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.