

Title: Potential Role of Senescence in PSC
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Lay Summary of Research Progress:

Primary sclerosing cholangitis (PSC) is a multifactorial disease with genetic, microbial, and environmental components. Emerging evidence suggests that cholangiocytes, i.e. the cells that line the bile ducts in the liver, may not only be affected in PSC, but may actually participate in driving disease progression. In recently published work, we demonstrated that cholangiocytes, in response to biologically-relevant injurious stimuli, transition from a proliferative to a senescent phenotype, a metabolically active cellular state in which the cell is no longer capable of cell division. Furthermore, these cells secrete excess amounts of inflammatory mediators (**Hepatology 2014, PMID: 24390753**). In this manuscript we also demonstrate that the number of senescent cholangiocytes present in the bile ducts of PSC patients is increased compared to normal and those of other liver diseases. In other recent work we set out to better understand the nature of cholangiocytes isolated from PSC livers. We therefore developed a technique for cholangiocyte isolation from PSC patient liver specimens and characterized these primary PSC cholangiocytes by cellular, molecular, and next-generation RNA-sequencing techniques (a method to assess what genes are “on” or “off”) and compared them to normal human cholangiocytes (**Laboratory Investigation. 2014 Jul 21. doi: 10.1038/labinvest.2014.94. [Epub ahead of print]**). We found that isolated PSC cells showed epithelial cell (i.e. cholangiocyte) markers and were negative for markers of other liver cells. We further determined basic cellular characteristics including proliferation rate, and the cells ability to form an epithelial layer (i.e. form junctions between adjacent cells). We found that PSC cells proliferated at a slower rate and were less efficient at forming junctions between cells compared to normal cholangiocytes. We also found, in support of our previous observations, that PSC-isolated cholangiocytes had a high proportion of senescent cells. Lastly, next-generation RNA-sequencing confirmed the expression of cholangiocyte markers and the absence of non-cholangiocyte markers and extended our findings regarding pro-inflammatory gene expression. Therefore, we have demonstrated that high-purity cholangiocytes can be isolated from human PSC liver and grown in culture and that isolated PSC cholangiocytes exhibit features that may reflect their *in vivo* contribution to disease. In summary, we continue to obtain novel findings related to **a relatively unexplored area of cholangiocyte biology (stress-induced cellular senescence) that may have implications for the initiation, progression, and treatment of the cholangiopathies, particularly PSC**. Based on our recent work, we propose that chronic exposure to injurious molecules promotes cholangiocyte senescence and secretion of inflammatory molecules, thereby contributing to the development and progression of PSC. This is a novel approach to understanding the development and progression of PSC that may have important implications for understanding disease initiation/progression and provide insights for the development of novel therapies. In future work we aim to better understand: i) the molecular mechanisms mediating the cholangiocyte transition to senescence, ii) pharmacologic techniques that may selectively eliminate senescent cholangiocytes; and iii) the therapeutic benefits of interfering with senescence cholangiocyte secretion of proinflammatory mediators.

References:

Tabibian JH, O'Hara SP, Splinter PL, Trussoni CE, LaRusso NF. Cholangiocyte senescence by way of N-Ras activation is a characteristic of primary sclerosing cholangitis. *Hepatology*. 2014 Jun;59(6):2263-75.

Tabibian JH, Trussoni CE, O'Hara SP, Splinter PL, Heimbach JK, LaRusso NF. Characterization of cultured cholangiocytes isolated from livers of patients with primary sclerosing cholangitis. *Laboratory Investigation*. 2014 Jul 21. doi: 10.1038/labinvest.2014.94. [Epub ahead of print]