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Title of project: Stellate Cell Cyclic Nucleotide Signalling in Hepatic Vascular Disease

ABSTRACT

In Europe alone, liver cirrhosis mainly resulting from alcoholic and non-alcoholic steatohepatitis (NASH) is responsible for an estimated 170000 annual deaths. Cirrhosis patients commonly develop potentially fatal portal hypertension. Portal hypertension is believed to result from active contraction of the hepatic microvasculature and passive obstruction of blood flow by extracellular matrix (ECM) deposition. Evidence suggests a role for hepatic stellate cells (HSCs) in the physiological regulation of intrahepatic vascular tone. In NASH, HSCs become activated and transform into ECM-secreting myofibroblasts with profoundly altered contractile properties making them an attractive therapeutic target in cirrhosis, portal hypertension and beyond. In a recent single-cell-transcriptomics study of HSCs dynamics in experimental NASH, we found full repression of highly expressed, HSC-specific Gs protein-coupled receptors (GsPCRs) during HSC activation. cAMP signaling appears to promote hepatic vasodilation and HSC quiescence by maintenance of transcriptional programs including expression of the soluble guanylate cyclase (sGC), known to trigger vasodilation and prevent fibrosis through cGMP. Conversely, loss of cAMP signaling could drive fibrogenesis and increase vascular resistance. In my proposed project, I will explore the role of this putative GsPCR-cAMP-sGC-cGMP axis in human and murine fibrogenesis. I will catalogue the human HSC GPCR repertoire in patient livers at different NASH stages and apply these insights to target HSC-selective GPCRs in precision-cut liver slices from healthy and cirrhotic donors. I will investigate mechanistic aspects of cAMP and cGMP signaling in mouse models of NASH where both pathways can be selectively modulated in HSCs *in vivo*. Consistent with the translational scope of my project, expression of key elements of the above axis is conserved between human and mouse stellate cells. In summary, I envision that a better understanding of the vasoregulatory properties of the HSCs and knowledge of their surface receptors combined with strategies for targeted receptor activation could unlock a huge therapeutic potential for the treatment of cirrhosis, portal hypertension and beyond.