

A STUDY OF HEPATIC PURINERGIC RECEPTOR X7 MOLECULAR MECHANISMS IN ECTOPIC INTESTINAL INFLAMMATION IN ENVIRONMENTAL NAFLD.

by

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Due to the increased consumption of unhealthy foods rich in sugar and fat along with a highly sedentary lifestyle the prevalence of obesity has steadily increased in the United States and the rest of the world. In America about one third of the adult population is obese putting them at a greater risk for diseases such as cancer, cardio-vascular disorders, inflammation and metabolic diseases such as diabetes and non-alcoholic fatty liver disease (NAFLD). NAFLD can be classified into two major categories non-alcoholic fatty liver (NAFL) and non-alcoholic steato-hepatitis depending on the extent of damage which ranges from simple fat accumulation (steatosis) to fibrosis and cirrhosis. The major concern with this disease is that it is largely asymptomatic. About 25% of adult Americans have a fatty liver. High fat diet and common environmental pollutants such as trihalomethanes can act as an important predisposition for the progression of NAFLD. Although there have been reports of fatty liver and intestinal inflammation and carcinogenesis, the exact mechanism for this process remains largely elusive. In this study, I looked at the mechanisms of the cation channel Purinergic receptor X7 (P2X7_r) in liver inflammation and fibrosis and subsequent ectopic crosstalk between the liver and the intestines. Bromo-dichloromethane (BDCM) metabolism in the liver hepatocytes activated P2X7_r channels in the hepatic stellate cells inducing GLUT4 expression and translocation leading to increased intracellular glucose levels via AKT phosphorylation. Increased glucose consumption activated the stellate cells causing extensive fibrosis and scarring. Simultaneously the liver resident macrophages (Kupffer cells)

underwent pyroptosis by NLRP3 inflammasome assembly releasing damage associated molecular patterns (DAMP's) such as High mobility group box 1 (HMGB1) into circulation. HMGB1 thus released could bind to and activate receptor for advanced glycation end products (RAGE) in the intestines. Activated RAGE in-turn could recruit the NADPH oxidase enzyme complex at the cell membrane generating peroxynitrite in association with the nitric oxide synthase. Peroxynitrite could recruit Toll like receptor 4 (TLR-4) to the lipid rafts via AKT phosphorylation. Upon membrane recruitment TLR-4 could itself bind to excess HMGB1 in circulation leading to inflammation by TLR4 signaling. Thus, this study sheds new light on a mechanism of cross talk between two organ systems and opens new avenues to use therapeutic interventions for liver fibrosis and ectopic inflammation.