Using vitamin A to target early and late liver diseases via mechanotransduction

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Video Abstract

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Abstract

A new study reports that treating certain liver cells with a metabolite of vitamin A could lead to better disease management, particularly for conditions linked to liver fibrosis. The cells in question are hepatic stellate cells, which play a key role in liver function. In healthy tissue, the cells are mostly inactive. But when the liver is injured, they kick into gear to help repair the damage. The problem is that unabated activation of the cells can lead to the development of conditions such as nonalcoholic fatty liver disease, a global public health concern. The cells can even become permanently activated, triggering more serious conditions like fibrosis or cirrhosis. Liver function often becomes impaired once fibrosis sets in, and the scarring can also provide a fertile environment for tumor growth. For example, hepatocellular carcinoma occurs more frequently in patients with liver cirrhosis than those without it. A team of researchers at Imperial College London hypothesized that turning off activated stellate cells could interrupt this potentially deadly cascade of events and help restore liver health. One thing the cells need for sustained activation is a stiff microenvironment. And that's where vitamin A comes in. When the researchers exposed activated hepatic stellate cells to the vitamin A metabolite known as all-trans retinoic acid, or ATRA, they saw a drop in levels of the protein myosin-2. Perhaps best known as the protein responsible for causing muscle cells to contract, myosin-2 has a key role in maintaining tissue stiffness in the liver, which it achieves through its involvement with the cellular cytoskeleton. Myosin-2 gene expression is also regulated through the RAR-beta receptor, a direct target of ATRA. Interestingly, the team found that patients with cirrhosis and hepatocellular carcinoma have low levels of RAR-beta receptor and very high levels of active myosin-2. By lowering myosin-2 expression, the researchers could essentially mechanically deactivate stellate cells, returning them to a healthier status. Although more work is needed to translate the findings to the clinical setting, the report lays a foundation for potentially reversing liver disorders through targeting the mechanobiology of hepatic stellate cells, which opens new avenues for treating early and late liver diseases.