Nature Reviews Gastroenterology & Hepatology **11**, 456 (2014); published online 17 June 2014; doi:10.1038/nrgastro.2014.101

BILIARY TRACT

IL-33, innate lymphoid cells and IL-13 are required for cholangiocyte proliferation

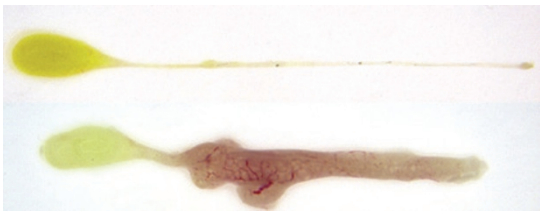
Injury to the epithelium lining of biliary ducts can cause severe inflammatory diseases and cancer. A study has pinpointed IL-33 as a potent cholangiocyte mitogen that has a role in the repair of biliary epithelium but might also be involved in malignant transformation. IL-33-mediated proliferation of cholangiocytes was found to be affected—in a paracrine fashion—by IL-13 secretion from nearby type 2 innate lymphoid cells (ILC2s).

"Previous analyses of the hepatic transcriptome showed increased expression of IL-33 and its receptor in the livers of children at the time of diagnosis of biliary atresia," says Jorge Bezerra, corresponding author of the study. "Therefore, we began studies to investigate the biological relevance of IL-33 to the biliary system in health and disease."

Blocking the IL-33 receptor, ST2, with injections of an anti-ST2 antibody in a mouse model of biliary injury caused diffuse loss of epithelium compared with mice injected with IgG isotype antibodies. To determine if IL-33 is involved in cholangiocyte proliferation, IL-33 was injected into adult mice, which led to a 76-fold increase in proliferating cholangiocytes in extrahepatic bile ducts compared with control mice not receiving IL-33. These data demonstrate that IL-33–ST2 signalling is involved in cholangiocyte proliferation.

Furthermore, after 1 week of daily IL-33 injections, populations of $ST2^+$ ILC2s expressing IL-13 were identified in the livers of these mice. The expansion of ILC2s led Bezerra and colleagues to hypothesize that IL-33/ILC2s/IL-13 form a paracrine circuit, stimulating the proliferation of neighbouring cholanciocytes.

In mice with genetic defects that induce deficiency of ILC2s, bile duct epithelial cells did not proliferate in response to IL-33 stimulation. IL-33-induced proliferation was rescued with adoptively transferred, wild-type ILC2s. In addition, cholangiocytes in *Il13*$^{-/-}$ mice did not respond to IL-33. However, administration of IL-13 and IL-33 restored the proliferative reaction seen in wild-type mice.



Mouse gall bladder and extrahepatic bile duct at baseline (top) and after 7 days of IL-33 injections (bottom). Image courtesy of J. Bezerra.

Future experiments will include translational research to determine the activity of the IL-33/ILC2s/IL-13 circuit during disease progression, with a focus on biliary inflammation and cancer.

Gillian Patman

Original article Li, J. *et al.* Biliary repair and carcinogenesis are mediated by IL-33-dependent cholangiocyte proliferation. *J. Clin. Invest.* doi:10.1172/JCI73742