

## Role of the secretin/secretin receptor axis in the modulation of the liver fibrosis

Romina Mancinelli<sup>1</sup> - Shannon Glaser<sup>2</sup> - Gianfranco Alpini<sup>3</sup> - Eugenio Gaudio<sup>1</sup>

<sup>1</sup> Sapienza Università di Roma, Dipartimento Scienze Anatomiche, Istologiche, Medico Legali e dell'Apparato Locomotore, Roma, Italia - <sup>2</sup> Scott & White Hospital, Digestive Disease Research Center, Temple, Texas, USA - <sup>3</sup> Texas A&M Health Science Center, Department of Medicine and Medical Physiology, Temple, Texas, USA

Proliferating cholangiocytes, the cells that line the biliary ducts, secrete and respond to neuroendocrine hormones, including secretin. Secretin stimulates biliary proliferation by downregulation of *let-7a* and subsequent upregulation of the growth-promoting factor NGF [1]. It is not known if the secretin/secretin receptor (SR) axis plays a role in subepithelial fibrosis observed during cholestasis [2]. Our aim was to determine the role of secretin/SR axis in the development of biliary fibrosis in animal models and human primary sclerosing cholangitis (PSC). Studies were performed in Wild-type (WT) mice with bile duct ligation (BDL), BDL SR<sup>-/-</sup> mice or Mdr2<sup>-/-</sup> mouse models of cholestatic liver injury. In selected studies, the SR antagonist (Sec 5-27) was used to block the secretin/SR axis. Biliary proliferation and fibrosis were evaluated as well as the secretion of secretin (by cholangiocytes), the expression of markers of fibrosis, TGF- $\beta$ 1, TGF- $\beta$ 1R, *let-7a* and downstream expression of NGF. Correlative studies were performed in human control and PSC liver tissue biopsies, serum and bile. SR antagonist reduced biliary proliferation and hepatic fibrosis in BDL WT and Mdr2<sup>-/-</sup> mice. We found a decreased expression of *let-7a* in BDL and Mdr2<sup>-/-</sup> cholangiocytes that was associated with increased NGF expression. Inhibition of *let-7a* increased liver fibrosis due to cholestasis. Moreover, we showed an increased expression of TGF- $\beta$ 1, TGF- $\beta$ 1R. Significantly higher expression of secretin, SR and TGF- $\beta$ 1 was observed in PSC patient liver samples compared to controls. In addition, there was higher expression of fibrosis genes and an important decreased expression of *let-7a* with an increased expression of NGF compared to the control. In conclusion, we found that in proliferating cholangiocytes during cholestasis there is an upregulation of the secretin/secretin receptor axis.

This work was supported by grants from Ricerche Universitarie Sapienza # C26A15SE8Z.

### References

- [1] Glaser et al. (2014) Secretin stimulates biliary cell proliferation by regulating expression of microRNA 125b and microRNA *let7a* in mice. *Gastroenterology* 146(7):1795-808. e12. doi: 10.1053/j.gastro.2014.02.030.
- [2] Onori et al. (2013) Role of follicle-stimulating hormone on biliary cyst growth in autosomal dominant polycystic kidney disease. *Liver Int* 33(6):914-25. doi: 10.1111/liv.12177.

### Keywords

Biliary epithelium; secretin; cholestasis.