**Biomechanical aspects of nonalcoholic fatty liver disease**

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Mechanobiology is an interdisciplinary field that explores the impact of physical force (e.g., compression, stretch, and shear stress) on biological functions, such as development, growth, and differentiation. Mechanical cues are perceived by various mechanosensors of living cells (e.g., focal adhesions, adherencs junctions, flow-sensitive ion channels), propagated by the contractile cytoskeleton (mechanotransmission) and intracellular biochemical cascades (mechanosignaling), and integrated into mechanoresponses by the nucles. There is evidence that mechanical forces extensively inform the biological behavior of liver cells. Liver sinusoids represent a unique microenvironment in which a number of cell types are subjected to a variety of physical forces originating in the cytoskeleton and at interfaces with adjacent cells, the extracellular matrix, and vascular or interstitial fluids. However, the impact of mechanoresponses on the development and progression of liver disease remains relatively unexplored.

Recent studies suggest that early mechanical changes have a key role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), a globally prevalent disorder with heterogeneous outcomes. Steatosis and steatohepatitis profoundly alter liver tissue viscoelasticity associated with changing architecture and hemodynamic properties. These changes can be detected by noninvasive methods such as shear wave elastography and provide important diagnostic information about the stage and severity of NAFLD. Moreover, hepatocellular lipid accumulation and lipotoxic injury (ballooning), activation of inflammatory responses, dysfunction of liver sinusoidal endothelial cells, and transdifferentiation of hepatic stellate cells initiate mechanoresponses that may contribute to a pro-angiogenic, pro-fibrotic, and pro-oncogenic milieu and foster the development of portal hypertension, cirrhosis, and hepatocellular carcinoma (HCC). A number of studies indicate that the paralogous transcription co-activators YAP/TAZ have a prominent role in regulating mechanoresponses in health and disease. In the liver, YAP/TAZ have been associated with liver cell zonation, metabolic reprogramming, activation of hepatic stellate cells, and fibrogenesis.

Several lines of evidence indicate that a better understanding of liver mechanobiology will help us gain new insights into the pathogenesis of NAFLD. One concept emerging from current research is that fibrosis is not a prerequisite to the initiation of portal hypertension in NAFLD. Evidence shows that steatosis, inflammation, and angiogenesis increase sinusoidal pressure that may stimulate the development of subsequent fibrosis, establishing a bidirectional relationship, in part mediated through mechanosignaling. Another intriguing concept relates to the early development of HCC in noncirrhotic NAFLD. Recent work demonstrated that accumulation of large lipid droplets in hepatocytes cause nuclear deformation and YAP/TAZ activation, which may activate oncogenic pathways in fatty liver.

Identifying molecular targets to prevent or mitigate the impact of physical forces on liver cells may represent novel approaches to the treatment of NAFLD.

**Learning Objectives:**

* Understand how mechanical forces shape the behavior of liver cells in health and disease
* Appreciate the potential of mechanics-based strategies in the management of NAFLD

**References:**

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