

Molecular Mechanisms of Duct Injury in Biliary Atresia

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Biliary atresia, a condition of unknown etiology, is both the leading cause of neonatal cholestasis and the leading indicator for pediatric liver transplant. Prior studies have linked the pathogenesis of biliary atresia to an innate immune response, with NK and CD8⁺ cells being the primary effectors of bile duct obstruction. Dendritic cells (DCs) are among the primary antigen presenting cells that activate the immune response. In this study, we investigated the role of DCs in the pathogenesis of biliary atresia, proposing that liver DCs activate NK and CD4⁺ cells following neonatal rotavirus challenge. In our model, administration of rotavirus in Balb/c mice within 24 hours of birth results in inflammatory obstruction of extrahepatic bile ducts at 7 days and the phenotype of atresia by 10 days. First, we sought to determine the location of DCs in relation to the biliary system. This was done using dual immunofluorescence to detect plasmacytoid dendritic cells (pDCs) and biliary epithelium (cholangiocytes) in the livers and biliary trees of rotavirus challenged mice. We were able to localize pDCs within the liver lobule, in the portal tract and in extrahepatic bile ducts. Secondly, we conducted flow cytometric analysis of hepatic immune cells and found liver pDCs numerically increase and undergo activation soon after challenge with rotavirus. We also found conventional dendritic cells (cDCs) exhibit a similar response. Finally, to test whether rotavirus challenged DCs can induce proliferation of naïve CD4⁺ T and activate NK cells, we incubated magnetic bead purified, rotavirus challenged DCs (pDCs and cDCs) with carboxyfluorescein diacetate succinimidyl ester (CFSE) labeled naïve NK cells or CD4⁺ T cells. Rotavirus-primed DCs induced proliferation of CD4⁺ T cells and activation of NK cells when compared to DCs from unchallenged mice. Individually, however, neither pDCs nor cDCs were able to modify the functional status of NK or CD4⁺ cells. Based on these data, we conclude that pDCs do localize to the liver and biliary tract and, with the help of cDCs, induce proliferation of effector immune cells in biliary atresia. This study was supported in part by NIH grant T35 DK 60444.