High Fat Diet-Mediated p38α Activation in the Liver Contributes to the Onset of Insulin Resistance and Hepatic Steatosis

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Abstract

The mechanisms underlying the paradox of selective hepatic insulin resistance, whereby insulin fails to suppress gluconeogenesis while continues to stimulate lipogenesis, are not well understood. Mitogen-activated protein kinases play a pivotal role in the onset of hepatic metabolic dysregulation, however current data fails to establish a definitive role for p38. We generated a liver-specific p38α knockout (KO) mouse model to investigate the role of p38α in regulating hepatic glucose and lipid metabolism following 1 week of high fat diet (HFD) feeding. We demonstrated that short-term HFD feeding was sufficient to increase hepatic p38 activation in mice. Moreover, liver-specific p38α KO mice were protected from the development of HFD-induced glucose intolerance and HFD-induced hepatic and peripheral insulin resistance. HFD-mediated hepatic p38α activation increased plasma interleukin-6 and interferon-γ, suggesting a possible mechanism driving liver-periphery cross-talk in the development of peripheral insulin resistance. Lastly, we demonstrated that HFD-induced activation of hepatic p38α promoted hepatic fat accumulation, potentially via enhanced hepatic PPAR-γ expression. These findings ultimately suggest that selective p38α inhibition may provide a new approach for treatment of insulin resistance and hepatic steatosis, as seen in models of type 2 diabetes and non-alcoholic fatty liver disease.