

# Biliary tree stem cells and peribiliary glands are involved in primary sclerosing cholangitis and cholangiocarcinoma

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Peribiliary glands (PBGs) represent the niche of biliary tree stem/progenitor cells (BTSCs) [1]. BTSCs are multipotent stem cells able to differentiate into hepatocytes, cholangiocytes, and pancreatic islets. Primary sclerosing cholangitis (PSC) is a chronic inflammation involving extra-hepatic biliary tree, and is complicated by the risk of cholangiocarcinoma (CCA) development [2]. We aimed to evaluate the involvement of PBGs and BTSCs in PSC and their role in CCA insurgence [2]. Specimens from normal liver (N=5), PSC (N=20), and CCA arising in PSC patients (N=20) were included and processed for histology, immunohistochemistry and immunofluorescence. In vitro experiments were performed on human BTSCs and primary CCA cell cultures. PSC-affected ducts were characterized by the activation of BTSCs and by PBG hyperplasia. In PSC, ducts showed higher microvascular density around PBGs compared to normal ducts. In CCA arising in PSC patients, PBGs showed dysplastic and neoplastic aspects. Compared to non-cancerous ducts, neoplastic ducts showed higher inflammation, wall thickness, and PBG activation. CCAs were characterized by higher expression of epithelial-to-mesenchymal transition (EMT) traits in PBGs and by the absence of primary cilia in BTSCs compared to control ducts. In vitro study confirmed that human BTSCs, under inflammatory milieu, increased proliferation rate and expression of EMT traits, and lost primary cilia compared to control conditions. In conclusion, patients affected by PSC are characterized by PBG involvement and activation of BTSC niche; the insurgence of CCA was characterized by involvement of PBG niche, suggesting a key role of this cell compartment in progressive tumorigenesis.

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## References

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## Key words

Peribiliary glands, stem cells, angiogenesis, primary sclerosing cholangitis.