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Metabolic complications in an animal model of congenital generalized lipodystrophy type 2

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Mutations in BSCL2 gene underlie human Congenital Generalized Lipodystrophy type 2 (CGL2) diseases. CGL2 is an autosomal recessive disorder characterized by a near total absence of body fat from birth or infancy associated with earlier diabetes onset and debilitating metabolic complications. We recently inactivated Bscl2 in mice to examine the mechanisms whereby absence of BSCL2 leads to adipose tissue loss and metabolic disorders. *Bscl2*–/– mice recapitulate many of the major metabolic manifestations in CGL2 individuals, including lipodystrophy, organomegly, hepatic steatosis and insulin resistance. Lipodystrophy has been attributed to unbridle cyclic AMP-dependent protein kinase A-activated lipolysis which inhibits terminal adipocyte differentiation in *Bscl2*-/- mice. However, the development of metabolic complications in CGL2 has been less characterized. We found *Bscl2*-/- mice exhibit a fasting-dependent insulin signaling in liver and muscle. They are hyperphagic, and rely exclusively on glucose as the main energy source. They display improved glucose homeostasis and insulin response under hyperinsulinemic-euglucemic clamp after overnight fast. The oxidative soleus muscle, but not gastrocnemius muscle, exhibits elevated glucose uptake rate in *Bscl2*-/- mice. Unexpectedly, different from other lipodystrophic animals, *Bscl2*-/- mice display reduced triglyceride contents in both soleus and gastrocnemius muscles; while significant elevation of glycogen levels was only observed in the oxidative soleus muscle but not in gastrocnemius muscle of *Bscl2*-/- mice. More importantly, lipid pre-infusion in *Bscl2*-/- mice mitigates glucose uptake in soleus muscle under hyperinsulinemic-euglucemic clamp, suggesting extreme lower NEFA after prolonged fasting could sensitize muscle insulin sensitivity in lipodystrophic *Bscl2*-/- mice. Moreover, *Bscl2*-/- mice also develop cardiac hypertrophy accompanied with cardiac dysfunction. These data provide a systemic view of metabolic disorders in lipodystrophic *Bscl2*-/- mice, which have important clinical implications in treating patients with CGL2.

Biography

Weiqin Chen studied the role of dyslipidemia on Diabetic Retinopathy, a microvascular complication in diabetic patients with Dr. Julia Busik at Michigan State University and received her PhD degree in Molecular Genetics in 2005. Subsequently, she worked as a Post-doctoral associate for five years with Dr. Lawrence Chan at Baylor College of Medicine, where she was promoted as an Instructor in 2010. At BCM, she established two animal models based on genes that are associated with non-alcoholic fatty liver disease (NALFD) and human congenital generalized lipodystrophy (CGL) and characterized their functions in energy metabolism. In 2012, she was recruited as an Assistant Professor in the Department of Physiology at Georgia Regents University. The focus of her current research is to dissect the mechanisms underlying adipose tissue dysfunction and development of obesity and lipodystrophy using both *in vivo* and *in vitro* strategies.

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