MODELING HEPATIC STELLATE CELL miRNA REGULATORY NETWORKS DRIVING CHRONIC ALCOHOL EFFECTS ON LIVER REGENERATION

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Chronic alcohol intake disrupts liver regeneration and repair, a potential cause for alcoholic liver disease. The interactions between the liver cell types play a major role in liver regeneration. Among the liver cell types, Hepatic stellate cells (HSC) are an important source of cytokines and one of the significant mediators of cell-cell interactions driving liver regeneration process. In this study, we employed a model-based approach to analyze key miRNA-mediated regulatory networks in HSCs responding to liver regeneration following adaptation to chronic alcohol intake. Rats were fed a liquid diet containing 36% of total calories derived from ethanol for 5 weeks per established Lieber-DiCarli protocol, paired with a control isocaloric liquid diet. We make use of a parallel global gene expression profiling study using Affymetrix Rat 1.0 ST microarrays, to characterize the impact of chronic ethanol treatment during the early regeneration time course (1, 6, 24 hrs after PHx). Additionally, novel NanoString digital assay platform was used to measure expression of 420 well-annotated miRNAs during PHx and in response to in vivo manipulation of miR-21 levels.

We developed an initial Boolean model whose structure was based on published literature on miR-21 and miR-146a interactions with the elements of NF-κB, STAT3 and TGFβ pathways. miR-21 and miR-146a are oppositely regulated in a wide range of contexts, including HSC activation. Our results on inhibition of miR-21 levels reveal an up-regulatory effect on miR-146a in whole liver samples. We performed model simulations to test whether known interactions between signaling and miRNAs can explain the anti-parallel regulation of miR-21 and miR-146a. Our results indicate that the initial model containing differential activation of miR-146a vs miR-21 via NF-κB and STAT3 signaling pathways is not sufficient to account for the anti-parallel regulation of these miRNAs. Based on these results, we expanded the model using a deterministic ordinary differential equation based model kinetics to consider regulatory interactions between the two miRNAs that may occur via as yet unknown direct or indirect mechanisms. The results will provide new insights into our observations on HSC activation during liver regeneration following adaptation to chronic ethanol intake. Research support: NIH/NIAAA R01 AA018873, K05 AA017261 and T32 AA007463.