Dr. Tim Wang

This supplement is requested for the U54 grant “Myofibroblasts in Gastrointestinal Cancers” at Columbia University (5U54CA163111-02). The research proposed in this supplement is directly related to the subproject “Promotion of Hepatocellular Carcinoma by Myofibroblasts” (Sub-Project ID: 5298), and will investigate mechanisms by which Toll-like receptor 4 (TLR4) signaling in the tumor microenvironment (TME) promotes the development of hepatocellular carcinoma (HCC). We will determine TLR4-expressing cell types responsible for HCC promotion in the setting of chronic liver injury and obesity. Our main focus will be on the hepatic stellate cells, based on data from the parent grant that shows a major contribution of this cell type to the hepatic TME. While the experimental design is fully based on the parent grant, we will include one additional liver tumor model in which a tumor-promoting environment and HCC are driven by obesity and obesity-induced liver fibrosis. Notably, obesity increases the risk for liver cancer 1.4- to 4.5-fold, and will be a leading cause for HCC development in the future. Both obesity and liver fibrosis increase the hepatic exposure to TLR4 ligands, making it likely that they contribute to a tumor-promoting microenvironment through similar mechanisms and targets. To test the contribution of TLR4 in the hepatic TME in the setting of chronic injury and obesity, we will pursue two subaims: In Aim 1A, we test the hypothesis that TLR4 is an essential component of the hepatic TME through which obesity promotes HCC. We will test the role of TLR4 in obesity-driven HCC by comparing HCC development of HCC in wild type and TLR4-null mice using the combination of diethylnitrosamine and high fat/high fructose diet, which causes obesity, liver injury, inflammation and fibrosis. In Aim 1B, we will test the hypothesis that TLR4 in hepatic stellate cells promotes HCC development in setting of chronic liver injury and obesity. For this purpose, we will employ mice with a stellate cell-specific deletion of TLR4, which will be subjected to CCl4- and obesity-induced HCC. Overall, the proposed research will provide a better understanding of how TLR4 in the hepatic TME affects hepatocarcinogenesis in two settings that most commonly lead to HCC development.