

LAY SUMMARY: Our data to date supports that the cells that line the bile ducts (cholangiocytes) are not only targets but central actors in PSC pathogenesis. Under conditions of persistent stress, a subset of cholangiocytes become senescent, a cellular state where cells remain metabolically active but are no longer capable of cell division. Cellular senescence is emerging as an important aspect in progression of many liver diseases and is being investigated by us as a key process in the pathogenesis of PSC. Cholangiocyte senescence is driven by robust alterations in induced gene expression. In work supported by PSC Partners Seeking a Cure, we've continued our studies to better understand the "epigenome" of senescent and PSC patient cholangiocytes. Epigenetics refers to localized modifications to chromatin (a complex of DNA and proteins) that influence the packaging and accessibility of DNA without altering the DNA sequence itself. These modifications either promote or suppress gene expression. Our ongoing work has shown that the bromodomain and extra-terminal domain (BET) family of "epigenetic readers", a group of proteins that interpret epigenetic marks on chromatin and drive gene expression: **i)** are increased in cholangiocytes of PSC patient tissue samples and mouse models of PSC (e.g., the Mdr2^{-/-} mouse), **ii)** influence the proinflammatory and fibrogenic gene expression profile of experimentally induced senescent and PSC patient-derived cholangiocytes, and **iii)** interact with the senescence-associated transcription factor, ETS1. We've further shown that pharmacologic inhibition of BET proteins in mouse models of PSC reduced cholangiocyte senescence, as well as liver fibrosis and inflammation. Our ongoing work continues to define the role of the BET proteins in the pathogenesis of PSC, including their specific role in driving cholangiocyte senescence and inflammatory gene networks. The support from PSC Partners has given us the opportunity to interrogate the role of the epigenome in PSC and explore "epigenetic therapeutics" as a potential viable option for the treatment of PSC.