Adipose tissue in 2022

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Adipose tissue in communication: within and without

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Adipose tissue is highly versatile, dynamic and essential for metabolic health. In 2022, several exciting discoveries provided a high-resolution view of cellular composition and cell–cell communication within the adipose niche, and revealed how adipose tissue communicates with other organs and modulates metabolism during normal and pathophysiological states.

Adipose tissue, once viewed as an unimportant tissue mass, is now recognized as a critical metabolic organ that regulates whole-body energy homeostasis via the regulation of energy storage and dissipation and secretion of metabolically-active factors[1]. Two functionally different types of adipose tissue exist: white adipose tissue (WAT), the primary site of triglyceride storage and thermogenic adipose tissue, which includes brown adipose tissue (BAT) and the related beige (also known as brite) adipose tissue. The presence of different adipose depots throughout the body and the diverse cell types that compose each specific depot highlight the heterogeneity of the adipose tissue, which shapes metabolism.

The advance of single-cell technology has revealed the presence of multiple cell populations within a tissue microenvironment and has illustrated complex cell–cell communications. Adipocytes are notoriously challenging to analyse using single-cell techniques due to their fragile nature, high buoyancy and large size. To overcome this challenge, Emont et al. used single-nucleus RNA-sequencing (snRNA-seq) coupled with computational algorithms to deconvolute the cellular compositions in subcutaneous and visceral WAT from humans and mice[2]. Although this study was not the first to use snRNA-seq to dissect adipose cellular heterogeneity, the Emont et al. study was comprehensive. That is, the authors included two different WAT depots from humans with various metabolic statuses, as well as the corresponding WAT in mice fed with a high-fat diet (HFD) or normal chow. They identified genes, cell types and intercellular interactions that potentially contribute to the metabolic disorders that are associated with obesity or over-nutrition at single-cell resolution. For example, one of the human adipocyte subpopulations was found to be inversely correlated with insulin resistance, albeit representing only about 1% of detected adipocytes. The exact contributions of the identified adipocyte population and its associated gene markers need to be experimentally validated. Nevertheless, these data serve as an invaluable resource for exploring the cellular compositions and cell–cell interactions of the WAT niche and for linking these factors to the risk of developing metabolic disorders.

The various types of cells and the rich cell–cell communication within the adipose niche orchestrate adipose tissue development and function, and have a crucial role in adipose turnover, expansion and remodelling in response to nutritional or environmental stimuli[3]. Immune cells, particularly macrophages, are known to contribute to adipose inflammation and insulin resistance in obesity[4]. Beyond macrophages, Hagglof et al. demonstrated that T-bet-expressing (T-bet$^+$) B cells are also involved in adipose tissue inflammation[5]. This specific population of B cells expresses the T helper 1-lineage transcription factor T-bet. In obesity, T-bet$^+$ B cells accumulate in the adipose tissue of humans and mice. The expansion of T-bet$^+$ B cells in obesity requires another type of immune cell, called invariant natural killer T (iNKT) cells, although paradoxically, the number of adipose iNKT cells is reduced in obesity for both humans and mice. Upon activation, T-bet$^+$ B cells secrete the proinflammatory chemokine CXCL10, which worsens metabolic abnormalities in obesity. Ablation of T-bet$^+$ B cells in mice improves HFD-induced adipose inflammation and glucose intolerance. These findings highlight the new roles of two specific immune cell populations, T-bet$^+$ B cells and iNKT cells, and their interactions in the pathogenesis of obesity-associated metabolic syndrome.

Key advances

- Single-cell mapping of human and mouse white adipose tissue across different depots and body masses revealed cellular heterogeneity, and identified distinct subpopulations of adipocytes, adipose progenitors and immune cells across species and types of diet[2].
- In obesity, T-bet$^+$ B cells, which express the T helper 1-lineage transcription factor T-bet, accumulated in the adipose tissue of humans and mice, and activated T-bet$^+$ B cells secreted the proinflammatory chemokine CXCL10 to exacerbate obesity-associated metabolic abnormalities[5].
- Extracellular vesicles (EVs) produced by dysfunctional adipose tissue could deliver microRNAs to the brain and cause synaptic damage in the hippocampus and cognitive impairments; targeting adipose tissue-derived EVs or microRNAs prevented cognitive defects in mice[7].
- Cold exposure inhibited tumour growth in mice carrying various xenografted solid tumours, an effect mediated via the activation of brown adipose tissue, leading to decreased circulating levels of glucose and attenuated glycolytic and lipid metabolism in tumours[8].
- SARS-CoV-2 directly infected human adipocytes and altered cell metabolism in a depot-specific and viral lineage-dependent fashion; visceral adipocytes were more susceptible to SARS-CoV-2 infection than subcutaneous adipocytes[10].

Beyond its role in regulating energy storage or dissipation, adipose tissue is recognized as the largest endocrine organ in the body. Adipose tissue produces different bioactive molecules that communicate with and regulate the function of other organs[3]. In the past decade, extracellular vesicles (EVs) have been found to have a critical role in inter-organ crosstalk, and adipose tissue is among the tissues known to produce EVs[6]. The study from Wang et al. identified that EVs produced by dysfunctional adipose tissue delivered microRNAs (miRNAs) to the brain and caused cognitive impairment in mice[7]. Adipose tissue dysfunction has been proposed to contribute to cognitive impairment, but the underlying mechanisms are unclear. Wang et al. showed that adipose-derived EVs from HFD-fed mice or from patients with diabetes mellitus caused marked synaptic damage in the hippocampus and cortex, and impaired cognitive function in recipient mice. Mechanistically, they identified that miR-9-3p was enriched in adipose-derived EVs from obese mice; miR-9-3p targeted and reduced the levels of brain-derived neurotropic factor in the brain, resulting in synaptic dysfunction. To show the causality, they injected adeno-associated viruses expressing miR-9-3p sponge (which sequesters this miRNA) into the adipose tissue of HFD-fed mice and found that the treated mice showed reduced synaptic loss and cognitive impairment, compared with the HFD-fed control mice[7]. These findings link adipose tissue and cognitive dysfunction, which is mediated via adipose-derived EVs and their cargo miRNAs.

In 2022, scientists have continued to push the envelope and uncover new functions of adipose tissue that could open up new therapeutic avenues. One exciting finding was discovering the anti-cancer effect of cold exposure via BAT activation[8]. An important feature of cancer cells is their highly elevated metabolic rate and consumption of considerable amounts of nutrients. BAT is specialized in thermogenic energy expenditure and serves as a metabolic sink for its ability to utilize nutrients[9]. To investigate if activated BAT would compete with tumours for circulating nutrients, Seki et al. grafted various types of solid tumours into mice and then exposed them to cold (4°C) or thermoneutrality (30°C) for 15–30 days. They observed a striking reduction of tumour growth in cold-exposed mice, compared with mice housed at thermoneutrality. The cold-induced tumour suppression was attributed to BAT activation, as mice without BAT or with *Ucp1* deficiency showed diminished anti-cancer effects. Using RNA-seq and metabolomic analyses, the authors demonstrated that cold-induced BAT activation reduced circulating levels of glucose and attenuated glycolytic and lipid metabolism in tumours. While these findings are exciting, the obvious question remains as to whether BAT activation could be a therapeutic approach for patients with cancer.

Although the threat of COVID-19 has gradually lessened in 2022, understanding the pathogenesis of SARS-CoV-2 remains a key topic of medical research. Obesity has been recognized as a risk factor for severe COVID-19, which can lead to hospitalization and even death. The notion that adipose tissue serves as a reservoir for SARS-CoV-2 was challenged at the early stage of the pandemic, however, recent evidence supports that adipocytes are target cells of SARS-CoV-2. The study by Saccon et al. showed that SARS-CoV-2 directly infected human adipocytes and altered cell metabolism in a depot-specific and viral lineage-dependent manner[10]. Visceral adipocytes express more of the viral entry receptor ACE2 and hence are more susceptible to SARS-CoV-2 infection than subcutaneous adipocytes. Different SARS-CoV-2 variants exert differential effects on adipocytes that are derived from different depots. SARS-CoV-2 infection inhibited lipolysis in subcutaneous adipocytes and increased proinflammatory gene expression in visceral adipocytes. Compared with the original SARS-CoV-2, the gamma variant P.1. is more virulent in inducing inflammatory responses and cell death in adipocytes. These findings provide critical mechanistic insights into the role of adipose tissue in the aetiology of COVID-19.

Taken together, multiple studies published in 2022 highlight that adipose tissue exerts its functions via different methods of communication. Adipose tissue orchestrates systemic metabolism via the regulation of nutrient storage and utilization, as well as through the production of bioactive molecules in tissue crosstalk. With the advances in single-cell technology and spatial multi-omics analyses, we envision obtaining ultra-resolution maps of the intercellular network for various adipose depots in the coming years. The knowledge gained will solidify our fundamental understanding of adipose tissue and will also enable the development of new therapeutic approaches for various metabolic diseases.

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Competing interests

The author declares no competing interests.