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Journal Club

Shall We Begin the Voyage of Adipose Tissue Exploration?

A comprehensive atlas of adipose tissue at the single-cell level

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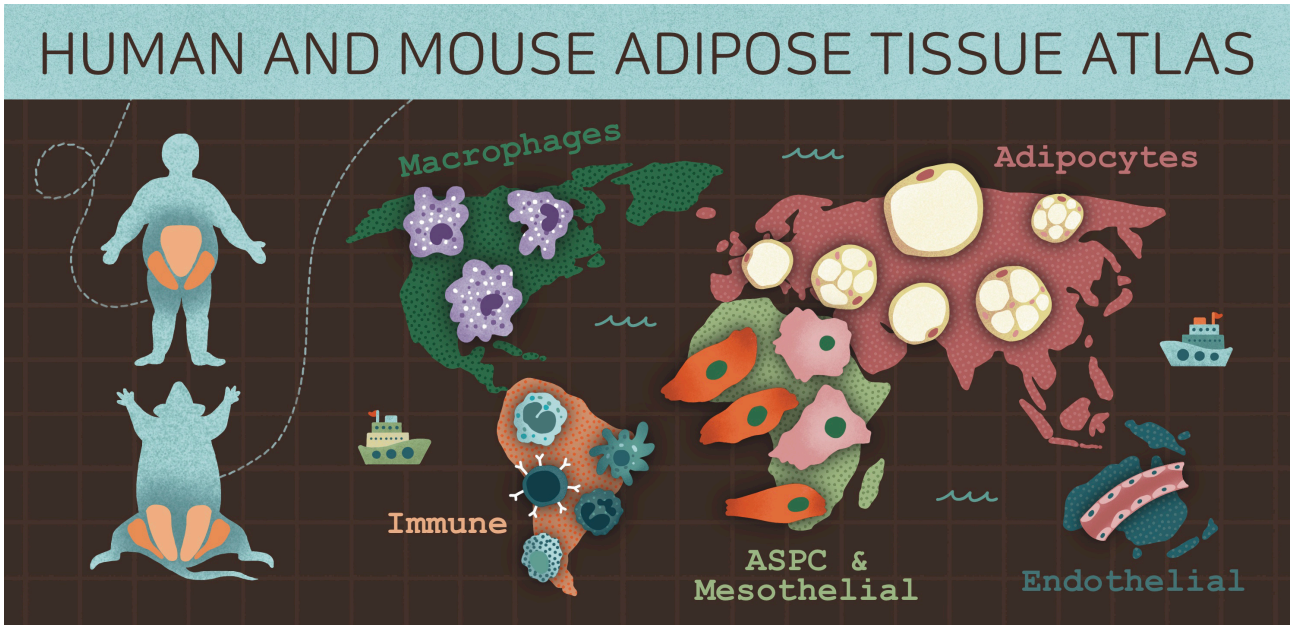

A comprehensive adipose tissue atlas. Single-cell and single-nucleus RNA sequencing of human and mouse adipose tissue across the fat depots and body mass reveals a diverse subpopulations of each cell types such as adipocytes, adipose stem and progenitor cells, immune cells, lymphatic vascular cells, and mesothelial cells.

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Adipose tissue is a central metabolic organ for systemic energy homeostasis (Choe et al., 2016). Accumulating evidence suggests that adipose tissue regulates various biological processes such as energy storage, supply, thermogenesis, and immune modulation (Rosen and Spiegelman, 2014). Upon metabolic stimuli, adipose tissue exhibits dynamic changes in its structure and function, so-called adipose tissue remodeling, which appears to differ between fat depots (Hwang and Kim, 2019; Rosen and Spiegelman, 2014).

The recently developed single-cell RNA sequencing (scRNA-seq) has unveiled that adipose tissue consists of diverse subpopulations of immune cells and stem cells, and each of these subpopulations executes distinct biological functions (Jaitin et al., 2019; Lee et al., 2021; Nahmgoong et al., 2022). However, since mature adipocytes are too large and fragile to apply single-cell analysis, it has been difficult to investigate the entire subpopulations of adipose tissue at a single-cell level.

Using scRNA-seq and single-nucleus RNA-sequencing (snRNA-seq), Emont et al. (2022) recently provided a comprehensive white adipose tissue atlas from lean and obese humans and mice. They identified several subpopulations of adipocytes, adipose stem and progenitor cells (ASPCs), vascular, mesothelial, and immune cells. In addition, they compared visceral and subcutaneous adipose tissue (VAT and SAT, respectively), lean and obese subjects, and humans and mice. Further, they examined the cell–cell interaction and the relationship between the metabolic disease risk and subpopulations. Following are the highlights of their new findings.

1) Cell-type composition: In human adipose tissue, adipocytes and ASPCs accounted for the largest proportion (about 25%, respectively), followed by 10%-20% endothelial cells, and 10% macrophages. The rest of the population was comprised of smooth muscle cells, endothelial cells, and various immune cells such as T cells, NK cells, mast cells, and monocytes. Notably, mesothelial cells, which exist only in VAT, comprised over 30% of the VAT, and the proportion was increased in obese humans.

2) Immune cells: Macrophages ($CD14^+$) and monocytes were the major immune cell types in adipose tissues (60% in humans and 90% in mice) followed by T cells and NK cells ($CD96^+$) (30% in humans and 3% in mice). Furthermore, dendritic cells ($FLT3^+$), B cells ($MS4A1^+$), mast cells ($CPA3^+$), and neutrophils ($CSF3R^+$) were also identified. In human adipose tissue, hMac3 subpopulation exhibited unique features, which were found only in VAT, and the proportion was upregulated according to body mass index. hMac2 and mMac3 expressed *TREM2*, *LPL*, and *CD36*, which are similar to the recently identified $Trem2^+$ lipid-associated macrophages (Jaitin et al., 2019).

3) ASPCs: ASPCs have the potential to differentiate into adipocytes, which maintains adipocyte pools. $PDGFRA^+$ ASPCs were categorized into six subpopulations in humans and mice. In terms of adipogenic potential, $DPP4^+$ multipotent stem cells (hASPC2/5, mASPC2/3), $ICAM1^+$ adipocyte progenitors (hASPC1, mASPC1/5/6), and $CD142^+$ subpopulations (hASPC3/4, mASPC4) were found. hASPC3/6 were VAT-specific, and hASPC1/4/5 were SAT-enriched subpopulations. Under obese conditions, the $DPP4^+$ multipotent stem cells (mASPC2) proportion decreased, while the $ICAM1^+$ adipocyte progenitors (mASPC5) proportion increased. This trend was only observed in visceral fat, which is consistent with the recent reports stating that obesity would stimulate ASPCs to be differentiated into adipocytes in VAT (Nahmgoong et al., 2022; Sarvari et al., 2021).

4) Adipocytes: In humans, adipocytes were classified into seven subpopulations including fat-depot-specific adipocyte subpopulations (hAD2/6 in VAT and hAd1/3/4/7 in SAT). Remarkably, hAd6 expressed thermogenic genes such as *EBF2*, *ESRRG*, and *PGC1A*, and this subpopulation was exclusively found in VAT. Unlike humans, thermogenic adipocytes are rarely found in murine visceral epididymal fat, suggesting a possibility the origin of human and mouse thermogenic adipocytes would be different. In mice, mAd4 subpopulation, whose proportion was increased in obesity, expressed low levels of insulin signaling genes and high levels of actin cytoskeleton genes. Given that actin cytoskeleton is involved in insulin-stimulated glucose uptake (Kim et al., 2019), it will be interesting to investigate whether mAd4 subpopulation would be related to insulin resistance in obesity.

5) Cell–cell communications and human diseases: The ligand-receptor interactions between adipocytes and vascular cells or ASPCs were potentiated in obesity. In obese humans, the expression levels of angiogenic factors JAG1 and VEGFC in adipocytes were increased, and concomitantly, the expression levels of receptors in endothelial cells were also upregulated. hAd7 proportion and hAd7-enriched gene expression were related to insulin resistance.

In conclusion, Emont et al. (2022) provided a comprehensive map of human and mouse white adipose tissue across anatomical location and body mass. In future, it would be important to elucidate the (patho)physiological roles of these subpopulations of adipocytes, ASPCs, immune, vascular, and mesothelial cells. Specifically, the characterization of heterogeneous adipocyte subpopulations would be crucial to understanding the role of adipocytes in energy homeostasis. In addition, the data provided in this study will also serve as an important resource. Several comparative analyses such as visceral-subcutaneous, lean-obese, and human-mouse would not only improve the understanding of adipose tissue but also be valuable resource data for translational research. Furthermore, since this study used both scRNA-seq and snRNA-seq, it would be helpful to understand the different features of these two techniques. Together, the adipose atlas in this study will broaden and deepen our understanding of adipose biology. The data in this study are readily available via Single Cell Portal (https://singlecell.broadinstitute.org/single_cell). Thus, it is recommended to embark on an adipose tissue expedition with this atlas.

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CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

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