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PSMD9 identified as a novel regulator of hepatic acylglycerol metabolism using an integrated systems-biology approach

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Disruptions in hepatic lipid homeostasis can promote the onset of conditions such as hepatosteatosis and insulin resistance. In order to interrogate hepatic lipid metabolism, we developed an integrated systems-biology discovery platform, consisting of 107 inbred mouse strains and performed proteomic and lipidomic analyses on the livers of these mice. We assessed protein:lipid associations in order to identify proteins/pathways not previously associated with hepatic lipid metabolism. This led to the identification of a protein known as 26S proteasome non-ATPase regulatory subunit 9 (PSMD9). PSMD9 highlights a previously underappreciated inter-play between proteostasis and acylglycerol metabolism. Moreover, the proteosomal associated protein was negatively associated with 65 lipid species in plasma and positively associated with 39 lipid species in the liver. Utilising the human hepatic cell line, Hep3B we sought to validate PSMD9 as a novel regulator of acylglycerol metabolism *in vitro*. PSMD9 overexpression resulted in a reduction in DGAT2 mRNA expression and an increase ABHD5 mRNA expression consistent with modulation of acylglycerol metabolism. Conversely, when PSMD9 was knocked down in cells DGAT2 expression increased and ABHD5 decreased. Acute over-expression of PSMD9 via an adenovirus (pAdV: PSMD9) in C57BL/6J and DBA/2J mice resulted in an accumulation of pathological acylglycerol and ceramide species in both the plasma and livers of these mice. Moreover, proteomic analysis of the livers of these mice revealed a significant enrichment of proteins associated with ER/lipid signalling and the proteasome. C57BL/6J mice injected with anti-sense oligonucleotides against PSMD9 resulted in robust hepatic knockdown and modulation of hepatic and plasma lipid species.

These findings validate the discovery platform as a resource for identifying novel regulators of hepatic lipid metabolism. Moreover, they provide a novel link between proteostasis and acylglycerol accumulation, and validate PSMD9 as a driver of acylglycerol metabolism, which has implications for hepatic steatosis.

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Metabolic effects of acquired obesity–lessons from twin studies

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Basic research in obesity: incredible insights but limited effects on clinical outcomes

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Challenges to obesity research in humans: the power of human phenomic studies

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Obesity is one of the greatest public health threats of the 21st century. Its prevalence has increased rapidly over the last few decades, particularly in developed countries. The importance of these observations relates to the comorbidities associated with obesity, including type 2 diabetes, cardiovascular disease and cancer. Lifestyle, environment and genetic factors are key drivers of the obesity epidemic. Many challenges exist in human obesity research. First, unlike animal studies, mechanistic based studies are limited in humans. Indeed, differences between animals and humans limit translatability between species. This is most classically exemplified by studies of molecules involved in the leptin-melanocortinergic pathway, which governs appetite regulation in animals and humans, albeit with some differences. Second, various phenotypic tools have been employed in clinical studies in obesity and metabolic disease. The quality of the outcomes of these studies is often proportional to the 'deepness' of the phenomic measures used. Tensions exist between studies of large numbers (e.g. in Genome Wide Association Studies) *vs* smaller phenomic studies of humans with monogenic obesity disorders. Third, it has not yet been established that personalised prevention and treatment of obesity will be successful. Detailed documentation of the underlying phenotype in obesity, with careful elucidation of substrate utilisation, fat distribution, muscle, liver and adipose tissue insulin sensitivity and circulating markers of insulin action and hormonal function, is essential in paving the way for individualised and more targeted treatment of obesity.

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