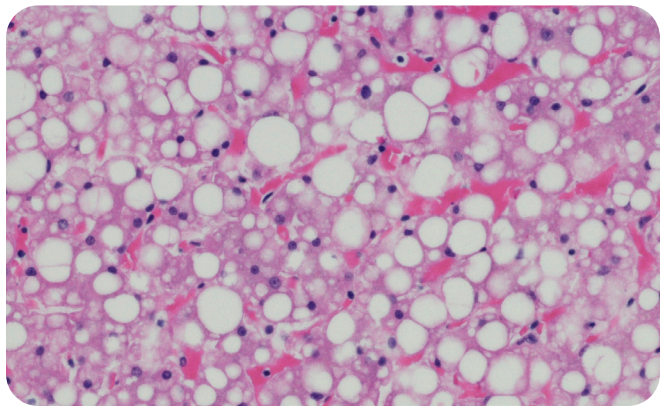
Inhibiting Interleukin 11 Signaling Reduces and Reverses Many Dangerous Effects of NAFLD/NASH in Mouse Models

Accumulation of fat in liver cells, a process called steatosis, is a common health problem that has many possible causes. Nonalcoholic fatty liver disease (NAFLD) is a group of conditions caused by the buildup of fat in the liver, with some sources estimating that one in four people develop it in their lifetime. NAFLD, if left untreated, may progress to nonalcoholic steatohepatitis (NASH). NASH kills hepatocytes, causes structural changes to the liver, and creates inflammation that could be deadly. NAFLD and NASH begin with the abnormal accumulation of lipids inside hepatic stellate cells (HSC). When profibrotic factors stimulate HSCs, the cells transform into myofibroblasts, beginning a process of fibrosis that impedes liver function.

Dr. Anissa A. Widjaja et al. recently examined the connection between interleukin 11 (IL-11) signaling and the development of liver disease. They examined the effects of IL-11 on mouse and human HSCs *in vitro*, and on multiple mouse models analogous to human NAFLD/NASH. Their *in vitro* analysis confirmed that IL-11 is the most upregulated gene in HSCs when modeling a cirrhotic liver. They replicated their initial protein analysis from mouse cells with human cell samples. In addition, they found increased IL-11 levels in samples from patients with known fibrotic liver diseases, including NASH.

In vivo analysis involved multiple mouse models chosen to differentiate between factors that could independently trigger liver disease. This was necessary to isolate the effects of lipid accumulation from common comorbid conditions, such as obesity and insulin resistance. IL-11 transformed



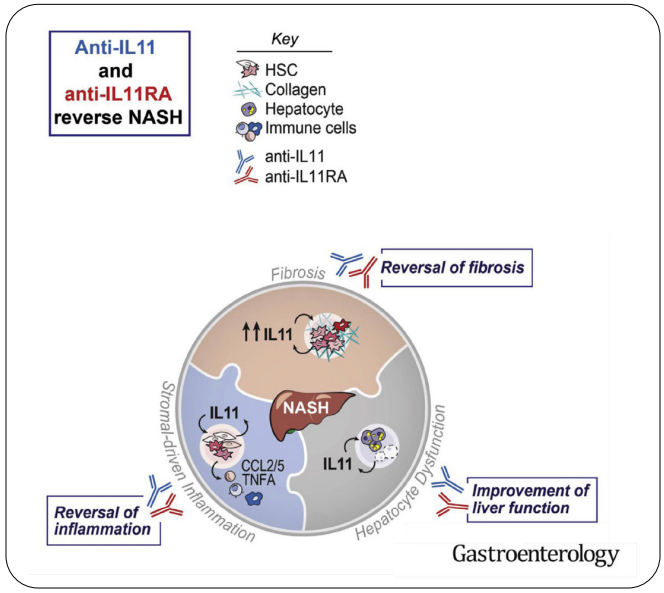


Figure 1: Basic and Translational Liver

HSCs into myofibroblasts *in vivo*, whether it was wild-type, recombinant, or an engineered variant. Administration of IL-11 also increased hepatic collagen content and expression of proinflammatory genes. Expression of profibrotic genes also increased, and IL-11 promoted migration of HSCs within the extracellular matrix. An auto-endocrine loop formed when HSCs began secreting IL-11 after being stimulated with that interleukin. These physical and chemical changes, taken together, promoted fibrosis and structural changes within mouse livers *in vivo*.

A loss of function mouse model, in which IL-11 receptor subunit alpha (ILRA) was deleted, avoided many of the physical and chemical changes associated with NAFLD/NASH progression. This knockout model suffered less inflammation and less liver damage after IL-11 administration. It also experienced less steatosis and was largely protected from fibrosis. These findings suggested that IL-11 is involved in multiple aspects of NAFLD/NASH pathology. However, this mouse model was not obese or insulin resistant, so results from this model alone were not applicable to human NAFLD/NASH analogues.

A mouse model mirroring human NASH confirmed the role of IL-11 in disease progression. The mice modeling human NASH started out obese, insulin resistant, and hyperglycemic. Knockout mice fed a high fructose diet to attain that same profile gained a similar amount of weight as their NASH counterparts. Their physical and metabolic profiles were dramatically different: they experienced less steatosis, inflammation, fibrosis, and hepatocyte damage. They also had lower fasting blood glucose, lower serum cholesterol, and lower triglycerides, giving them a lower overall cardiovascular risk.

To further test the reliance of NAFLD/NASH symptoms on IL-11 signaling, Dr. Widjaja et al. administered anti-IL-11 antibodies to mouse models with established steatosis and NASH. Neutralizing antibodies could be identified using Operetta High Content Imaging system and Wizard Gamma Counter, offered by Revvity. Anti-IL-11 antibodies inhibit or reverse fibrosis, inflammation, and liver damage if administered early enough in disease progression. Combining these antibodies with metabolic change through transition to a diet without high fructose lowers hepatic collagen content and creates a favorable environment for reversal of established fibrosis. Early application of anti-IL-11 antibodies reduces severe inflammation, potentially preventing liver necrosis, and may substantially reverse existing liver damage.

Inhibition of IL-11 signaling reduces and reverses many dangerous effects of NAFLD/NASH in mouse models. Since IL-11 appears redundant in adult mammals, it may be useful as a novel drug target to combat NAFLD/NASH. Dr. Widjaja et al. suggest that targeting IL-11 may also give NAFLD/NASH patients an added benefit of greater cardiovascular health, since those patients often have cardiovascular diseases and inhibition of IL-11 improves cardiovascular biomarkers.

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