-induced immune tolerance, and the results demonstrated that an immunostimulatory HBx-siRNA might reverse the HBV-mounting immunotolerant environment of liver, which is helpful to break the generation of liver-derived regulatory T cells.