An integrated view of anti-inflammatory and antifibrotic targets for the treatment of NASH

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Abstract

Successful development of treatments for non-alcoholic fatty liver disease and its progressive form, non-alcoholic steatohepatitis (NASH), has been challenging. Because NASH and fibrosis lead to progression towards cirrhosis and clinical outcomes, approaches have either sought to attenuate metabolic dysregulation and cell injury, or directly target the inflammation and fibrosis that ensue. Targets for reducing the activation of inflammatory cascades include nuclear receptor agonists (e.g. resmetirom, lanifibranor, obeticholic acid), modulators of lipotoxicity (e.g. aramchol, acetyl-CoA carboxylase inhibitors) or modification of genetic variants (e.g. PNPLA3 gene silencing). Extrahepatic inflammatory signals from the circulation, adipose tissue or gut are targets of hormonal agonists (semaglutide, tirzepatide, FGF19/FGF21 analogues), microbiota or lifestyle interventions. Stress signals and hepatocyte death activate immune responses, engaging innate (macrophages, innate lymphocyte populations) and adaptive (auto-aggressive T cells) mechanisms. Therapies have also been developed to blunt immune cell activation, recruitment (chemokine receptor inhibitors), and responses (e.g. galectin-3 inhibitors, anti-platelet drugs). The disease-driving pathways of NASH converge to elicit fibrosis, which is reversible. The activation of hepatic stellate cells into matrix-producing myofibroblasts can be inhibited by antagonising soluble factors (e.g. integrins, cytokines), cellular crosstalk (e.g. with macrophages), and agonising nuclear receptor signalling. In advanced fibrosis, cell therapy with restorative macrophages or reprogrammed (CAR) T cells may accelerate repair through hepatic stellate cell deactivation or killing, or by enhancing matrix degradation. Heterogeneity of disease – either due to genetics or divergent disease drivers – is an obstacle to defining effective drugs for all patients with NASH that will be overcome incrementally.