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LIVER

Delineating the role of angiogenesis in liver fibrosis

A novel *in vitro* culture system sheds new light on the role that liver sinusoidal endothelial cells (LSECs) have in liver fibrogenesis at different stages of disease.

Hepatic fibrosis is a key feature of progressive liver disease and an important therapeutic target. Hepatic stellate cells (HSCs) are activated by damage-related stimuli, which promote their transdifferentiation to proliferative myofibroblasts and the secretion of extracellular matrix components. It is believed that LSECs are regulators of HSC activation and subsequent fibrogenesis. However, evidence on their roles at different fibrosis stages has, to date, been conflicting.

To address this uncertainty, Liu and colleagues constructed fibrotic microniches to model LSEC–HSC interactions and their respective contributions to liver fibrosis. LSECs were cultured on 2D substrate and then overlaid with a 3D collagen hydrogel embedded with HSCs. As progressive tissue stiffening is a key feature of worsening liver fibrosis, the LSEC substrate stiffness was adjusted to model early-stage fibrosis (200 Pa) and late-stage fibrosis or cirrhosis (>1,200 Pa). LSECs cultured on these substrates recapitulated features of LSECs from human liver tissue at respective fibrosis stages. In addition, the disease-stage-specific gene expression in cultured LSECs was similar to LSECs derived from mouse liver fibrosis models, notably in terms of signalling pathways related to angiogenesis and fibrogenesis.

Next, the researchers used their model to investigate how LSECs activate HSCs. By modulating culture conditions and excluding the role of paracrine factors, they showed that HSC activation by LSECs required mechanical force, induced by LSEC-mediated condensation of collagen fibrils. This finding was then confirmed in HSCs using atomic force microscopy. Using a series of knockdown experiments, HSCs were found to be activated by mechanical force through the membrane-bound DDR2 receptor, which interacts with extracellular collagen fibres. DDR2 stimulation promoted JAK–PI3K–AKT pathway signalling to upregulate fibrogenesis, particularly in the early-stage fibrosis microniches.

> “HSCs were found to be activated by mechanical force through the membrane-bound DDR2 receptor”

Finally, the authors used their model system to assess anti-angiogenic therapies in liver fibrosis. In line with their earlier findings, the anti-angiogenic drug sorafenib was effective at reducing fibrosis only in early fibrosis stages; by contrast, a lysyl oxidase inhibitor, which prevents collagen condensation, was effective in later stages. The authors plan to use their fibrotic microniche system to conduct high-throughput screens of anti-fibrotic compounds specific to disease stage.

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ORIGINAL ARTICLE Liu, L. *et al.* Mechanotransduction-modulated fibrotic microniches reveal the contribution of angiogenesis in liver fibrosis. *Nat. Mat.* http://dx.doi.org/10.1038/nmat5024 (2017)