UKE Paper of the Month September 2025

Single-nucleus mRNA-sequencing reveals dynamics of lipogenic and thermogenic adipocyte populations in murine brown adipose tissue in response to cold exposure

Janina Behrens, Tongtong Wang, Christoph Kilian, Anna Worthmann, Mark A. Herman, Joerg Heeren, Lorenz Adlung, Ludger Scheja

Mol Metab. 2025 Sep, Volume 101

ABSTRACT:

Objectives and Methods: Brown adipose tissue (BAT) comprises a heterogeneous population of adipocytes and non-adipocyte cell types. To characterize these cellular subpopulations and their adaptation to cold, we performed single-nucleus mRNA-sequencing (snRNA-seq) on interscapular BAT from mice maintained at room temperature or exposed to acute (24h) or chronic (10 days) cold (6°C). To investigate the role of the de novo lipogenesis (DNL)-regulating transcription factor carbohydrate response element-binding protein (ChREBP), we analyzed control and brown adipocyte-specific ChREBP knockout mice.

Results: We identified different cell populations, including seven brown adipocyte subtypes with distinct metabolic profiles. One of them highly expressed ChREBP and DNL enzymes. Notably, these lipogenic adipocytes were highly sensitive to acute cold exposure, showing a marked depletion in BAT of control mice that was compensated by other brown adipocyte subtypes maintaining DNL. Chronic cold exposure resulted in an expansion of basal brown adipocytes and adipocytes putatively derived from stromal and endothelial precursors. In ChREBP-deficient mice, lipogenic adipocytes were almost absent under all conditions, identifying the transcription factor as a key determinant of this adipocyte subtype. Detailed expression analyses revealed Ttc25 as a specific marker of lipogenic brown adipocytes and as a downstream target of ChREBP. Furthermore, pathway and cell-cell interaction analyses implicated a Wnt-ChREBP axis in the maintenance of lipogenic adipocytes, with Wnt ligands from stromal and muscle cells providing instructive cues.

Conclusion: Our findings provide a comprehensive atlas of BAT cellular heterogeneity and reveal a critical role for ChREBP in lipogenic adipocyte identity, with implications for BAT plasticity and metabolic function.

STATEMENT:

Brown adipose tissue (BAT), a central organ of energy homeostasis research, is highly responsive to cold exposure in mice, but underlying metabolic mechanisms and cellular changes during BAT activation are not conclusively studied. Our work closed an important gap in the BAT research field by providing single cell data with high resolution of BAT in different activation states. Moreover, our data underlined the heterogeneity and plasticity of this tissue and allows comprehensive analysis of changes with regard to metabolism and signalling in response to low environmental temperatures. We identified a novel and highly specific marker for lipogenic adipocytes (Ttc25) and provided evidence that the DNL regulator ChREBP is a central regulator for lipogenic cell identity. Taken together, we are confident that our comprehensive cell atlas of BAT will pave the way for future discoveries in the BAT research field with potential therapeutic implications for metabolic disease.

BACKGROUND:

This work was performed as a shared project at the Institute of Biochemistry and Molecular Cell Biology in the group of Dr. Ludger Scheja and at the I. Department of Medicine in the group of Dr. Lorenz Adlung. It was part of the PhD thesis of Janina Behrens within the DFG research training group “TRR333 BATenergy”. Both groups have strong research interests in the field of brown adipose tissue heterogeneity, plasticity and metabolic adaptation following a systems biology methodology.