Mark D. Gorrell, J Diabetes Metab 2018, Volume 9
DOI: 10.4172/2155-6156-C6-093

Understanding the roles of the proline-specific protease fibroblast activation protein alpha (FAP) in liver steatosis, insulin resistance and glucose intolerance

Mark D. Gorrell
Centenary Institute and University of Sydney, Australia

Introduction: Fibroblast activation protein-alpha (FAP) is an extracellular protease with a unique post-proline specificity. FAP substrates include neuropeptide Y and the hepatokine FGF-21. This study examined metabolic outcomes of specific genetic ablation of FAP enzyme activity (FAPgki mouse) or FAP protein (FAPgko mouse) in diet induced obesity (DIO) causing fatty liver.

Results: FAP concentrations were greater than controls in pancreas from humans and mice with diabetes. In humans with severe fatty liver disease (NASH), circulating FAP levels correlated with circulating insulin and insulin resistance levels. Mice received atherogenic high fat diet (HFD) for 8 to 20 weeks. Compared to co-caged wild type control mice, FAPgki and FAPgko male and female mice had less insulin resistance, pancreatic and plasma insulin, glucose intolerance, micro-vesicular steatosis, hepatocyte ballooning, total liver lipid, serum alanine transaminase and circulating cholesterol. FAP deficiency increased intrahepatic non-esterified free fatty acids, indicative of increased lipolysis. Moreover, lipogenic genes (Pparg, Gck, Acc and Fasn) and hepatic triglyceride and fatty acid uptake genes (Cd36, Apoc3, Ldlr) were downregulated. Plasma LDL cholesterol and intrahepatic PCSK9 and CD36 were decreased whereas FGF-21 was increased in FAP deficient mice. Using proteomic methods, novel putative FAP substrates involved in energy metabolism, fibrosis and coagulation were identified.

Conclusion: This is the first study to show that specific genetic ablation of FAP activity, which mimics a specific potent enzyme inhibitor, confers some protection from DIO-driven poor metabolic outcomes. The FAPgki phenotype was similar to that of FGF-21 transgenic mice. Thus, FAP enzyme activity has important roles in glucose and lipid regulation.

Biography

Professor Mark Gorrell heads the Liver Enzymes in Metabolism and Inflammation Program of the Centenary Institute in Sydney, affiliated with University of Sydney. Mark trained in Australian National University, University of Melbourne and Johns Hopkins University. He is known for his pioneering biochemical studies on the diabetes drug target DPP4. He seeks to understand and develop therapies for chronic liver diseases, in particular roles of post-proline oligopeptidases. He has authored over 135 publications attracting >6,400 citations and H-index 43. He is an editor for Scientific Reports, and active in the International Proteolysis Society and Australian societies for cell biology and for gastroenterology.

m.gorrell@centenary.org.au

Notes: