Diabetes, Metabolic Syndrome and Obesity

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HYPOTHESIS

Orbital Fat is an Observation Model to Provide Insights into Adipocyte Hypertrophy and Hyperplasia During White Adipose Tissue Expansion

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Introduction: Obesity is a global health problem characterized by excessive white adipose tissue (WAT) distribution. Adipocyte hypertrophy (increased cell size) and hyperplasia (differentiation into new adipocytes from pre-adipocytes) are two ways for WAT to expand. The precedence of hypertrophy over hyperplasia leads to an enlarged adipocyte size, which is associated with multiple metabolic dysfunctions. Compared with abdominal subcutaneous fat (SF), orbital fat (OF) has smaller adipocytes with less inflammatory infiltration, better vascularization, and higher adipogenic and proliferative capacities, reflecting a healthy metabolic state. Polyunsaturated fatty acids (PUFAs) can stabilize energy homeostasis via G protein-coupled receptor 120 (GPR120) to alleviate insulin resistance and inflammation.

Methods: We used lipidomics analysis to reveal a greater accumulation of two PUFAs—arachidonic acid (AA) and docosapentaenoic acid (DPA) in OF than in SF and then hypothesized that AA/DPA is one factor regulating WAT morphological and biological heterogeneity.

Results: Mechanistically, the existing literature evidence suggests that AA/DPA signals may stimulate the co-activation and interaction of GPR120 and peroxisome proliferator-activated receptor γ (PPARγ), at least partially contributing to adipose metabolic health.

Conclusion: As the differential metabolites between OF and SF, AA and DPA, along with the relevant GPR120/PPARγ pathways, offer new therapeutic approaches for morbid obesity.

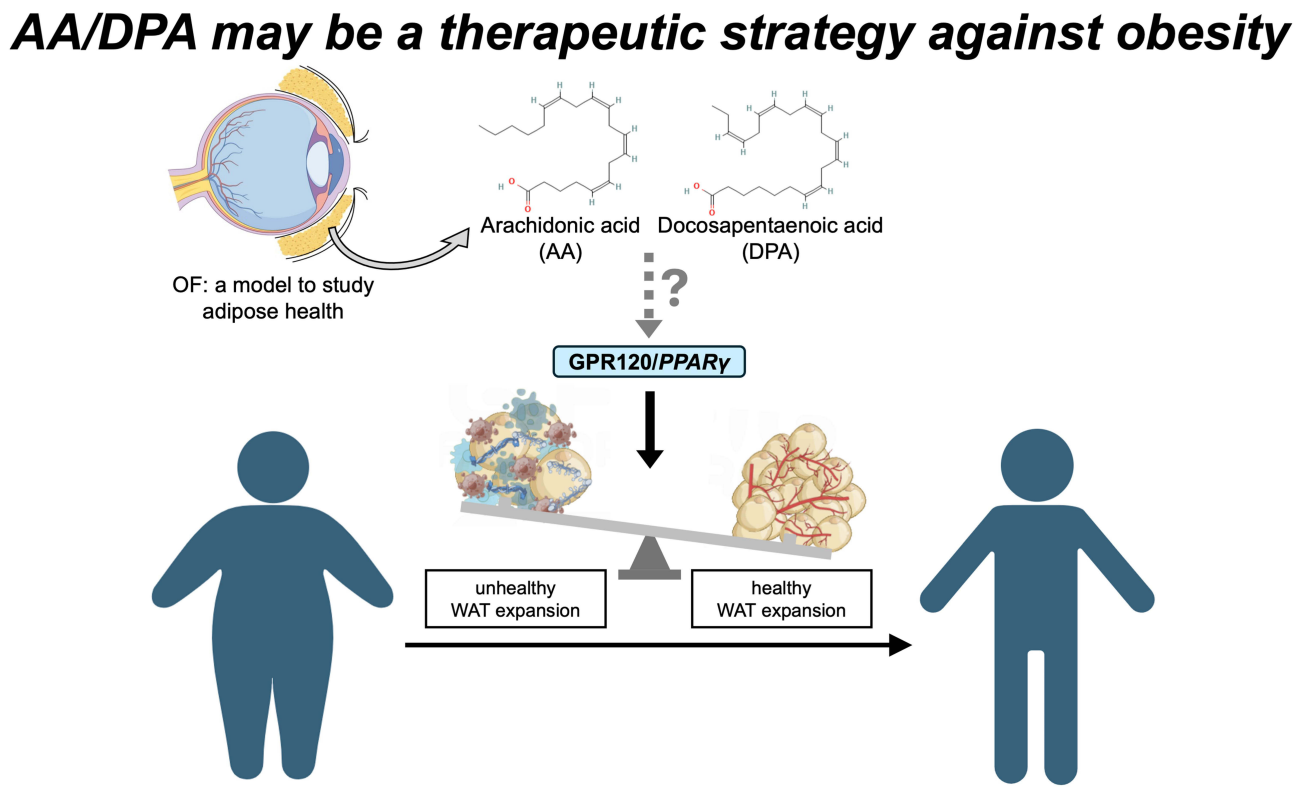
Keywords: adipose tissue, orbital fat, arachidonic acid, docosapentaenoic acid, GPR120, obesity

Introduction

Obesity is characterized by the expansion of white adipose tissue (WAT) and has become a challenging issue for public health.[1] WAT expands through a combination of two ways: hypertrophy—enlargement in the size of mature adipocytes and hyperplasia—differentiation of pre-adipocytes to produce new small adipocytes.[2] Increased adipocyte size is associated with numerous adverse metabolic consequences, such as inflammation, fibrosis, and insulin resistance.[3,4] Conversely, the formation of new small adipocytes (adipogenesis) mitigates these metabolic declines and represents a healthy metabolic condition in WAT.[5,6] Therefore, exploring factors that shift adipocyte development from hypertrophy to hyperplasia during WAT expansion, thereby storing surplus calories more safely, is crucial for promoting a "metabolically healthy obesity" (MHO) state.[7]

Received: 19 February 2025
Accepted: 28 July 2025
Published: 20 August 2025

Graphical Abstract



Orbital fat (OF) is a highly specialized WAT occupying the orbital cavities around the eyeballs. Healthy WAT is characterized by a high degree of vascularization, minimal hypoxia and fibrosis, and low-level inflammation.[8] Our previous work, along with other scholars', has identified that OF possesses smaller adipocytes and is likely to be a healthier adipose tissue than abdominal subcutaneous fat (SF).[9–14] Consequently, OF may represent a natural MHO model to study ways to reverse "metabolically morbid obesity" (MMO) by prioritizing adipocyte hyperplasia over hypertrophy.

Studies have demonstrated the beneficial effects of polyunsaturated fatty acids (PUFAs) on obesity-associated metabolic disorders, including anti-inflammation, increasing insulin sensitivity, and healthy adipose tissue remodeling.[15,16] As one of the lipid-sensitive G protein-coupled receptors highly expressed in adipose tissue, the G protein-coupled receptor 120 (GPR120), also known as the free fatty acid receptor 4 (FFAR4), plays an essential part in PUFA-regulated adipose metabolic homeostasis.[17] In our comparisons of the lipid compositions between OF and SF, we found that the relative amounts of two specific PUFAs, arachidonic acid (AA, C20:4n-6) and docosapentaenoic acid (DPA, C22:5n-3), were unexpectedly higher in OF than in SF. Therefore, in this study, we hypothesized that, in addition to adipose cell-intrinsic heterogeneity (eg, distinct developmental origins and physiological properties), cell content, and cell subtype composition, the differential AA and DPA levels in adipose microenvironment may also influence the morphological differences between OF and SF and regulate adipose metabolism via GPR120.

Methods and Materials

Adipose tissue samples in both groups (n = 6) were, respectively, harvested from different overweight female patients (mean age, 39 years old (range 27–68); mean BMI, 28.3 kg/m^2 (range 25–30)) undergoing lower eyelid blepharoplasty or abdominal liposuction in the plastic and reconstructive surgery department of Shanghai Tenth People's Hospital. The OF samples were specifically obtained from the central orbital fat pads in the lower eyelid, and the SF samples were from the

lower abdomen area. We confirmed that there were no significant inter-group differences in basic individual characteristics, including age, sex, ethnicity, BMI, percentage of fat, and waist-to-hip ratio, to ensure the comparability. None of the participants had any ophthalmologic diseases, obesity-related metabolic syndromes, or other severe systemic diseases, and none had a significant weight change within 3 months.

Lipid metabolomics analysis was performed after the digestion and extraction of adipose tissue samples, and the detailed procedures were shown in our previous work.[11] Briefly, the total lipid extractions from OF and SF were centrifuged, and the supernatants were collected, dried, and reconstituted in a solvent mixture for the final sample preparation. A volume of 20 μL from each individual sample was pooled as a quality control (QC) sample, aiming to assess and ensure the analytical reproducibility and consistency. Subsequently, with specific setting parameters, an Ultimate 3000 UPLC coupled with a mass spectrometer Q-Exactive Plus (Thermo Fisher Scientific, USA) controlled by *Xcalibur* software was performed for LC-MS analysis. The raw data was further processed for peak extraction, peak alignment, lipid identification, and peak intensity quantification. Based on the processed metabolomics data, an online metabolomics data analysis tool—MetaboAnalyst (https://www.metaboanalyst.ca) was used to perform the classic univariate receiver operating characteristic (ROC) curve analyses. For statistical analysis, the Shapiro–Wilk test and Levene test were performed to assess the normality and homogeneity of variances, respectively. Comparisons between the two groups were conducted using the independent sample *t*-test or the Mann–Whitney *U*-test (as appropriate). The SPSS software (version 26.0; IBM Corp, USA) was used with a statistical significance set at $p < 0.05$.

Results and Evaluation of the Hypothesis

Importance of Studying the OF Microenvironment to Promote MHO

WAT depot-based morphological and biological differences have been widely proposed, but few have focused on the metabolic distinctions.[18,19] Compared with SF, OF may be metabolically healthier, since OF has: (1) morphologically smaller adipocytes,[9–11] which are associated with high insulin sensitivity and low-level inflammation;[20] (2) more vascularization;[10,13] (3) a more dynamic extracellular matrix (ECM) that better supports WAT expansion;[10,13,21] (4) less macrophage infiltration (our unpublished data); (5) higher proliferative and adipogenic capacities in adipose-derived stem cells (our unpublished data and reference[14]).

The adipose microenvironment has been proven to cause regional WAT heterogeneity by both in vitro differentiated cells and in vivo adipose transplantation experiments.[22,23] Therefore, we compared the lipid differences between OF and SF, hoping to find key metabolites in the OF microenvironment to improve metabolic disorders.

The Findings of AA/DPA Content Differences Between OF and SF

In this study, more accumulations of AA and DPA in OF than in SF were identified by lipidomics analysis (Figure 1a). ROC curves further demonstrated their discriminatory power between the OF and the SF microenvironments, with the

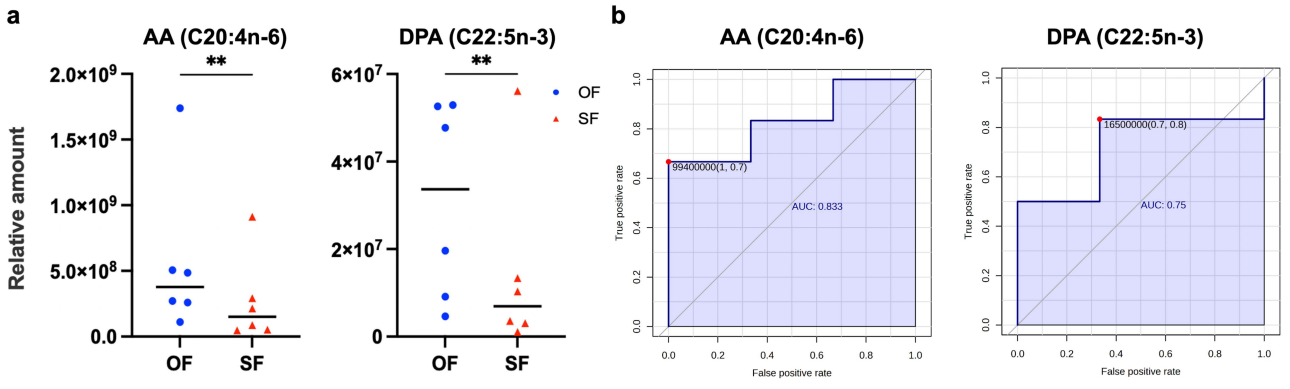


Figure 1 The findings of AA/DPA content differences between OF and SF. (**a**) Comparisons of the relative amounts of AA (C20:4n-6) and DPA (C22:5n-3) between OF and SF. Each spot represented a sample, and the median was shown as a short horizontal line in each group (n = 6, $^{**}p < 0.01$). (**b**) Receiver operating characteristic (ROC) curves of AA and DPA.

https://doi.org/10.2147/DMSO.S521845

mean area under the ROC curve (AUC) values of 0.833 (95% CI: 0.785–0.881) for AA and 0.750 (95% CI: 0.658–0.842) for DPA, respectively (Figure 1b). Both AA and DPA are common kinds of PUFAs with potential benefits to metabolic homeostasis.[24–27] Despite AA's dual pro- and anti-inflammatory properties in metabolism,[26] comprehensive transcriptional profiling during adipogenesis from human mesenchymal stem cells (hMSCs) has already highlighted the critical role of AA in adipogenic differentiation and its potential in improving fat metabolism disorders.[28] Therefore, we believe there is a link between differential AA/DPA levels and the morphological and biological distinctions between OF and SF, which is partly responsible for their eventual heterogeneity in metabolic health.

AA/DPA May Activate GPR120 to Promote MHO

Theoretically, AA and DPA can activate GPR120 to promote adipose health since these beneficial effects of GPR120 activation has been widely proven using other PUFAs.[17,29] In fact, we have found the elevated GPR120 expressions in OF both at the gene level using quantitative real-time polymerase chain reaction (qRT-PCR) and at the protein level utilizing Western blot analysis (the full data is in preparation), which may be attributable to the greater accumulation of AA and DPA in this adipose region. These results, combined with our ongoing adipose GPR120 immunofluorescence staining, are currently being compiled as part of our one unpublished study.

AA/DPA May Regulate GPR120 and PPARγ Co-Activation and Interaction in Pre-Adipocytes

PUFA-mediated GPR120 activation promotes adipogenesis in 3T3-L1 pre-adipocytes.[30] On the contrary, inhibiting GPR120 impairs adipogenesis significantly.[31,32] *PPARγ* also can be directly stimulated by fatty acids in pre-adipocytes.[33,34] Notably, the size of lipid droplets of PUFA-induced differentiated adipocytes is smaller than that of monounsaturated fatty acid (MUFA)-induced ones, indicating a positive effect of PUFA-mediated *PPARγ* activation on the adipocyte hypertrophy-hyperplasia balance.[33] Metabolites derived from PUFAs also induce *PPARγ*-related adipogenesis.[35,36] Moreover, *PPARγ* shows a similar pocket structure with GPR120,[30] implying the possibility that it could be co-activated by AA/DPA and their metabolites.

The interplay between GPR120 and *PPARγ* after the co-activation magnifies their positive metabolic effects. GPR120 augments *PPARγ*-initiated adipogenesis by activating its upstream signal pathways[37] and producing more *PPARγ* ligands.[38] Conversely, *GPR120* gene knockout inhibits *PPARγ* expressions.[32] On the other hand, *PPARγ* agonist rosiglitazone increases the expression of GPR120 gene,[39] which is subsequently confirmed to be a *PPARγ* target gene.[38] The relevant pathways in pre-adipocytes were speculated to be activated by AA/DPA and were illustrated in Figure 2a.

AA/DPA May Regulate GPR120 Activation in Mature Adipocytes

GPR120 is also highly expressed on the plasma membrane of mature adipocytes and coupled with $G_{\alpha q}$ to exert various positive biological functions.[17,31,40,41] For instance, n-3 PUFAs have anti-inflammatory and insulin-sensitizing effects on wild-type (WT) mice with a high-fat diet (HFD) through GPR120 activation; on the contrary, *GPR120*-deficient HFD-fed mice show obese phenotypes.[17,31,42] PUFAs suppress inflammation through GPR120 by disrupting the bonds between transforming growth factor-β activated kinase 1 (TAK1) and TAK1 binding protein 1 (TAB1) in adipocytes.[43] PUFAs also upregulate vascular endothelial growth factor A (VEGF-A) and WAT browning.[44,45] Taken together, adipocyte GPR120 activation might be stimulated by AA/DPA to increase glucose uptake, insulin sensitivity, angiogenesis, thermogenesis, and browning in WAT, thereby inhibiting cell hypertrophy and inflammation (Figure 2b).

AA/DPA May Regulate GPR120 Activation in Macrophages

AA/DPA may also mediate GPR120 signals to exert anti-inflammatory effects directly in macrophages (Figure 2c). Through the GPR120 activation, PUFAs: (1) inhibit TAK1/TAB1 interaction to block the downstream IKKβ/NF-κB and JNK/AP pathways;[17] (2) couple with β-arrestin2 to repress TLR4-induced inflammatory signaling;[46] (3) activate cytosolic phospholipase A2 (cPLA2) to release prostaglandin E2 (PGE_2), which subsequently stimulates prostaglandin E receptor 4 (EP4) to inhibit the NF-κB inflammatory pathway.[47] Additionally, there is an interplay between GPR120-regulated macrophages and adipocytes: Inflammatory cytokines from macrophages inhibit GPR120 expression in adipocytes,[48] and, in turn, metabolically disordered adipocytes induce pro-inflammatory macrophage phenotypes.[49]

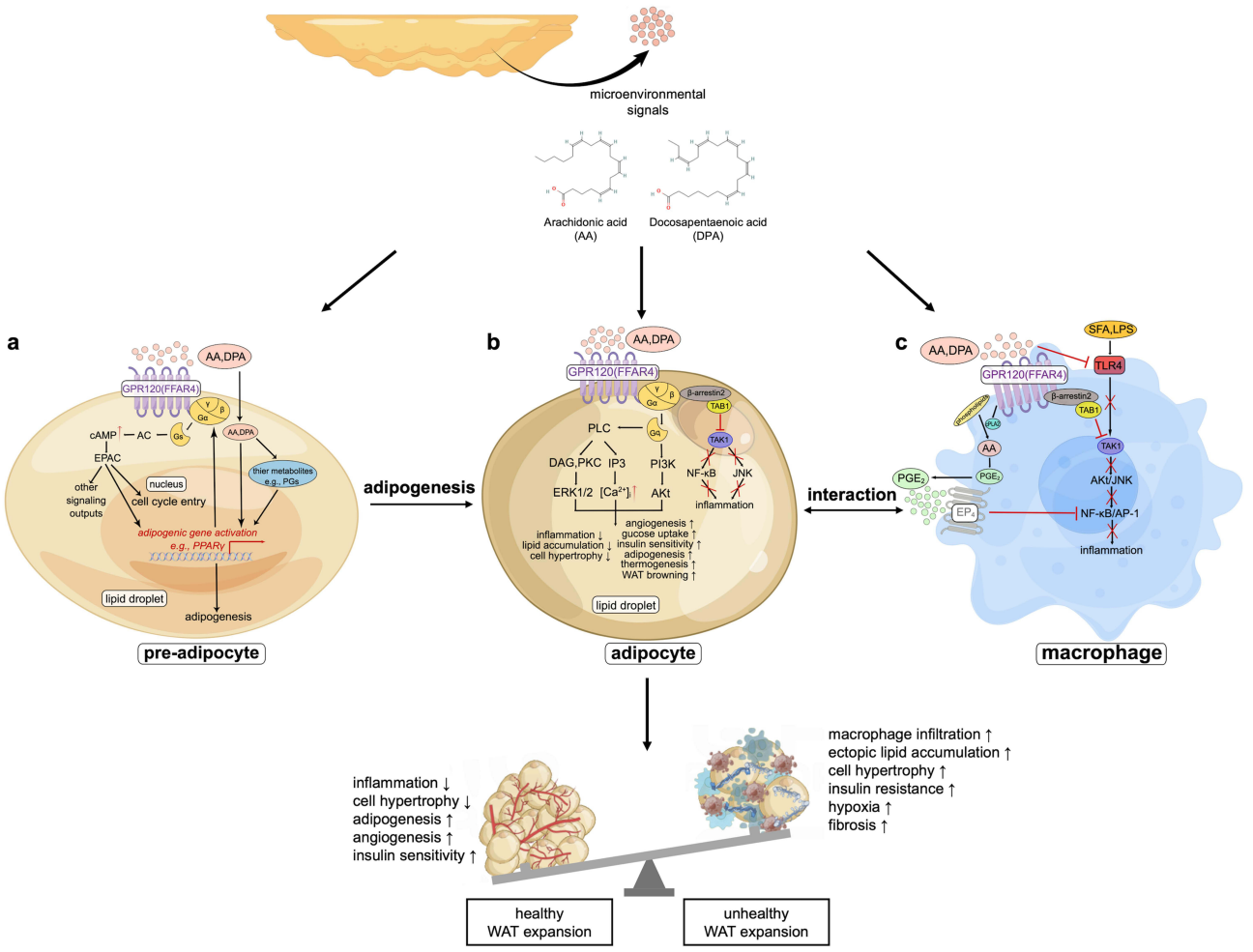


Figure 2 Hypothetical overview of the positive biological effects of AA/DPA on promoting metabolic health in WAT through GPR120 (FFAR4) and *PPARγ* co-activation and interaction. Specifically, as adipose tissue microenvironmental signals, AA/DPA could perhaps act on three kinds of cells: (**a**) In pre-adipocytes, AA/DPA may stimulate adipogenesis to increase hyperplasia over hypertrophy; (**b**) In mature adipocytes, AA/DPA may promote healthy cellular biological states; (**c**) In macrophages, AA/DPA may exert anti-inflammatory effects directly.

Abbreviations: AA, arachidonic acid; DPA, docosapentaenoic acid; PGs, prostaglandins; GPR120 (FFAR4), G protein-coupled receptor 120 (free fatty acid receptor 4); AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; EPAC, exchange factor directly activated by cAMP; *PPARγ*, peroxisome proliferator-activated receptor γ; PI3K, phosphatidylinositol 3-kinase; Akt, serine/threonine-protein kinase; PLC, phospholipase C; IP3, inositol trisphosphate; DAG, diacylglycerol; PKC, protein kinase C; ERK, extracellular regulated kinase; TAK1, transforming growth factor-β activated kinase 1; TAB1, TAK1 binding protein 1; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor-kappa B; SFA, saturated fatty acid; LPS, lipopolysaccharide; TLR4, toll-like receptor 4; cPLA2, cytosolic phospholipase A2; PGE_2, prostaglandin E2; EP_4, prostaglandin receptor 4; AP-1, activator protein 1.

Discussion

The WAT depot-based heterogeneity provides a comparison model for exploring ways to treat obesity-related metabolic dysfunctions. Numerous studies have compared SF and visceral fat (VF), showing that SF is metabolically healthier than VF, as accumulated VF is more closely associated with insulin resistance and lipotoxicity.[50] However, anatomically different SF depots also respond to weight gain differently and are associated with distinct metabolic statuses.[51,52] Abdominal SF mainly relies on fat cell hypertrophy to expand and demonstrates significant inflammatory insults, while lower-body (eg, gluteofemoral) SF seems to retain its biological functions and capacity to recruit new, small adipocytes and therefore is regarded as a metabolically protective WAT.[51,52] Compared with extensive research on SF and VF, OF is often overlooked and has never been utilized as a model for novel obesity treatment targets. Our OF-centric study innovatively compared OF with SF and proposed OF possesses smaller adipocytes and a relatively healthier metabolic state. Further, we identified higher levels of AA and DPA in OF and hypothesized their important roles in regulating adipose health.

https://doi.org/10.2147/DMSO.S521845

Almost all existing studies on the positive metabolic effects of the PUFA-mediated GPR120 activation focus on n-3 PUFAs.[17,30] DPA, despite being an n-3 PUFA, has been reported to improve inflammation, arteriosclerosis, and other obesity-related metabolic dysfunctions, but no research has linked these effects to GPR120.[25,27] As for AA, an n-6 PUFA, it plays a controversial and complicated role in obesity, as it is a precursor to multiple pro-inflammatory mediators, while its derivatives exert anti-inflammatory effects.[24,26,53] However, as for now, no one has studied the impacts of AA/DPA-GPR120 signaling, not to mention in the context of adipose metabolism. We propose for the first time that the AA/DPA-mediated co-activation of GPR120 and *PPARγ*, as well as their interplay, at least partly contributes to OF's metabolic profile, expanding the clinical applications of AA/DPA in metabolic diseases. Furthermore, based on our OF-SF comparison model to hypothesize the different GPR120 activation statuses caused by different adipose AA/DPA levels, we reinforce the feasibility and prospects of GPR120-related treatments in obesity (particularly through increasing GPR120 expression and its sensitivity). Nevertheless, the AA/DPA-GPR120/*PPARγ* axis we discuss here only offers a preliminary and partial explanation for the metabolic heterogeneity between OF and SF, as the effects of the axis itself need to be experimentally validated and numerous other undiscovered factors in OF also influence adipose health.[54]

To fully clarify our hypothesis that AA/DPA mediates WAT depot-specific distinctions in adipocyte hypertrophy–hyperplasia balance and metabolic health, we plan to: (1) Perform a target lipid metabolomics analysis to specify the differential AA/DPA metabolism patterns in OF and SF. (2) Study distinct transcriptomics profiles in OF and SF to explore the underlying mechanisms for the differential AA/DPA levels. (3) Observe whether AA/DPA eliminates the depot-based heterogeneity in vitro adipose stem and progenitor cells (ASPCs), like the tumor necrosis factor (TNF) stimulation reducing differences between visceral and subcutaneous ASPCs in a previous study.[23] Concurrent with this, we will observe positive biological effects induced by AA/DPA in ASPCs, such as improved adipogenic and angiogenic capacities, insulin sensitivity, inflammatory level, etc. (4) Validate the anti-obesity effects of AA/DPA and the related GPR120/*PPARγ* signaling activation in an animal model. (5) Employ GPR120 antagonists and/or *GPR120* gene-knockout experiments to prove that AA/DPA confers these biological benefits via the GPR120/*PPARγ*-related pathways. In addition, we could compare OF with other adipose sites to provide a more comprehensive view of adipose depot-specific heterogeneity in morphology and metabolic health.

Conclusion

This study introduces OF as a depot-specific adipose model with small adipocytes and a relatively healthy metabolic profile. This OF-based healthy adipose model offers a more valid and ideal way to study healthy WAT expansion by eliminating the intrinsic biological variables of individuals, such as genes, dietary structures, and exercise habits. Based on our OF observation model, we hypothesized that higher AA and DPA levels in adipose microenvironments may improve adipose inflammation and metabolism via GPR120/*PPARγ*. AA/DPA could perhaps serve as biomarkers for assessing adipose metabolic health, and new AA/DPA-related nutritional or pharmaceutical interventions may benefit clinical obesity. Altogether, AA/DPA and their targets—GPR120/*PPARγ*—inspire us with new therapeutic targets for improving metabolic profiles in obesity.

Data Sharing Statement

The data in this study are available upon request from the corresponding author.

Informed Consent and Institutional Review Board Statement

All participants provided written informed consent to participate in this study and to publish their case details. Experimental methods involving patients followed the tenets of the Declaration of Helsinki and were approved by the Medical Ethics Committee of Shanghai Tenth People's Hospital (approval number: SHSY-LYZX-223).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This work was supported by grants from the National Natural Science Foundation of China (grant number: 31870974).

Disclosure

All authors declare that no known competing interests influence the work reported in this paper.

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