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Hepatocyte-Intrinsic NF-κB Signaling Is Essential to Control a Systemic Viral Infection

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Abstract : The liver is one of the pivotal organs in vertebrate animals, serving a multitude of functions such as metabolism, detoxification and protein synthesis and including a predominant role in innate immunity. The innate immune mechanisms pertaining to liver in controlling viral infections have largely been attributed to the Kupffer cells, the locally resident macrophages. However, all the cells of liver are equipped with innate immune functions including, in particular, the hepatocytes. Hence, our aim in this study was to elucidate the innate immune contribution of hepatocytes in viral clearance using mice lacking Ikkβ specifically in the hepatocytes, termed IkkβΔ^{Hep} mice. Blockade of Ikkβ activation in IkkβΔ^{Hep} mice affects the downstream signaling of canonical NF-κB signaling by preventing the nuclear translocation of NF-κB, an important step required for the initiation of innate immune responses. Interestingly, infection of IkkβΔ^{Hep} mice with lymphocytic choriomeningitis virus (LCMV) led to strongly increased hepatic viral titers – mainly confined in clusters of infected hepatocytes. This was due to reduced interferon stimulated gene (ISG) expression during the onset of infection and a reduced CD8+ T-cell-mediated response. Decreased ISG production correlated with increased liver LCMV protein and LCMV in isolated hepatocytes from IkkβΔ^{Hep} mice. A similar phenotype was found in LCMV-infected mice lacking interferon signaling in hepatocytes (IFNARΔ^{Hep}) suggesting a link between NFkB and interferon signaling in hepatocytes. We also observed a failure of interferon-mediated inhibition of HBV replication in HepaRG cells treated with NF-kB inhibitors corroborating our initial findings with LCMV infections. Collectively, these results clearly highlight a previously unknown and influential role of hepatocytes in the induction of innate immune responses leading to viral clearance during a systemic viral infection with LCMV-WE.

Keywords : CD8+ T cell responses, innate immune mechanisms in the liver, interferon signaling, interferon stimulated genes, NF-kB signaling, viral clearance
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