

Biliary tree stem cells are involved in the pathogenesis of primary sclerosing cholangitis

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Biliary tree stem cells (BTSCs) are multipotent stem cells located in peribiliary glands (PBGs) of extrahepatic and large intrahepatic bile ducts (1). Primary sclerosing cholangitis (PSC) is characterised by fibro-stenosing strictures involving extrahepatic and/or large intrahepatic bile ducts. Mechanisms leading to bile duct injury are poorly understood (2). Our aims are to study the role of BTSC in the pathogenesis of biliary fibrosis in PSC. Specimens containing extrahepatic or large intrahepatic bile ducts were obtained from normal liver (n=6), liver explants from patients with PSC (n=11), and primary biliary cirrhosis (n=6). Specimens were processed for histology, immunohistochemistry and immunofluorescence. In PSC samples, progressive hyperplasia and mucinous metaplasia of PBGs were observed in large ducts with fibrosis, but not in inflamed ducts without fibrosis. PBG hyperplasia was associated with progressive biliary fibrosis and the occurrence of dysplastic lesions. Hyperplasia of PBGs was determined by the expansion of biliary tree stem cells, which sprouted towards the surface epithelium. In PSC, PBGs and myofibroblasts displayed enhanced expression of Hedgehog pathway components. PBGs in ducts with onion skin-like fibrosis expressed epithelial-to-mesenchymal transition traits associated with components of Hedgehog pathway, markers of senescence and autophagy. The biliary tree stem cell compartment is activated in PSC, its activation contributes to biliary fibrosis, and is sustained by the Hedgehog pathway. Our findings suggest a key role for peribiliary glands in the progression of bile duct lesions in PSC and could explain the associated high risk of cholangiocarcinoma.

This work was supported by grants from MIUR FIRB 2010 and MIUR PRIN-2009.

References

- [1] Cardinale et al. (2011) Multipotent stem/progenitor cells in human biliary tree give rise to hepatocytes, cholangiocytes, and pancreatic islets. *Hepatology*: 2159-72; doi: 10.1002/hep.24590.
- [2] Carpino et al. (2016) Stem/Progenitor Cell Niches Involved in Hepatic and Biliary Regeneration. *Stem Cells Int*: 3658013; doi: 10.1155/2016/3658013.

Keywords

Stem cells; biliary tree; hedgehog; liver cirrhosis.