00417 Neutralizing Anti-IL-11 Antibodies Protect Against Hepatic Fibrosis in Non-alcoholic Steatohepatitis

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Aims: Non-alcoholic steatohepatitis (NASH) is a progressive liver disease and hepatic fibrosis, which precedes liver failure and cancer, is a major indicator of disease severity. We recently documented an important role for IL-11 in cardiac fibrosis and here, we aim to extend our studies to liver fibrosis in NASH.

Methodology: In vitro, hepatic stellate cells (HSCs) were treated with IL-11 (5 ng/ml) or various pro-fibrotic stimuli, in the presence of either IgG or neutralizing IL-11 antibodies (2 µg/ml) and monitored for HSC activation, marked by the presence of ?-smooth muscle actin (ACTA2) and increased collagen production. In vivo, we investigated the role of Il-11 by inducing Il-11 expression specifically on Col1a2-expressing cells. The effect of genetic inhibition of IL-11 signalling was investigated by feeding mice lacking functional allele for Il11rα (Il11ra-/-) and their wild-type counterparts (Il11ra1+/+) with NASH diets. In therapeutic studies, we injected NASH diets-fed mice with either neutralizing anti IL-11 antibodies or isotype IgG control (10-20 mg/kg, twice a week, IP).

Result: We found that IL-11 is upregulated in human fibrotic liver diseases, including NASH. In vitro, IL-11 was secreted from TGFβ1-stimulated human liver slices and IL-11 was sufficient to drive HSCs to become collagen-secreting myofibroblasts. HSCs secreted IL-11 after stimulation with various pro-fibrotic factors and IL-11 activity was necessary for fibrosis phenotypes downstream of these stimuli. We then examined the role of Il-11 in vivo and found that fibroblast-specific transgenic expression of Il-11 drives hepatic fibrosis. In mouse model of diet-induced NASH, Il11ra-deleted mice were protected from liver fibrosis and had lower serum ALT, as compared to controls. In therapeutic studies, we developed then used neutralizing anti-IL-11 antibodies during the steato-fibrosis stage of NASH and found that targeting IL-11 could arrest and even reverse hepatic fibrosis while limiting hepatotoxicity.

Conclusion: We propose targeting IL-11 as novel therapeutic approach for treating NASH.