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Preview

AdipoAtlas: Mapping out human white adipose tissue

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In this issue of *Cell Reports Medicine*, Lange and colleagues[1] significantly improve lipid identification accuracy, detection, and quantification to provide *AdipoAtlas*, an in-depth lipidomic profile of human white adipose tissue (WAT). Importantly, they define obesity-mediated lipid alterations, which may provide insight into the etiology of associated diseases.

Obesity is a risk factor for numerous comorbidities, including heart disease, type 2 diabetes (T2D), stroke, hypertension, and cancer. However, how obesity alters white adipose tissue (WAT) to promote such distinct pathologies is currently unknown. Previously developed comprehensive multi-omics approaches using human WAT were implemented to gain insight into this complex problem. Transcriptomics, epigenomics, and proteomics of WAT point to obesity-mediated alterations in the extracellular matrix, mitochondria, lipid metabolism, and inflammation.[2,3] Although these multi-omics studies provide an intriguing perspective on obese adipose, lipidomics analysis is required to dissect the obesity-mediated changes in lipid composition that may contribute to pathology.

Thousands of lipid species exist in a eukaryotic cell, and their various functions include providing energy storage, serving as signaling molecules, and maintaining membrane dynamics.[4] Obesity disrupts lipid homeostasis, and it is thus imperative to establish how obesity alters lipid composition and the consequence thereof on cellular function and whole-body physiology. Previous studies comparing the lipidome of lean and obese WAT reported obese adipose-specific lipid signatures. However, these studies faced major limitations because of the lack of comprehensive coverage of different lipid (sub)classes and only relative (obese versus lean) quantification of the identified species.[5,6] To address this challenge, Lange and colleagues[1] optimized the lipid extraction and fractionation protocol for WAT to obtain exhaustive coverage of both polar and nonpolar lipids. The use of three distinct liquid chromatography systems coupled to high-resolution accurate mass tandem mass spectrometry allowed for deep lipidomic profiling, identifying more than 1,600 lipid species qualitatively. Most importantly, using an adipose-tissue-tailored internal standard mixture that was designed and validated in house, a semi-absolute quantification of about 700 lipid species was achieved.[1]

Deep lipidomic profiling of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) of lean and obese individuals by Lange et al.[1] revealed the upregulation of PUFA-containing triglycerides (TG-PUFA) and sphingadienine-containing ceramides (Cer) to be hallmarks of obese adipose tissue. Moreover, plasmalogen phospholipid (PL) signatures varied between obese SAT and VAT; specifically, plasmalogen phosphatidylcholine (PC) and plasmalogen phosphatidylethanolamine (PE) accumulated in SAT and VAT, respectively. How do these new findings fit with the previous understanding of WAT dysfunction? Ceramides have long been associated with the negative metabolic effects of obesity.[7] The technical advances in WAT lipidomics reveal new obesity-associated ceramide species as well as a wealth of complexity in the sphingolipidome. In this report, the authors show an unexpected abundance of "atypical" ceramides, sphigadienineCer and deoxyCer, in obese human WAT. Given that ceramides have significant functions in inflammation, cell death, mitochondrial dysfunction, and insulin resistance,[7] it will be important to establish the role of these ceramide species on metabolic health in future studies.

Intriguingly, the authors of the study report that TG-PUFA are significantly up-regulated in obesity, although the functional consequence of this regulation is not clear. The authors discuss the association of TG-PUFA with larger lipid droplets, which may suggest an adaptive response to improve lipid storage. However, this uncontrolled increase in adipocyte size ultimately leads to deleterious consequences such as hypoxia, fibrosis, and inflammation of WAT. With the progression of WAT dysfunction, nutrients can no longer be safely stored in adipocytes, and fat accumulates ectopically in non-adipose tissues.[8] Therefore, it is possible that this initially protective elevation of TG-PUFA may have detrimental effects on WAT if chronically sustained.

Finally, the authors determined that phospholipid PE is enriched in VAT, while PC is enriched in SAT. These phospholipids have an opposing effect on membranes: PE promotes rigidity, but PC supports membrane fluidity.[4] These differences in membrane lipid composition between VAT and SAT likely impact adipocyte remodeling and nutrient storage. Given that the increase in the size of VAT is associated with insulin resistance, it will be critical to examine the contribution of phospholipids and membrane fluidity in this depot on obesity-mediated pathology.

Although the study provides an exceptional wealth of information on how obesity alters the lipidome, there are some limitations remaining. Even though obesity is a risk factor for numerous diseases, adiposity can also serve as a protective mechanism from lipotoxicity. This raises the possibility that lipidomic changes observed in the study are a result of an adaptive, rather than a maladaptive, response to excess nutrients. In addition,

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the obese group in the study has more younger and female subjects than the lean group. Therefore, the possibility that the sex and age of the subjects account for some of the lipidomic differences between the two groups cannot be excluded.

WAT is a complex tissue consisting of adipocyte, stromal, vascular, and immune compartments. Obesity not only increases the number and size of adipocytes but also leads to inflammation and hypoxia that alter immune and vascular compartments.[9] Granted that obese WAT-specific lipidomic changes have been identified by Lange and colleagues[1] in this sophisticated work, the spatial information as to which cellular compartments harbor these changes remains to be identified. Perhaps, future studies using mass spectrometry-based imaging approaches or lipidomics of sorted cell types from WAT will further our understanding of obesity-mediated adipose tissue dysfunction. Looking to the future, improved accuracy of detection and quantification of lipids from different tissues with deep lipidomic technology will pave the way for the identification of novel lipid biomarkers of diseases. Moreover, pairing such technology with other multiomic approaches will be pivotal to broaden our knowledge of biological systems and pathology.

DECLARATION OF INTEREST

The authors declare no competing interests.

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