Hippo meets metabolism: divergent YAP/TAZ programs coordinate adipose plasticity and leptin production

Jae Myoung Suh
徐在明
Korea Advanced Institute of Science and Technology, Daejon, Korea

Adipose tissue maintains systemic energy balance by functioning as both an energy reservoir and an endocrine organ, yet the mechanisms coordinating these roles remain poorly defined. Here we identify the Hippo pathway effectors YAP and TAZ as key integrators of adipose plasticity and leptin production. Adipocyte-specific YAP/TAZ activation induces profound lipoatrophy, driven by dedifferentiation of mature adipocytes and repression of PPARγ transcriptional programs, establishing a YAP/TAZ–PPARγ axis as a potent regulator of adipocyte identity and fat mass. Strikingly, despite severe adipose loss, these mice remain metabolically healthy and do not develop the insulin resistance and dyslipidemia typically associated with lipodystrophy. This phenotype is explained by a compensatory endocrine response in which leptin is markedly elevated, promoting lipid oxidation and energy expenditure and thereby uncoupling leptin levels from adipose mass. Mechanistically, leptin induction is mediated by a second, PPARγ-independent transcriptional arm in which a YAP/TAZ–TEAD complex directly engages a conserved enhancer at the *Lep* locus. Physiological relevance of the newly identified YAP/TAZ–TEAD-Leptin axis is supported by the requirement for adipocyte YAP/TAZ activity for appropriate leptin regulation during fasting–refeeding transitions and in high-fat diet–induced obesity. Together, these findings extend Hippo–YAP/TAZ signaling beyond canonical organ-size control and establish it as a central regulatory node that coordinates adipose plasticity with endocrine regulation of whole-body energy balance.