

A digital liver twin demonstrating the interplay between biomechanics and cell kinetics can explain fibrotic scar formation

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Abstract

Formation of liver fibrosis patterns is a complex process that can only be marginally investigated experimentally. A digital twin (DT), a computational model of the liver, is warranted, as it permits integration and modulation of multiple mechanisms. We develop a DT on chronic injury-mediated formation of CCl₄-induced septal fibrosis based on experimental iterations. This DT closely reproduces the spatial-temporal pattern of hepatocytes, hepatic stellate cells (HSCs), macrophages (Mphs), collagen fibers secreted by activated HSCs, blood vessels and cell-cell communication through literature and quantitative imaging. It simulates formation of septal fibrosis and predicts that attraction of activated HSCs and Mphs is controlled by hepatocytes, damaged by CCl₄ intoxication. Meanwhile, undamaged hepatocytes proliferate to replace the dead ones, thereby mechanically compressing the fibrotic network formed by collagen into "wall"-like shapes. Importantly, simulations assuming loss of spatial pattern of CYP2E1 expressing hepatocytes match with experimental data from mice with deleted transcription factor GATA4 in endothelial cells displaying a decreased CYP2E1 expression and disturbed distribution pattern in hepatocytes, thereby validating the DT.