Lipolysis as a major regulator of transcription in brown adipocytes

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Introduction

Lipolysis constitutes a fundamental metabolic process in many cell types of importance for the ability of cells to dynamically regulate energy storage and fatty acid concentrations in cells. Brown adipocytes have a particularly high lipolytic capacity, which supplies fatty acids for oxidation and non-shivering thermogenesis. Lipolysis is activated by β-adrenergic signals leading to PKA-dependent activation of core lipases in brown adipocytes. In addition, β-adrenergic signals activate transcription of thermogenic genes, thereby expanding the capacity for oxidative metabolism. This activation has been ascribed primarily to PKA-dependent transcription factors, and the role of lipolysis in transcriptional regulation is unknown.

Methods

We have used pharmacological inhibitors and a novel direct activator of lipolysis to acutely modulate the activity of lipases in cultured brown adipocytes. To provide genome-wide unbiased insight into the acute transcriptional effects of lipolysis, we have performed RNA-seq and ATAC-seq.

Results

we show that lipolysis acts as an important signaling nexus sufficient to regulate a broad spectrum of gene programs and is required for the acute transcriptional effects of β-adrenergic signaling in brown adipocytes. While PPARs play an important role in the activation of gene programs involved in lipid metabolism by ISO, the majority of genes are regulated by PPAR-independent mechanisms involving UPR-activated transcription factors, as well as key regulators of circadian rhythm.

Conclusions

Our results demonstrate that lipolysis generates important metabolic signals that exert profound pleiotropic effects on brown adipocyte transcription and function.