The interplay between biomechanics and cell kinetics explains the spatial pattern in liver fibrosis

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Autoren

Jieling Zhao **Seddik Hammad** Mathieu de Langlard Pia Erdoesi Yueni Li Paul Van Liedekerke Andreas Buttenschoen Manuel Winkler Sina W. Kürschner Philipp-Sebastian Reiners-Koch Niels Grabe **Björn Hartleben** **Stephanie D. Wolf** **Johannes Bode** **Jan G. Hengstler** Matthias P. Ebert **Steven Dooley** **Dirk Drasdo**

Abstract

The formation of liver fibrosis patterns, characterized by excess extracellular matrix (ECM), is a complex process that is difficult to investigate experimentally. To complement experimental approaches, we developed a digital twin (DT) model to simulate the pattern formation of septal and biliary fibrosis, the two common forms of liver fibrosis. This model is based on iterative calibration with experiments from animal models treated with the hepatotoxic substance CCl4 (septal form) and Abcb4-knockout mice (biliary form). Septal fibrosis is characterized by ECM accumulation along the connective line between the central veins of neighboring liver lobules, while biliary fibrosis is marked by a scattered ECM pattern within the portal fields. This mechanistic DT model includes the components of hepatocytes (Heps♠), hepatic stellate cells (HSCs), macrophages (Mphs), bile duct (BD) cells, collagen fibers secreted by activated HSCs, blood vessels, and cell-cell communication. It allows for the integration and simultaneous modulation of multiple hypothesized mechanisms underlying fibrotic wall formation.

The model simulates the formation of liver fibrosis pattern and demonstrates that ECM distribution results from the pattern of cell death zones and biomechanical compression due to cell proliferation. "Healthy" Heps proliferate to compensate for cell loss. In septal fibrosis, where the cell death zones are several cells thick, the proliferating Heps surrounding a zone mechanically compress the deposited collagen network. After a transient phase of collagen scattered between/around Heps, the ECM eventually adopts a sharp, "wall"-like structure. Whereas, in biliary fibrosis, the pattern of cell death is more scattered, leading to a corresponding scattered ECM pattern. In this case, a pattern of scattered distributed collagen forms without transitioning to a sharp wall. Notably, the failure of fibrotic wall formation in endothelial cell-specific GATA4LSEC-KO mice, due to the disrupted pattern of CYP2E1-expressing Heps, validates our DT model.

In conclusion, the DT model provided a deeper understanding of liver fibrosis pattern formation. It enabled comparison between simulated outcomes of hypothesized mechanisms and experimental data. Additionally,

it guided the design of validation experiments and enabled the identification of optimal strategies for drug testing and extrapolation to humans.