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

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

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CASPASE-1-DEPENDENT, IL-1ß-MEDIATED ALCOHOLIC STEATOHEPATITIS IS AMELIORATED BY IL-1 RECEPTOR ANTAGONIST TREATMENT IN MICE

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Alcoholic liver disease (ALD) is characterized by steatosis and upregulation of pro-inflammatory cytokines, including interleukin (IL)-1β. IL-1β, 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-1β 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-1β was required for development of alcohol-induced steatosis, inflammation and injury. Increased IL-1β 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-1β induced steatosis and upregulated the inflammatory and pro-steatotic chemokine MCP-1. MCP-1, but not IL-1β induced hepatocyte cytotoxicity at concentrations found in ALD.

In conclusion, we demonstrate that Caspase-1-dependent upregulation of IL-1β 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.