

Selective Coldness in White Adipose Tissue: Metabolism Energetics Rewiring toward Thermogenesis

Hsin-Yi Chang

hsinyi.chang@pharm.kyoto-u.ac.jp

Adipocytes are essential regulators of whole-body energy homeostasis. Limiting obesity via the browning of white adipose tissues (WAT) is an appealing therapy for preventing type 2 diabetes. Despite several transcriptional regulations have been revealed to induce beige adipocytes from white ones, modulations at protein level remain exclusive. Here, we applied mass spectrometry-based quantitative proteomics to map the scope of post-translational modifications (PTMs) in agreement with thermogenesis in WAT. As a negative regulator, casein kinase 2 (CK2) was found to prevent energy expenditure by upregulating class I histone deacetylase activity and compromising the cAMP-induced uncoupling effects in WAT. High fat diet fed obese mice displayed markedly reduction in subcutaneous fat but not lean mass while silencing CK2, potentiating CK2 as an anti-obesity target. We revealed that blockade of CK2 elevated carbon metabolism by increasing enzyme activity through PTM regulations. The impact of CK2 inhibition on energetic metabolism was confirmed by metabolomic profiling, demonstrating cAMP-induced glucose oxidation, pyruvate utilization and TCA cycling were boosted by CK2 inhibition. CK2 silencing mice exhibited phenotype of improved insulin sensitivity, glucose tolerance and oxygen consumption, which were consistent with the observations at molecular level. By comprehensively integrative analysis on multi-omics data, we exhibit novel roles of PTMs to prime central metabolism for cell fate determination.