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Metabolism-dependent mTORC1 Activation Contributes to Palmitate Lipotoxicity in Hepatocytes

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Abstract:

Lipotoxicity, induced by saturated fatty acids (SFAs), plays a central role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). However, the underlying mechanisms remain unclear. Palmitate is the most abundant SFA in the circulation. We have previously reported that inositol-requiring enzyme 1α (IRE1α), one of three canonical signaling pathways of ER stress, is implicated in palmitate-induced cell death in hepatocytes. In this study, via a small-scale screening of available chemical inhibitors using AML12 hepatocytes, we identified mTORC1 as a critical culprit in palmitate-induced cell death in that mTOR inhibitor, torin1 and rapamycin, were protective against palmitate-induced cell death. Palmitate activation of mTORC1 involves its intracellular metabolism since inhibiting the long-chain acyl-CoA synthetases, the enzyme converting palmitate to palmitoyl-CoA, blunted mTORC1 activation upon palmitate exposure and conferred protection against cell death, whereas inhibition of SCD-1, the enzyme desaturating palmitate to palmitoleate, enhanced mTORC1 activation and exacerbated cell death. Intriguingly, the protective effect of mTORC1 inhibition was independent of autophagy induction, in that autophagy inhibition via both pharmacologic and genetic approaches failed to ablate mTORC1 inhibitorconferred protection. Further investigation revealed that IRE1α is the downstream target of mTORC1 upon palmitate exposure and inhibition of either its endonuclease activity or kinase activity protects against hepatocyte lipotoxicity. Collectively, our data identify that mTORC1 and ER stress is coordinately implicated in hepatocyte cell death in response to palmitate exposure and suggest that this pathway may potentially serve as a therapeutic target for the treatment of NAFLD as well as other metabolic disorders involving lipotoxicity.)

Publication:

Nicotinamide ameliorates palmitate-induced ER stress in hepatocytes via cAMP/PKA/CREB pathway-dependent Sirt1 upregulation", Biochim Biophys Acta. 1853:2929-36, 2015.

"Rectification of impaired adipose tissue methylation status and lipolytic response contributes to hepatoprotective effect of betaine supplementation in a mouse model of alcoholic liver disease", The British Journal of Pharmacology 171:4073-86, 2014.

"Nrf2 activation-induced hepatic VLDL receptor overexpression in response to oxidative stress contributes to alcoholic liver disease in mice", Hepatology. 59:1381-92, 2014.

Biography:

ResearchFocus:

Investigating the cellular/molecular mechanisms underlying the pathogenesis of metabolic liver diseases, including alcoholic liver disease (ASD) and obesity-associated non-alcoholic fatty liver disease (NAFLD) using both in vitro and in vivo models.

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