From Adipocyte Plasticity to Systemic Energy Balance: How YAP/TAZ Signaling Regulates Metabolic Health

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Adipose tissue is essential for maintaining systemic energy balance and metabolic health, functioning as both an energy reservoir and an endocrine organ. While extensive research has explored individual adipose tissue functions, the molecular mechanisms coordinating these critical processes have remained elusive. Our recent work identifies the transcriptional coregulators YAP and TAZ (YAP/TAZ) as key regulators that exert direct coordinated control over both adipose tissue mass and leptin levels, providing new insights into the orchestration of adipose tissue functions and their impact on systemic energy balance. To investigate the in vivo role of YAP/TAZ in adipose tissues, we developed mouse models with adipocyte-specific activation of YAP/TAZ, achieved by deletion of conditional alleles of Lats1 and Lats2 by adiponectin-Cre (LATS1/2 AKO) or adiponectin-CreER (LATS1/2 iAKO). In both mouse models, YAP/TAZ activation in adipocytes resulted in a marked reduction in fat mass, driven by the transformation of mature adipocytes into delipidated cells exhibiting progenitor-like features. RNA-seq analysis revealed that this YAP/TAZ-induced lipoatrophy was associated with suppressed activity of PPARG, a master transcriptional regulator of adipocyte differentiation and function. Treatment with rosiglitazone, a synthetic PPARG agonist, was sufficient to normalize fat mass in LATS1/2 iAKO mice, indicating that the suppression of PPARG transactivation activity is the primary mechanism underlying YAP/TAZ-induced lipoatrophy. Remarkably, despite the complete loss of adipose tissue lipid storage capacity, these mice did not develop the metabolic dysfunctions typically associated with lipodystrophy, such as insulin resistance or fatty liver disease. This unexpected finding was attributed to a paradoxical increase in circulating leptin levels, which effectively offset the energy storage deficit by stimulating increased fat oxidation and energy expenditure. Mechanistic investigations uncovered that a YAP/TAZ-TEAD transcriptional complex directly enhances leptin expression by binding to an active enhancer site of the leptin gene. The physiological significance of this regulatory axis was further confirmed by demonstrating that YAP/TAZ activity is both regulated and essential for appropriate leptin modulation during feeding-fasting cycles in wild-type mice. Collectively, this work reveals a crucial role for the adipocyte LATS1/2-YAP/TAZ signaling pathway in integrating adipose storage and endocrine functions to regulate systemic energy homeostasis. These findings bridge a critical gap in our understanding of adipose tissue biology, offering new perspectives on the mechanisms underlying metabolic flexibility and potential therapeutic interventions targeting the adipocyte YAP/TAZ signaling pathway.