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Confounding issues in the "humanized" BAT of mice

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The recent study by de Jong et al. reports the molecular analysis of brown adipose tissue (BAT) in mice kept under a thermoneutral condition (at 30°C) on a high-fat diet (45%) for over 20 weeks. They claim these mice are, therefore, "humanized" in regard to their cellular composition in BAT. The authors concluded that the morphology and molecular characteristics of interscapular BAT from these mice are somewhat similar to human BAT. However, the authors' conclusions are confounded by the following flaws.

First, the premise in this paper is that keeping mice at 30˚C on a high-fat diet recapitulates the human condition. However, this is clearly not correct because most humans do not live at thermoneutrality. In fact, studies in humans using ^{18}F-FDG-PET scans show dynamic seasonal changes in the BAT activity where glucose uptake is higher in winter than summer[1, 2]. Acclimation to thermoneutrality reduces the sympathetic nerve-derived signals, such as norepinephrine and the downstream beta-adrenoceptor (AR) signaling – the dominant activator of BAT thermogenesis. Accordingly, BAT from thermoneutral animals merely becomes dormant; however, it does not "humanize" the cellular composition or cellular fate of BAT.

This claim by the authors is also puzzling when considering the developmental lineage literature. Morphologically, BAT adapts a "whitening" unilocular-lipid morphology because of reduced lipolysis and increased lipid droplet size. In this regard, many obese mouse models, such as ob/ob mice, have a similar BAT morphology. However, brown adipocytes in the ob/ob BAT do not transform to a different cell lineage - it merely has reduced sympathetic signaling and mitochondrial biogenesis. In fact, many of the transcriptional changes in BAT following thermoneutral acclimation, as described in this paper, are under the control of the sympathetic/beta-AR signal pathway, including *Ucp1, Pgc1a*, and *Dio2*. To determine the lineage of a cell, comprehensive analyses of chromatin architecture may provide a useful insight in case lineage-tracing technique is not applicable (*e.g.*, human samples). Of note, a recent paper demonstrated that classical brown adipocytes in the interscapular BAT maintain the chromatin architecture of brown adipocytes even though

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Competing interests

The authors declare no competing interests.

BAT acquires a whitening phenotype with unilocular lipid-droplets[3]. This result suggests that morphological characteristics, *i.e.*, unilocular vs. multilocular lipid droplets, do not alter the cellular identity of brown adipocytes. Rather, the changes are mostly attributed to the changed functionality of existing brown adipocytes.

Second, human BAT is highly heterogeneous, and the distribution varies among individuals, such that the nature of biopsied tissues significantly influences the transcriptome data. For instance, Cypess and colleagues[4] showed that the cellular composition of human BAT varies depending on the biopsy location, *e.g.*, deeper the tissue the BAT is composed of mitochondria-rich thermogenic adipocytes. Besides, clonal isolation and characterization of human BAT resolved the issue of cellular heterogeneity[5, 6]. The BATLAS is a sophisticated algorithm; however, comparison of the bulk transcriptome of BAT from random biopsy samples would lead to misinterpretation of the data. Given the recent advance in single-cell RNA-seq technology, one may and should revisit these study at the single-cell resolution.

Third, the idea of two-type of thermogenic cells, “brown vs. beige” is most likely oversimplified. Emerging evidence suggests the existence of several subtypes of thermogenic fat cells. For instance, glycolytic beige fat is a subset of beige fat in the subcutaneous WAT whose developmental regulation is independent of beta-AR signaling[7]. Besides, UCP1-independent mechanisms in brown/beige fat play a significant role in the regulation of energy homeostasis[8, 9].Although UCP1 is the most-established molecular marker for many, but not all, of thermogenic fat cells, it is functionally dispensable for the beige fat’s anti-obesity and anti-diabetic action[9–11]. Discussion merely based on UCP1 protein expression level would not reflect the biological significance of brown/beige fat in humans because UCP1-independent thermogenesis via Ca^{2+} cycling and creatine cycling is active in humans[8, 9].

Accordingly, we suggest the authors refrain from using the term “humanized” brown fat in their study. We are concerned that this term confuses the field of BAT biology and metabolism: it is true that environmental temperature profoundly affects the function of adipose tissues and other metabolic organs, but it does not transform mouse BAT to human BAT with respect to their cellular composition, developmental lineage, and function.

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