Basal MET Phosphorylation is an Indicator of Hepatocyte Dysregulation in Liver Disease (preprint)

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Abstract

Chronic liver diseases are worldwide on the rise. Due to the rapidly increasing incidence, in particular in Western countries, Non-alcoholic fatty liver disease (NAFLD) is gaining importance as the disease can develop into hepatocellular carcinoma. Lipid accumulation in hepatocytes has been identified as the characteristic structural change in NAFLD development, but molecular mechanisms responsible for disease progression remained unresolved. Here, we uncover in primary hepatocytes from a preclinical model fed with a Western diet (WD) a strong downregulation of the PI3K-AKT pathway and an upregulation of the MAPK pathway. Dynamic pathway modeling of hepatocyte growth factor (HGF) signal transduction combined with global proteomics identifies that an elevated basal MET phosphorylation rate is the main driver of altered signaling leading to increased proliferation of WD-hepatocytes. Model-adaptation to patient-derived hepatocytes reveal patient-specific variability in basal MET phosphorylation, which correlates with patient outcome after liver surgery. Thus, dysregulated basal MET phosphorylation could be an indicator for the health status of the liver and thereby inform on the risk of a patient to suffer from liver failure after surgery.