May 22nd, 4:30 PM - 6:00 PM

Caspase-1-dependent, IL-1β-mediated alcoholic steatohepatitis is ameliorated by IL-1 receptor antagonist treatment in mice

Jan Petrasek
University of Massachusetts Medical School, Jan.Petrasek@umassmed.edu

Shashi Bala
University of Massachusetts Medical School, shashi.bala@umassmed.edu

Dora Lippai
University of Massachusetts Medical School, Dora.Lippai@umassmed.edu

See next page for additional authors

Follow this and additional works at: http://escholarship.umassmed.edu/cts_retreat

Part of the Digestive System Diseases Commons, Gastroenterology Commons, and the Immunology and Infectious Disease Commons

http://escholarship.umassmed.edu/cts_retreat/2012/posters/53

This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in UMass Center for Clinical and Translational Science Research Retreat by an authorized administrator of eScholarship@UMMS. For more information, please contact Lisa.Palmer@umassmed.edu.
CASPASE-1-DEPENDENT, IL-1ß-MEDIATED ALCOHOLIC STEATOHEPATITIS IS AMELIORATED BY IL-1 RECEPTOR ANTAGONIST TREATMENT IN MICE

Jan Petrasek, Shashi Bala, Dora Lippai, Karen Kodys, Victoria Menashy, Matthew Barrieau, Evelyn A. Kurt-Jones, Gyongyi Szabo

Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA

Contact: Jan.petrasek@umassmed.edu

Alcoholic liver disease (ALD) is characterized by steatosis and upregulation of pro-inflammatory cytokines, including interleukin (IL)-1ß. IL-1ß, Type-I IL-1 receptor (IL1R1) and IL-1 receptor antagonist (IL-1Ra) are all part of the IL-1 superfamily that play a role in inflammation. IL-1ß maturation is dependent on Caspase-1. Using wild-type (WT), Caspase-1-, IL-1R1- and IL-1Ra deficient mice fed with Lieber-DeCarli alcohol or control diet, we have identified that signaling mediated by the active IL-1ß was required for development of alcohol-induced steatosis, inflammation and injury. Increased IL-1ß was due to upregulation of Caspase-1 activity and inflammatory activation. The pathogenic role of IL-1 signaling in ALD was attributable to the presence of IL-1R1 on liver parenchymal cells. Importantly, in vivo intervention with recombinant IL-1Ra, Anakinra, which blocks IL-1 signaling, significantly attenuated both liver steatosis and inflammation. In primary hepatocytes, physiological doses of IL-1ß induced steatosis and upregulated the inflammatory and pro-steatotic chemokine MCP-1. MCP-1, but not IL-1ß induced hepatocyte cytotoxicity at concentrations found in ALD.

In conclusion, we demonstrate that Caspase-1-dependent upregulation of IL-1ß and signaling mediated by IL-1 is crucial in the pathogenesis of ALD in a cell specific manner. Our findings suggest a potential role of IL-1Ra in the treatment of ALD.