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Bscl2 mediated lipolysis, a rheostat essential for adipose tissue development and metabolic diseases

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Abstract

Adipose tissue plays a major role in whole body energy homeostasis. The increasing prevalence of obesity and metabolic syndrome requires investigations that identify the causes and consequences of adipose tissue dysfunction. Both obesity (excessive fat) and lipodystrophy (lack of fat) develop similar metabolic disorders including insulin resistance, dyslipidemia, diabetes and cardiovascular diseases. Mutations in BSCL2 underlie human congenital generalized lipodystrophy type 2 disease. 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 complication. We recently inactivated Bscl2 in mice to examine the mechanisms whereby absence of Bscl2 leads to adipose tissue loss and metabolic disorders. *Bscl2*$^{-/-}$ mice develop severe lipodystrophy of white adipose tissue (WAT), dyslipidemia, insulin resistance and hepatic steatosis. Notably, they rely exclusively on glucose as the energy source and display improved glucose homeostasis and insulin response under fasting conditions. *In vitro* differentiation of both *Bscl2*$^{-/-}$ murine embryonic fibroblasts (MEFs) and stromal vascular cells (SVCs) reveals normal early-phase adipocyte differentiation but a striking failure in terminal differentiation due to unbridled cyclic AMP (cAMP)-dependent protein kinase A (PKA)-activated lipolysis, which leads to loss of lipid droplets and silencing of the expression of adipose−specific transcription factors. Importantly, such defects in differentiation can be largely rescued by inhibitors of lipolysis but not PPARγ agonist. The residual epididymal WAT (EWAT) in *Bscl2*$^{-/-}$ mice displays enhanced lipolysis. It also assumes a “brown-like” phenotype with marked upregulation of UCP1 and other brown adipose specific markers. Together with decreased Pref1 but increased C/EBPβ, these changes highlight a possible increased cAMP signaling which impairs terminal adipocyte differentiation in the EWAT of *Bscl2*$^{-/-}$ mice. Our study underscores the fundamental role of regulated cAMP/PKA-mediated lipolysis in adipose differentiation, and identifies Bscl2 as a novel cell-autonomous determinant of activated lipolysis essential for terminal adipocyte differentiation.

Biography

Dr. Weiqin Chen studied microbiology at China Agricultural University, China, where she obtained her Msc (1999). She then came to the United States and 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 Postdoctoral 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-alchoholic 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.