Dr. Robert Schwabe

Hepatocellular carcinoma (HCC) is the fifth most common cancer causing about 500,000 deaths/year worldwide. In the US, the incidence of HCC has almost doubled over the last three decades. Despite increases in HCV- and non-alcoholic fatty liver disease-induced HCC, alcohol is still considered a leading risk factor for the development of HCC. It is well established that (i) LPS levels are highly elevated in all stages of alcoholic liver disease (ALD), and that (ii) inflammation and injury in early stages of ALD are largely mediated by lipopolysaccharide (LPS) and its receptor TLR4. Recently, inflammatory pathways such as NF-κB, IL-1, IL-6 and lymphotoxin α and β have been identified as key contributors to non-alcoholic hepatocarcinogenesis. We hypothesize that inflammatory signals play an essential role in alcoholic hepatocarcinogenesis, and that LPS and TLR4 act as key promoters of inflammation-driven proliferation and hepatocarcinogenesis in ALD. We hypothesize that LPS and TLR4 represent the most upstream regulators of inflammatory procarcinogenic signaling cascades such as NF-κB, JNK, IL-1, IL-6, IL-17, lymphotoxin α and β. The long-term goal of this application is to establish LPS and TLR4 as key contributors to an inflammatory gut-liver axis that promotes alcoholic hepatocarcinogenesis, and to develop new concepts for the prevention or treatment of alcoholic HCC. The role of TLR4 in alcoholic hepatocarcinogenesis will be tested in TLR4ko and wt mice subjected to a priming dose of diethylnitrosamine (DEN) and subsequent alcohol-containing diets (AIM 1). The contribution of the gut microbiota to alcoholic HCC will be assessed gut-sterilized and germ-free mice treated with DEN and alcohol-containing diets (AIM 2). Target cells and molecular mechanisms by which LPS and TLR4 promote alcoholic HCC will be determined in bone marrow-chimeric mice and mice with conditional deletion of TLR4 in Kupffer cells, hepatocytes or hepatic stellate cells (AIM 3). Downstream targets of TLR4 will be identified by microarray in whole liver and isolated cell populations, and the functional involvement of candidate genes such as IL-6, IL-1, TNF, LTα, LTβ or IL-17 will be investigated in knockout mice. Results from this study are likely to establish an important contribution of LPS and TLR4 to an inflammatory and procarcinogenic gut-liver axis pathway in ALD, and may lead to the development of novel therapeutic treatment strategies targeting the gut microbiota, TLR4 or specific downstream mediators.