

Set1a Acts as an Epigenetic Rheostat Governing Adipose Plasticity and Systemic Energy Homeostasis

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Abstract

Adipose tissue adapts to metabolic stress through epigenetic remodeling, yet the role of the histone methyltransferase Set1a remains poorly defined. We demonstrate that Set1a expression in subcutaneous and brown adipose tissues (SC/BAT) is dynamically regulated by environmental cues: upregulated during cold exposure or forskolin stimulation, but suppressed by high-fat diet (HFD) and obesity—a pattern conserved in human adipose samples. Adipocyte-specific Set1a knockout mice exhibited impaired cold-induced thermogenesis (reduced UCP1, ↓ whole-body energy expenditure) and exacerbated HFD-induced obesity. Human adipose datasets corroborated these observations: elevated SET1A expression in post-weight-loss individuals aligned with its cold-induced upregulation in mice, while downregulation of thermogenic pathways in obesity mirrored the transcriptional signatures of Set1a-deficient adipocytes. These data establish Set1a as an epigenetic sensor that gates adipose plasticity: its cold/forskolin-induced activation promotes thermogenic capacity, while nutritional excess suppresses Set1a to lock adipocytes in an energy-storing state. The conserved dysregulation of Set1a across species underscores its role in energy homeostasis, positioning it as a potential node for therapeutic intervention in metabolic disease.

Keywords

Set1a, Epigenetic Regulation, Adipose Plasticity, Thermogenesis, Energy Homeostasis, Obesity