Zonal Hepatic Stellate Cell (HSC) Activation in Nonalcoholic Steatohepatitis (NASH) Characterized by A Mathematical Model

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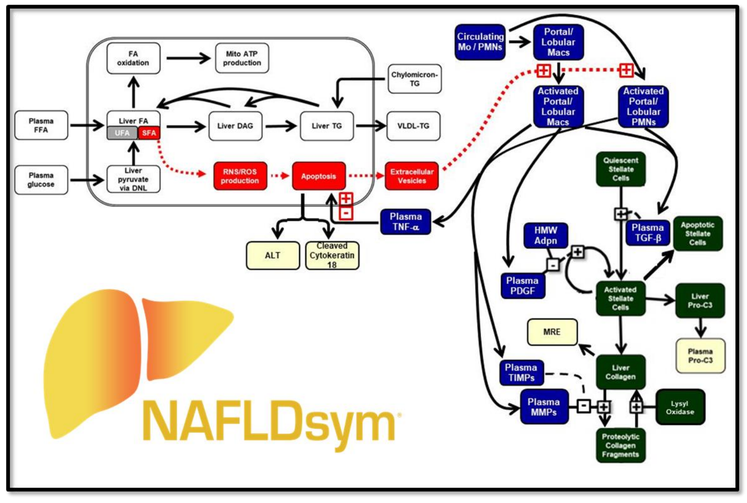
Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of pathophysiology, ranging from hepatic steatosis, through non-alcoholic steatohepatitis (NASH) and hepatic fibrosis, and in rare cases resulting in cirrhosis and liver failure. Hepatic fibrosis in NASH is caused by excessive synthesis of extracellular matrix (ECM) proteins with hepatic stellate cells (HSCs) playing an integral role. Following activation, quiescent hepatic stellate cells (qHSCs) proliferate and transform to an activated phenotype, in which they increase production of ECM proteins. Hepatic fibrosis progresses over time with an increase in the number of activated HSCs and production of hepatic ECM proteins. Fibrosis in NASH is histologically described by the accumulation of ECM proteins in different hepatic acinar zones, with stage I fibrosis occurring in the centrilobular (CL) zone; stage II fibrosis also includes the periportal (PP) zone. The differential activation of HSCs during the progression of fibrosis in NASH has not been well characterized to date; we have used a mathematical model to better characterize this aspect of NASH.

Methods

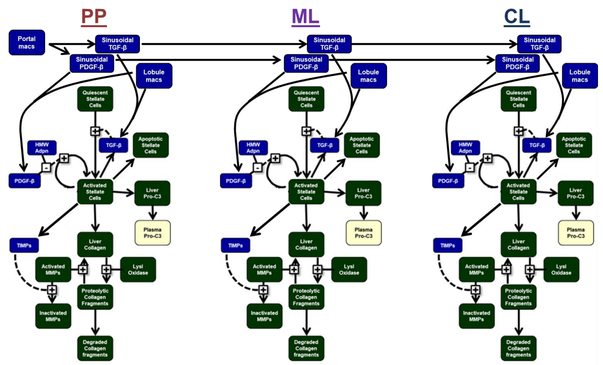
A mathematical model was developed as a submodel within the quantitative systems pharmacology (QSP) model, NAFLDsym, to represent the dynamics of HSC activation and proliferation during the development of hepatic fibrosis in NASH. The model consists of ordinary differential equations (ODEs) to describe the following processes in three discrete acinar zones of the liver (CL, midlobular (ML), and PP): TGF-β-induced activation of qHSCs, PDGF-dependent proliferation of activated HSCs, and apoptosis of activated HSCs.



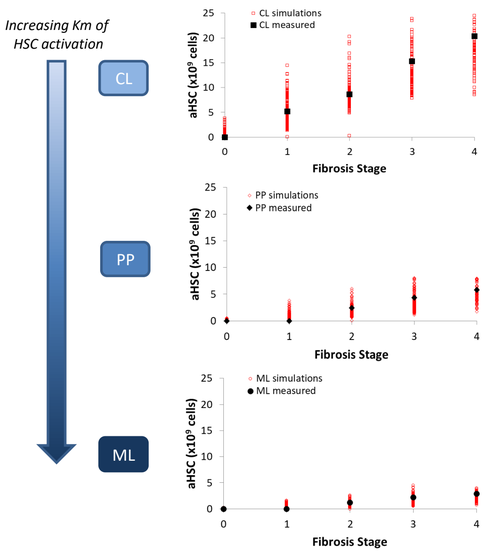
NAFLDsym QSP model. Components of the fibrosis submodel are shown in the green boxes.

Results

NAFLDsym Simulations Recapitulate the Zonal Activation of HSCs



- NAFLDsym simulates the increase in the number of activated HSCs during the progression of fibrosis.
- The simulated number of aHSCs varies across zones with a CL predominance, consistent with clinical data showing the degree of stellate cell activation in NASH patients was highest in CL.[1]
- Simulated zonal differences were driven by different Km values for TGF-β-induced activation of qHSCs.
- Zonal differences in HSC activation contribute to zonal differences in histologic fibrosis stages.



- Consistent with clinical data showing increased HSC activation with more extensive fibrosis[1,2,3], simulated patients have increasing number of aHSCs with increasing fibrosis stage.

Conclusions

The regulation of HSC activation and subsequent participation in hepatic fibrosis appears to have different sensitivities to key mediators across the hepatic acinus. CL HSCs appear to be most sensitive, with ML HSCs least sensitive to TGF-β-induced HSC activation; PP HSCs have intermediate sensitivity. Minimizing HSC activation could prove to be an important therapeutic approach to treating fibrosis, and the improved understanding of the zonal HSC differences provided with this mathematical model may help guide related treatment approaches.

References

[1] Washington et al. (2000) Hum Pathol 31:822-8.
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[3] El-Gendi et al. (2012) Egyptian Journal of Pathology 32:59-67.

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