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הנושא:

The role of HIF-1/iNOS axis in the progression of NAFLD

המפגש יתקיים
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Abstract:

Nonalcoholic fatty liver disease (NAFLD) comprises a wide spectrum of liver damage, ranging from simple steatosis through steatohepatitis (NASH) to cirrhosis. In this work we tried to elucidate the role of hypoxia-inducible factor-1/inducible nitric oxide synthase (HIF-1/iNOS) axis in the progression of NAFLD. We found that in steatotic hepatocytes, increased fat accumulation coincident with decreased HIF-1α activation under prolonged hypoxia leading to lower intracellular ATP levels and greater cell death. We also found that under NASH and endotoximic conditions, liver injury was exacerbated in iNOS-deficient mice and that HIF-1 signaling was markedly attenuated in these mice. Enhanced liver injury in these mice was also associated with a fatal hypoglycemia. We further illustrated the importance of HIF-1α under these conditions using hydrodynamic injection as it significantly ameliorated liver damage in these mice. Cholesterol is known to play a fundamental role in the progression of liver fibrosis during NASH. We found an increase in HIF-1 accumulation and transcriptional activation following cholesterol-load, which were due to mitochondria-induced ROS generation and iNOS activation, respectively. Finally we showed that chronic activation of HIF-1/iNOS axis, caused by cholesterol, leads to advanced liver fibrosis. Taken together, this work illustrates the important role of HIF-1/iNOS axis in the progression of NAFLD. Downregulation of HIF-1 pathway during hypoxia increases cell death and therefore promotes the transition of simple steatosis to NASH. Once NASH phenotype was established, HIF-1/iNOS axis also plays an essential role in glucose metabolism under acute inflammation. Conversely, chronic liver activation of this axis by cholesterol may mediate its deleterious effects in the liver, including liver fibrosis.

סגל וסטודנטים מוזמנים להשתתף