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Supplementary information

The cellular and functional complexity of thermogenic fat

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Supplementary Box1: BAT and the developmental lineage

Brown adipose tissue (BAT) is composed of multiple cell types, including thermogenic adipocytes, non-thermogenic adipocytes, progenitors, endothelial cells, fibroblasts, and various immune cells. Most human studies describe "BAT" because the analyses are largely at a tissue level; however, this does not imply the developmental lineage of the tissues.

"Classical" brown adipocyte is a term that originally intended to distinguish its prenatal dermomyotome-origin from the non-dermomyotome-derived recruitable form of thermogenic adipocytes, like beige adipocytes. Thus, "classical" represents its developmental lineage, but not the tissue location nor the cell morphology. For instance, supraclavicular BAT depots in adult humans contain multiple populations of thermogenic adipocytes, including beige adipocytes [1-4], and the cellular compositions vary depending on the depth within a BAT [5]. Also, the interscapular BAT of mice exhibits "whitened" when mice are acclimated to a thermoneutral condition for a prolonged time, but this morphological change does not alter the developmental lineage [6].

The existence of beige adipocytes in the subcutaneous WAT of humans was once questioned. This skepticism was partly due to the fact that earlier efforts using ^{18}F-FDG-PET-CT did not detect active glucose uptake in the subcutaneous WAT. However, a recent work using the high-sensitive ^{18}F-FDG-PET-CT detected active glucose uptake in human adipose tissues at broad anatomical locations, including the abdominal region [7]. More directly, repeated cold exposure (10 days of a 30-minute cold treatment per day), as well as chronic mirabegron treatment for 10 weeks, potently increased mitochondrial respiration and beige fat-enriched gene expression (*UCP1* and *TMEM26*) in the subcutaneous WAT of adult humans [8]. Notably, chronic mirabegron treatment in obese human subjects improved insulin sensitivity that showed a significant correlation with increased UCP1 expression in the subcutaneous WAT, *i.e.,* beige adipocytes in the subcutaneous WAT [9]. Thus, adult humans possess the recruitable, non-dermomyotome-origin beige adipocytes not only in dedicated BAT depots but also in the subcutaneous WAT.

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