CD103posCD11bneg Dendritic Cells are Crucial for Development of Primary Biliary Cholangitis

---
Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by immune-mediated destruction of intrahepatic bile ducts and typified by antigen specific autoantibodies and hepatic T cells, predominantly the CD8+ subset. GWAS point at a role of innate immunity and Interleukin-12. In addition to pDC, the mouse liver hosts two main subsets of classical DC: CD11b+CX3CR1+ and CD11b-CD103+ cells, the later depend on the transcription factor Batf3 for their development. CD11b-CD103+ DC are specialized in cross-priming and known as a major source for the cytokine IL-12. Our aim was to assess the role of Batf3-dependent DCs in PBC development.
Methods: We utilized two different murine models of immune-mediated cholangitis and took advantage of the Batf3-/- mice that specifically lack CD11b-CD103+ DC.
Results: Histopathology assessment of mice subjected to the induced PBC model (2OA-BSA) demonstrated peri-portal infiltration of mononuclear cells in WT mice, whereas, in Batf3-/- mice minor abnormalities were observed. Biochemical markers of cholangitis including alkaline phosphatase and total bile acids were decreased in Batf3-/- mice. Flow cytometry analysis revealed reduction in hepatic CD4/CD8 T cells ratio in Batf3-/- mice, suggesting reduced CD8+ T cells infiltration. Importantly, Sirius-red staining exhibited peri-portal collagen deposition only in the control group, and was further supported by an increased in pro-fibrotic hepatic gene-expression signature in this group.
The OVA-BIL mouse is characterized by ovalbumin expression restricted to the biliary epithelium. Adoptive transfer of OT-I and OT-II T cells to OVA-BILxBatf3-/- mice resulted in attenuated liver inflammation, as compared to OVA-BIL mice, assessed by liver histology and biochemical markers including serum ALT and bile acids. Flow cytometry analyses revealed massive accumulation of OT-I cells in OVA-BIL mice but not in OVA-BILxBatf3-/-, suggesting a crucial role for hepatic CD11b-CD103+ in T cell activation in this model.
Conclusions: Our results indicate a critical role for CD11b-CD103+ DC subset in the pathogenesis of PBC and improve our understanding concerning break of tolerance mechanisms in this pathology.

Keywords : Dendritic cells, Primary Biliary Cholangitis
Authors :
References : , , ,

Authors

Debby Reuveni 1,

1. The Research Center for Digestive Tract and Liver Diseases, Tel-Aviv Sourasky Medical Center, Tel Aviv, ISRAEL