Dr. Bishuang Cai

Project Summary/Abstract

Nonalcoholic steatohepatitis (NASH) has emerged as the leading cause of chronic liver disease worldwide, with liver fibrosis being the most important predictor of liver failure in NASH. The lack of definitive mechanisms of NASH progression, particularly fibrosis limits the design of mechanism-based therapeutic targets and treatment options. Several independent human GWASs have identified *MERTK* as a risk factor for liver fibrosis. However, the mechanisms of MerTK-mediated liver fibrosis are not completely understood. The overall objective of this proposal is to understand mechanisms of MerTK-induced NASH fibrosis and shed new light on novel therapeutic strategies to prevent NASH progression. Using a diet rich in fructose, palmitic acid, and cholesterol (FPC) developed by our group that promotes human-like NASH pathologic features in mice, I found that genetic targeting of MerTK decreases NASH fibrosis and that MerTK-mediated ERK activation increases the expression of TGFβ1 in macrophages (Mfs), and that MerTK activation increases AKT activity and collagen gene expression in hepatic stellate cells (HSCs). Moreover, I made an important discovery that MerTK cell-surface cleavage is decreased in fibrotic livers. Indeed, I found that all-trans retinoic acid (ATRA), a major active metabolite of retinol found in healthy liver, induces MerTK cleavage in both Mfs and HSCs. Accordingly, I propose that ATRA-induced MerTK cleavage protects against NASH fibrosis but this cleavage is hampered in fibrotic liver due to the loss of retinoids, leading to the progression of NASH. I propose 3 aims to study the mechanisms of MerTK-induced NASH fibrosis. Aim1 will explore the hypothesis that MerTK in Mfs contributes to NASH fibrosis. *Mertk*$^{fl/fl}$*LysmCre*$^{+/-}$ and the littermate control mice fed the FPC diet will be used to study the role of Mf MerTK in NASH fibrosis. I will determine whether Mf MerTK-induced NASH fibrosis is through the ERK1/2-AP1-TGFβ1 pathway. Aim2 will investigate the hypothesis that MerTK in HSCs contributes to NASH fibrosis. *Mertk*$^{fl/fl}$*LysmCre*$^{+/-}$ mice fed the FPC diet will be used to study the role of HSC MerTK in NASH fibrosis. I will determine whether HSC MerTK-induced NASH fibrosis is through activating PI3K/AKT. Aim 3 will explore the hypothesis that suppressing MerTK cleavage promotes NASH fibrosis. I will determine the association of fibrosis stages with hepatic ATRA and MerTK cleavage and determine whether ATRA-induced MerTK cleavage is through activating P38 and the MerTK cleaving enzyme, ADAM17 *in vivo*. This research will be accomplished in the setting of a comprehensive career development program designed to provide me with the skills needed to achieve my career goal as an independent scientist in the field of liver diseases. During the K99 phase, I will continue to gain expertise in molecular, cellular and biochemical approaches to study NASH fibrosis at Columbia University. An advisory committee of established scientists in the fields of NAFLD/NASH, liver fibrosis, HSC activation, and translational science will guide me in the steps towards successful transition to scientific independence over the course of the award period.