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Adipose tissue endothelial cells: insights into their heterogeneity and functional diversity

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Cardiovascular disease is the leading cause of death globally. Endothelial cells (ECs), the key units of all vascular segments, have a significant impact on the health and disease of organisms. Adipose tissue is vital to cardiovascular health, therefore, understanding adipose EC (AdEC) biology is important. Recent data have highlighted the presence of distinct AdEC subpopulations that govern adipose tissue homeostasis. In addition to their role in nutrient metabolism and transport, AdECs are involved in bidirectional cellular communication with adipocytes, among other cells. These interactions are mainly mediated by paracrine factors, including noncoding RNAs. In this review, we highlight recent results showcasing the functions of AdECs in adipose tissue biology, metabolic homeostasis, and changes occurring in obesity.

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Introduction

Adipose tissue, once thought to facilitate storage of excess nutrients, is now recognized as a key endocrine organ that regulates metabolic homeostasis. A number of acute and chronic diseases, including atherosclerosis, myocardial infarction, hypertension, and nonalcoholic fatty liver diseases, are associated with adipose tissue dysfunction. Many of these disorders are closely associated with blood vessel malfunction, indicating that defects in the vascular system also contribute pathologically.

Adipose tissue can be categorized into three different types: white (WAT), brown (BAT), and beige, dependent on origin, location, and function. While WAT comprises lipid-storing, unilocular, adipocytes, BAT comprises mitochondria-rich, multilocular, adipocytes that specialize in energy dissipation via nonshivering thermogenesis [1]. WAT depots are further subcategorized, based on their anatomical localization, into subcutaneous (SAT) and visceral adipose tissue (VAT). In addition to adipocytes, the adipose tissue consists of a stromal vascular fraction (SVF), containing fibroblasts, adipocyte precursors, immune cells, and blood vessels. Human SAT appears to have a lower vascular density in comparison to VAT, while murine fat depots display the opposite trend [2]. Despite being highly vascularized in the healthy state, adipose tissue of obese individuals exhibits vascular rarefaction; this promotes local hypoxia, leading to vascular dysfunction, adipose tissue inflammation, and fibrosis [3,4]. As healthy blood vessels are important in the maintenance of adipose tissue homeostasis, several approaches have been developed to modulate adipose tissue angiogenesis as a possible treatment for obesity and its related complications in preclinical models [5].

Depending on function, the anatomy and cellular composition of blood vessels may differ. However, the common unit of all vessels is endothelial cells (ECs), which line the vessel lumen and control oxygen, nutrient, and waste transport between the blood and organs. Blood vessels are supported by mural cells, including platelet-derived growth factor receptor beta (*PDGFRB*)-expressing pericytes, myosin heavy chain 11-expressing vascular smooth muscle cells, and *PDGFRB*-expressing pericyte-like perivascular cells [6,7]. Recent advances in technology involving single-cell and single-nucleus RNA sequencing (snRNA-seq), which have become an integral part of mapping cellular complexity, have identified numerous tissue-specific EC phenotypes [8], including adipose endothelial cells (AdECs) [9–11]. Furthermore, these results help us understand the interaction between AdECs, adipocytes, and other cells of the SVF. Gained knowledge could help establish strategies to target adipose tissue in metabolic diseases.

Here, we summarize the recent literature around AdEC transcriptomic heterogeneity, identified subpopulations, and their functions. We also highlight AdEC–adipocyte

crosstalk, and provide further suggestions for the advancement of this field of research.

Enhancing adipose tissue angiogenesis to improve tissue function

Adipose tissue expansion is associated with enhanced adipo- and angiogenesis. However, the angiogenic capacity of adipose tissue decreases during the progression of obesity [12], which has a detrimental impact on whole-body metabolic homeostasis [13]. Lack of sufficient tissue vascularization leads to obesity-induced hypoxia, which triggers adipose tissue inflammation and insulin resistance [13]. Therefore, strategies for maintaining vascular density and function in adipose tissues have been explored in recent years.

It has been already established that overexpression of vascular endothelial growth factor (VEGF), a potent pro-angiogenic trigger, promotes adipose tissue vascularization, improves glucose tolerance and insulin sensitivity, and enhances BAT thermogenic activity [3]. In adipose tissue, the pro-angiogenic signaling of VEGF is primarily mediated by VEGF receptor 2 (VEGFR2), since the deletion of endothelial VEGFR2 reduces adipose tissue angiogenesis and WAT browning [14]. In addition, deletion of endothelial VEGF receptor 1 (VEGFR1), which acts as a decoy receptor for VEGF, reduces metabolic dysfunction by promoting SAT browning [15]. Furthermore, while VEGF production is relatively unaltered during aging, VEGF signaling is impaired [16].

Aging is associated with the increased production of soluble VEGFR1 (sVEGFR1), which blunts the VEGF-induced pro-angiogenic response. Upregulating the expression of *sFlt1*, which encodes sVEGFR1, accelerates aging-associated metabolic dysfunction in mice, whereas VEGF treatment can ameliorate adverse age-associated changes in SAT and VAT [16]. Apart from VEGF/VEGFR-mediated angiogenic signaling, other pro-angiogenic factors, such as angiopoietins and platelet-derived growth factor CC, have recently been implicated in adipose tissue physiology [14,17]. This highlights the need to understand adipose tissue vascularization mechanisms and AdEC function in the maintenance of healthy adipose tissue expansion and thermogenesis. These areas could be a target for future therapeutic interventions.

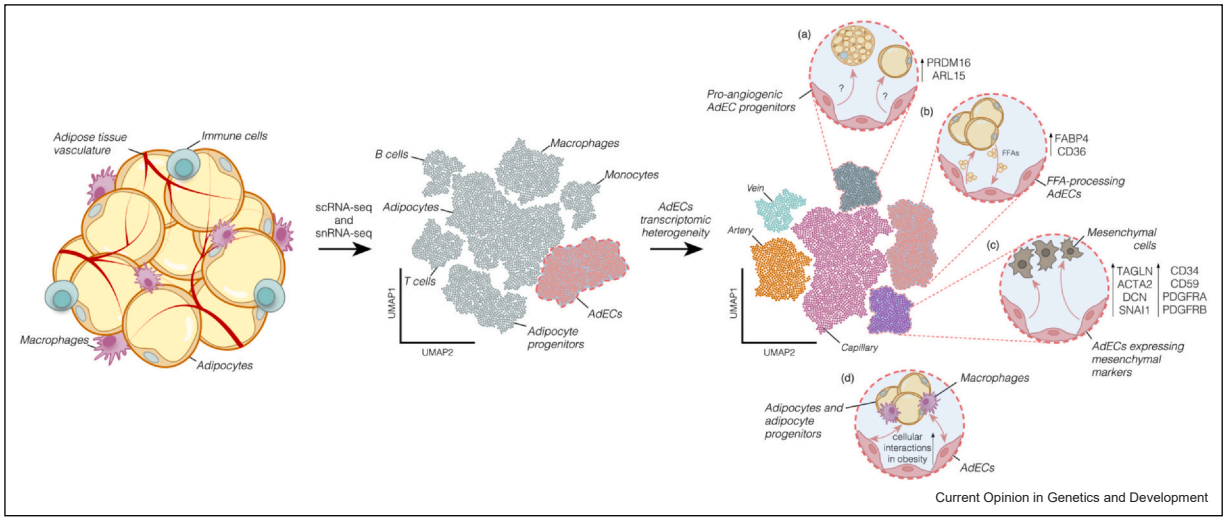
Transcriptomic and functional heterogeneity of adipose tissue endothelial cells

Through recent advances in sequencing technologies, our knowledge of EC tissue specialization and heterogeneity at the transcriptomic level is expanding [8,12] (Figure 1). Obesity has been shown to affect murine ECs in an organ- and a subtype-specific manner. Of the seven analyzed tissues, AdECs and liver ECs displayed the most differentially expressed genes in obese versus control mice [12], highlighting tissue-specific molecular changes and endothelial responses. Reflecting the enhanced angiogenesis accompanying obesity-associated adipose tissue expansion, a pronounced increase in the abundance of angiogenic and proliferating AdECs in SAT and VAT was noted [12].

In addition to identifying ECs of different vascular beds (arteries, veins, and capillaries), several other AdEC subpopulations have been described in humans, including pro-angiogenic progenitors, free fatty acid (FFA)-processing, and AdECs expressing mesenchymal markers [10,11,18]. Pro-angiogenic progenitor AdECs, characterized by their high expression of positive regulatory domain-containing 16 (*PRDM16*) and ADP ribosylation factor-like GTPase 15 (*ARL15),* are shown to be more prevalent in human SAT [10]. In addition to brown adipogenesis [19], *PRDM16* promotes the formation of arterial ECs [20], partly explaining the higher angiogenic capacity of SAT compared to that of VAT in humans [10] (Figure 1a). Interestingly, specialized capillary ECs were reported to give rise to both white and brown adipocytes [21]. Moreover, vascular AdECs expressing platelet-derived growth factor receptor alpha (PDGFRA) were recently reported to express marker genes for committed preadipocytes, including chemokine (C–X–C motif) ligand 14, complement factor D, and apolipoprotein D [7]. It is thus plausible that these AdEC populations present an intermediate cell state between endothelial and adipocyte precursor cells. It remains however to be investigated whether these vascular AdEC subpopulations give rise to other cellular populations, including white and brown adipocytes.

A subpopulation of AdECs, characterized as FFA-processing, displayed an upregulation of genes involved in lipid metabolism, including fatty acid-binding protein 4 (*FABP4*) and the scavenger receptor *CD36* [11,18] (Figure 1b). AdECs from human SAT have been reported with a mesenchymal transcriptome expressing cluster of differentiation 34 molecule (CD34) and cluster of differentiation 59 molecule (CD59), decorin (*DCN*, a known mesenchymal marker), and *PDGFRA* and *PDGFRB* [11]. Furthermore, the mesenchymal phenotype of AdECs, characterized by the expression of the mesenchymal markers Transgelin (TAGLN) and actin alpha 2 (ACTA2), has been identified in the SAT of patients with diabetes [22]. This phenotype is possibly driven by the transcription factor Snail family transcriptional repressor (SNAI1), which has been previously implicated in the endothelial-to-mesenchymal transition (EndMT) [22] (Figure 1c). It is likely that human AdECs undergo EndMT, particularly in disease conditions characterized by the presence of pro-inflammatory and pro-fibrotic signaling, such as obesity and diabetes [23]. However, it remains unknown whether AdEC subpopulations undergoing EndMT expand further in

Figure 1



Transcriptomic and functional heterogeneity of AdECs. Single-cell transcriptomic profiling using scRNA-seq and snRNA-seq of human adipose tissue from revealed pronounced endothelial cell diversity. In addition to classical EC clusters, including capillary, vein, and artery, other subpopulations have been identified: **(a)** SAT-enriched endothelial progenitor cells (AdEC progenitors) expressing PRDM16 and ARL15 have been described as having a pro-angiogenic capacity. The adipogenic potential, by which these cells can give rise to white and brown adipocytes, requires further investigation. **(b)** FFA-processing AdECs have been characterized by their expression of PPAR-γ-regulated lipid transporters and lipid-binding proteins, including FABP4 and CD36. **(c)** AdECs expressing mesenchymal markers have also been identified based on their expression of the mesenchymal markers CD44, CD59, DCN, PDGFRA/B, TAGLN, and ACTA2. The mechanism for these adaptations is possibly driven by the transcription factor SNAI1. **(d)** AdECs are implicated in interactions with adipocytes, adipocyte progenitor cells, and other SVF cells including macrophages. These interactions are upregulated in obesity. *Abbreviations*: PPAR-γ, peroxisome proliferator-activated receptor gamma.

metabolic diseases, and what functional consequences would this entail. Moreover, the presence of AdECs undergoing EndMT in the SAT of lean individuals suggests that these cells exert homeostatic functions, which require further investigation [11]. Intriguingly, a subpopulation of AdECs undergoing EndMT has been reported in porcine SAT and VAT [24]. These cells were characterized by the expression of genes encoding the transcription factors ZEB2 (Zinc finger E-box binding homebox), SNAI1, and SNAI2 in addition to the mesenchymal markers S100A4, CD44, and VIM (Vimentin) [24]. However, it is unknown whether similar AdEC phenotypes occur in murine obesity models, in which validation is instrumental to study their effects on disease progression.

AdECs can interact with adipocytes and other cells in the SVF, and this intercellular communication is altered in metabolic diseases (Figure 1d) [25]. For example, obesity is associated with increased interactions between AdECs, adipocyte stem and progenitor cells, and mature adipocytes in the human SAT and VAT, indicating a potential activation of these cells [9]. Signaling through JAG1/NOTCH3 (Jagged1/Neurogenic locus notch homolog protein) and VEGFC/KDR (Kinase insert domain receptor) is predicted to enhance the angiogenic response during adipose tissue expansion [9], however, more experimental insights into these interactions are needed. Similar altered interactions occur in murine SAT and VAT, suggesting the conservation of intracellular communication across these species [9]. It is also suggested that the interactions of AdECs with adipose tissue-resident macrophages in the SAT are altered in obese individuals [26]. However, these computationally inferred interactions require in-depth validation, by exploiting recently optimized complex three-dimensional AT culture systems [27] or using well-established in vivo models.

Even though we gain valuable insights into adipose tissue biology using single-cell/nucleus sequencing [6], one needs to interpret some of the data carefully; the findings may differ from previously published results, including differences in AdEC frequencies between different adipose depots. This inconsistency may be due to the individual capacities of sequencing technologies to capture ECs [9,28]. While the abundance of human SAT AdECs profiled using single-cell RNA sequencing (scRNA-seq) showed a positive correlation with subject BMI (Body mass index) [26], single-nucleus RNA-sequencing-profiled AdECs in human SAT showed the opposite trend [9]. Moreover, the frequency of AdECs in the VAT of lean and obese subjects showed no difference in abundance [9]. These differences in AdEC abundance may arise from intrinsic subpopulation-specific characteristics, including vascular density or by the used technique itself. A recent single-cell transcriptomic atlas of human WAT demonstrated that

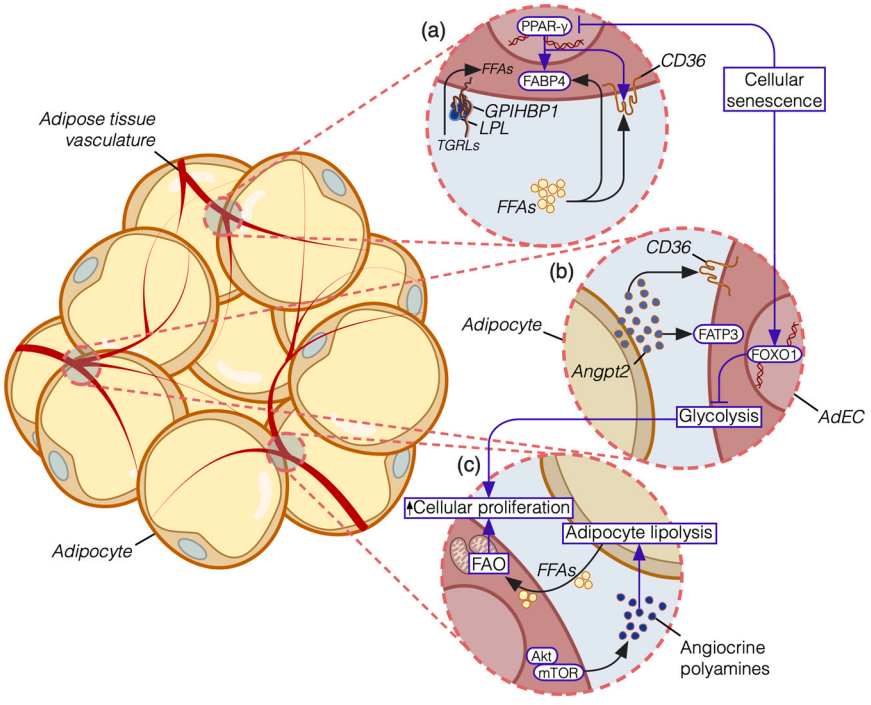
studies employing snRNA-seq profiled more vascular cells than did studies employing scRNA-seq [7], which is consistent with previous reports [9]. Therefore, the AdEC frequencies profiled by these techniques should be interpreted with caution.

Lipid metabolism and transport through the adipose tissue endothelium

AdECs mediate adipose tissue lipid influx and efflux, facilitating the lipogenic and lipolytic pathways [29]. AdECs anchor adipocyte-secreted lipoprotein lipase (LPL) to their luminal surface through its interaction with the LPL-anchoring protein glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) [30]. FFAs derived from LPL-mediated hydrolysis undergo transcytosis via vesicular transport [29]. Moreover, LPL-hydrolyzed triglyceride-associated lipoproteins are internalized by AdECs following their interaction with the scavenger receptor CD36, eventually targeting the endosomal/lysosomal compartment (Figure 2a) [30]. In addition to predominanting AdEC lipid vesicular transport, caveolae have also been shown to mediate intercellular communication between cells through an extracellular vesicle (EV) axis [31]. Particularly, these EVs are enriched in sphingolipids, a class of lipids with important signaling and structural properties [31]. This highlights the capacity of AdECs to uptake, package, and secrete lipids either facilitating lipid processing or mediating downstream signaling in neighboring adipocytes.

Microvascular AdECs express PPARγ-regulated proteins implicated in trans-endothelial transport of fatty acids, such as CD36, fatty acid transport proteins (FATPs), and fatty acid-binding proteins (FABPs) [11,12,18,32]. Exogenous fatty acid uptake into microvascular AdECs of human SAT has been shown to promote PPARγ activity and endothelial lipid transport through FABP4 and CD36 [33] (Figure 2a). Intriguingly, PPARγ transcriptional activity, and thus the expression of CD36, FATPs, and FABPs, decreases during AdEC senescence [34]. Senescent AdECs were shown to enhance adipocyte

Figure 2



An overview of the lipid metabolism and processing machinery in AdECs. AdECs express PPARγ-regulated proteins (CD36, FABPs, and FATPs) implicated in trans-endothelial transport of FFAs. **(a)** AdECs anchor adipocyte-secreted LPL to their luminal surface through the interaction with the LPL-anchoring protein, GPIHBP1. LPL hydrolyzes TGRLs into FFAs. FFAs can also be internalized by AdECs following their interaction with the scavenger receptor CD36. **(b)** Cellular senescence is associated with increased presence of nuclear FOXO1. FOXO1 is a gatekeeper of endothelial quiescence through regulating cell metabolism, for example, inhibiting glycolysis. Adipocyte-derived Angpt2 promotes FFA uptake and metabolism by promoting the expression of CD36 and FATP3 in AdECs. **(c)** AdECs secrete angiocrine polyamines through an Akt/mTOR signaling axis to induce adipocyte lipolysis. In return, adipocytes release FFAs that can be metabolized by AdECs, to promote cellular proliferation. *Abbreviations*: TGRLs, triglyceride-rich lipoproteins.

oxidative stress, impair adipocyte insulin signaling, and promote metabolic dysfunction through a senescence-associated secretory phenotype, including the pro-inflammatory cytokines interleukin (IL)-1 and IL-6 [34,35]. This is of particular interest, as the pro-inflammatory microenvironment of obese adipose tissue can induce AdEC senescence. However, the molecular mechanisms regulating this phenotype require further investigation. In addition to a reduction in PPAR transcriptional activity, senescent AdECs are shown to retain nuclear forkhead box O1 (FOXO1) transcriptional activity (Figure 2b) [34]. FOXO1 is a gatekeeper of endothelial metabolism, and its overexpression reinforces EC quiescence by inhibiting glycolysis [36] (Figure 2b). EC-specific FOXO1 knockout mice exhibit enhanced VAT microvascular angiogenesis secondary to increased endothelial glycolysis and proliferation [5].

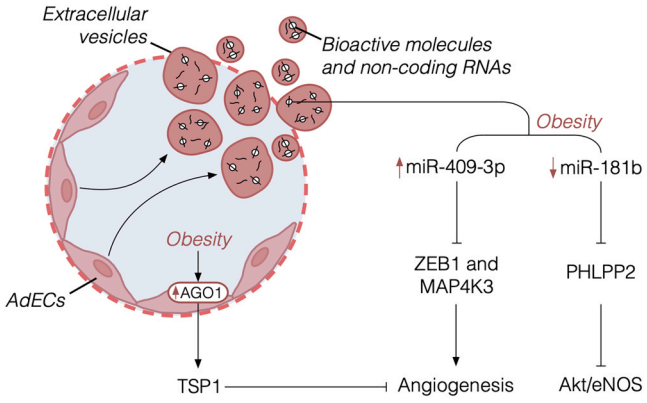
AdEC-mediated lipid uptake is, at least in part, modulated by adipocyte-secreted factors. For example, AdEC-mediated lipid uptake through CD36 and fatty acid transport protein 3 (FATP3) is governed by adipocyte-secreted angiopoietin-2 (ANGPT2) (Figure 2b) [37]. Mice with adipocyte-specific deficiency of Angpt2 display reduced adipocyte size in the SAT and impaired lipid uptake. When subjected to diet-induced obesity (DIO), these mice exhibited insulin resistance and ectopic fat accumulation in the liver and skeletal muscles [37]. Similarly, mice with EC-specific deficiency of CD36 exhibited impaired fatty acid transport into the heart, skeletal muscle, and BAT [38]. Therefore, when subjected to DIO, these mice showed improved glucose tolerance and insulin sensitivity. Nevertheless, mice with an EC-specific deficiency of CD36 showed unaltered WAT fatty acid uptake, suggesting either the dispensability of CD36-mediated lipid uptake in WAT, or the enhancement of compensatory pathways mediating lipid transport [38]. Additionally, it was shown that mitochondrial ATP production and acetyl-CoA formation in ECs is required for FATP4-mediated lipid acetylation [39]. In ECs, FATP4 resides in the endoplasmic reticulum [39], juxtaposed to mitochondria, which facilitates the utilization of the substrate acetyl-CoA. This highlights subcellular organization of lipid processing machinery to facilitate efficient execution of metabolic pathways. FFA uptake and metabolism are shown to promote EC proliferation [36]. Notably, AdECs secrete angiocrine polyamines via the protein kinase B–mammalian target of rapamycin (Akt–mTOR) pathway, stimulating adipocyte lipolysis to fuel endothelial fatty acid β-oxidation (FAO) and promote vascular growth [40] (Figure 2c). FAO promotes vascular growth and the disruption of endothelial FAO has been shown to promote endothelial dysfunction through increased oxidative stress [36].

Adipose endothelial cell-derived vesicles and noncoding RNAs modulate adipose tissue biology

In addition to trans-endothelial transport, AdECs are shown to secrete EVs that assist in intercellular communication with adipocytes and other cells from the adipose tissue SVF [31]. It was recently reported that ECs and adipocytes exchange cargo and plasma membrane fragments through secreted EVs expressing caveolin 1 [31]. The secretion of these AdEC-derived EVs is controlled by glucagon, suggesting that AdEC–adipocyte crosstalk is hormonally regulated [31]. EVs represent a diverse subpopulation of released, lipid bilayer-enclosed vesicles [41]. These subpopulations may have different cellular origins and cargo compositions, including bioactive molecules, and noncoding RNAs such as long noncoding RNAs (lncRNAs) and microRNAs (miRNAs). Adipose tissue-derived, EV-encapsulated noncoding RNAs were shown to regulate gene expression in distant organs [42]. Thus, it is likely that AdEC-derived noncoding RNAs participate in the regulation of gene expression in the adipose tissue and in distant organs.

MiR-409-3p, which is upregulated in obese mice, impairs adipose tissue angiogenesis by inhibiting the expression of the transcription factors zinc finger e-box-binding homeobox (ZEB1) and mitogen-activated protein kinase kinase kinase kinase 3 (MAP4K3) (Figure 3). Therefore, inhibiting EC miR-409-3p improves adipose tissue angiogenesis, promotes WAT browning, and ameliorates insulin resistance in DIO [43]. Similarly, AdECs of DIO mice exhibited reduced microRNA 181b (miR-181b) expression [44]. Upon miR-181b delivery, glucose homeostasis and insulin sensitivity in DIO mice improved. The pleckstrin homology domain leukine-rich repeat protein phosphatase isozyme 2 (PHLPP2) [44], a direct target of miR-181b, inactivates protein kinase B (PKB/Akt), an upstream regulator of endothelial nitric oxide synthase (eNOS), which is impaired in the VAT of obese patients [45]. Argonaute 1 (AGO1), a key component of the RNA-induced silencing complex [46], is an essential regulator of the endothelial response to hypoxia. Endothelial cell-specific deficiency of AGO1 renders mice resistant to DIO [47]. Moreover, mice with EC-specific knockout of AGO1 displayed higher vascular density in SAT and BAT [47]. At the molecular level, EC-specific *AGO1* deletion suppresses the expression of thrombospondin-1 (THBS1 (Thrombospondin)/TSP1), a potent angiogenic inhibitor and pro-inflammatory cytokine that promotes insulin resistance and adipose tissue inflammation. Therefore, exploring the down- and upstream regulators of the miRNA complex involved in adipose tissue angiogenesis could help identify potential therapeutic targets in obesity-related disorders.

Figure 3



Endothelial cell-derived noncoding RNAs modulate adipose tissue biology. AdEC-derived noncoding RNAs, particularly miRNAs (miR-409-3p and miR-181b), modulate adipose tissue biology in health and disease. Obesity is associated with the upregulation of miR-409-3p and the suppression of miR-181b. The increase of miR-409-3p downregulates the expression of the pro-angiogenic transcription factors ZEB1 and MAP4K3. Obesity-suppressed miR-181b downregulates the expression of PHLPP2. PHLPP2 inhibits Akt/eNOS signaling. AGO1, one of the key components of the miRNA-induced silencing complex, enhances the expression of THBS1/TSP1, a potent angiogenic inhibitor and pro-inflammatory cytokine.

Conclusions and future directions

Our understanding of the roles and functions of AdECs has grown substantially in recent years. Given that endothelial dysfunction is a hallmark of obesity, several studies have demonstrated that ameliorating endothelial function and promoting neovascularization improves adipose tissue inflammation and promotes metabolic homeostasis [5]. In particular, impaired angiogenic signaling promotes an aging-associated decline in metabolic health [16], highlighting the need for further investigation into the utility of treating metabolic disease by enhancing angiogenesis. Moreover, extensive efforts have been made to compare the functional and transcriptomic cellular components of adipose tissue in both the healthy and diseased states. Despite these efforts, AdEC heterogeneity in different depots, including BAT, requires further investigation. A recent obesity-exercise axis atlas of murine adipose tissue and skeletal muscle reported beneficial effects of exercise on skeletal muscle ECs, whereas such effects on AdECs have not been reported [48]. Another study reported that the impact of obesity on SAT and VAT AdECs at the transcriptomic level could be partially mitigated by diet reversion to standard chow in DIO mice [12]. Therefore, the effect of nonpharmacological lifestyle interventions, such as caloric restriction and exercise, on the transcriptomic and cellular diversity of AdECs, remains to be studied. Moreover, future studies should investigate the effects of such interventions on human AdECs to support the translational potential of these findings.

Furthermore, our understanding of AdEC paracrine communication with other cellular components of the adipose tissue remains limited. It was recently shown that white adipocytes release EVs containing oxidatively damaged mitochondria, which are transferred to neighboring cells, including macrophages [49,50]. In addition to maintaining WAT homeostasis, white adipocyte-derived mitochondria-containing EVs can exert a protective antioxidant response in the heart. To reach the heart, these mitochondria-containing EVs are channeled through the endothelial barrier. The mechanisms governing the endothelial uptake, transport, and disposition of these EVs remain unknown and require further investigation. Notably, thermogenically active brown adipocytes also release mitochondria-containing EVs [51]. Particularly, the uptake of these EVs by BAT-resident macrophages maintains BAT-efficient thermogenesis [51]. It has also been recently shown that ECs may be a major recipient of adipocye-derived mitochondria, particularly in BAT [52]. It remains unknown whether mitochondrial transfer from adipocytes to ECs modulates angiogenesis in white and brown fat. It also remains to be investigated whether this transfer event enables the delivery of adipocyte-derived mitochondria across the endothelial barrier into the general circulation and to distant organs.

It has been previously described that adipose tissue-derived noncoding RNAs modulate adipose tissue and distant organ biology [53]. Despite the characterization of AdEC-derived miRNAs and their contribution to adipose tissue homeostasis, AdEC-expressed lncRNAs have not been thoroughly characterized. A recent human adipose tissue cell-type transcriptomic atlas identified prostate cancer-associated transcript 19 (PCAT19) as an AdEC-enriched lncRNA [54]. PCAT19 was also reported to be enriched in quiescent ECs, and the reduction in its expression in quiescent ECs promotes cellular proliferation and angiogenesis [55]. It is worth noting that lncRNAs have also been shown to modulate adipocyte thermogenesis and adipose tissue expansion [56–58], and it is likely that AdEC-derived lncRNAs play a role in modulating adipose tissue homeostasis. Building upon these exciting findings, further research into AdEC lncRNAs and RNA-based therapies for AdEC functional manipulation is warranted.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which could have appeared to influence the work reported in this paper.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Wolfrum C, Gerhart-Hines Z: **Fueling the fire of adipose thermogenesis**. *Science* 2022, **375**:1229-1231.

2. Börgeson E, Boucher J, Hagberg C: **Of mice and men: pinpointing species differences in adipose tissue biology**. *Front Cell Dev Biol* 2022, **10**:1003118.

3. Elias I, Franckhauser S, Ferré T, Vilà L, Tafuro S, Muñoz S, *et al*.: **Adipose tissue overexpression of vascular endothelial growth factor protects against diet-induced obesity and insulin resistance**. *Diabetes* 2012, **61**:1801-1813.

4. Sung H-K, Doh K-O, Son JE, Park JG, Bae Y, Choi S, *et al*.: **Adipose vascular endothelial growth factor regulates metabolic homeostasis through angiogenesis**. *Cell Metab* 2013, **17**:61-72.

5. Herold J, Kalucka J: **Angiogenesis in adipose tissue: the interplay between adipose and endothelial cells**. *Front Physiol* 2021, **11**:624903.

6. Maniyadath B, Zhang Q, Gupta RK, Mandrup S: **Adipose tissue at single-cell resolution**. *Cell Metab* 2023, **35**:386-413.

7. Massier L, Jalkanen J, Elmastas M, Zhong J, Wang T, Nono Nankam PA, *et al*.: **An integrated single cell and spatial transcriptomic map of human white adipose tissue**. *Nat Commun* 2023, **14**:1438.

8. Kalucka J, de Rooij LP, Goveia J, Rohlenova K, Dumas SJ, Meta E, *et al*.: **Single-cell transcriptome atlas of murine endothelial cells**. *Cell* 2020, **180**:764-779 e20.

9. •• Emont MP, Jacobs C, Essene AL, Pant D, Tenen D, Colleluori G, *et al*.: **A single-cell atlas of human and mouse white adipose tissue**. *Nature* 2022, **603**:926-933.
The authors provide one of the most comprehensive single-cell atlases of human and mouse visceral and subcutaneous adipose tissue in states of health and disease to date. The authors describe vascular endothelial cell subpopulations, their cellular abundance, transcriptomic particularities, and intercellular interactions. The authors demonstrate that obesity alters endothelial cell interactions with other cells belonging to the adipose tissue, including adipocytes and adipocyte progenitors.

10. Barboza CS, Flesher C, Geletka L, Delproposto J, Eichler T, Akinleye O, *et al*.: **Single-nuclei transcriptome of human adipose tissue reveals metabolically distinct depot-specific adipose progenitor subpopulations**. *bioRxiv* 2022, https://www.biorxiv.org/content/10.1101/2022.06.29.496888v.

11. Whytock KL, Sun Y, Divoux A, Yu G, Smith SR, Walsh MJ, *et al*.: **Single cell full-length transcriptome of human subcutaneous adipose tissue reveals unique and heterogeneous cell populations**. *Iscience* 2022, **25**:104772.

12. •• Bondareva O, Rodríguez-Aguilera JR, Oliveira F, Liao L, Rose A, Gupta A, *et al*.: **Single-cell profiling of vascular endothelial cells reveals progressive organ-specific vulnerabilities during obesity**. *Nat Metab* 2022, **4**:1591-1610.
The authors have sequenced the transcriptome of 375 000 ECs from seven organs of lean and obese mice at the single-cell level. The authors demonstrate organ-specific vulnerabilities at progressive stages of obesity. Moreover, the authors demonstrate that AdECs are particularly vulnerable to obesity and that obesity-induced transcriptomic alterations are partially corrected by diet reversion.

13. Crewe C, An YA, Scherer PE: **The ominous triad of adipose tissue dysfunction: inflammation, fibrosis, and impaired angiogenesis**. *J Clin Investig* 2017, **127**:74-82.

14. Seki T, Hosaka K, Lim S, Fischer C, Honek J, Yang Y, *et al*.: **Endothelial PDGF-CC regulates angiogenesis-dependent thermogenesis in beige fat**. *Nat Commun* 2016, **7**:1-16.

15. Seki T, Hosaka K, Fischer C, Lim S, Andersson P, Abe M, *et al*.: **Ablation of endothelial VEGFR1 improves metabolic dysfunction by inducing adipose tissue browning**. *J Exp Med* 2018, **215**:611-626.

16. • Grunewald M, Kumar S, Sharife H, Volinsky E, Gileles-Hillel A, Licht T, *et al*.: **Counteracting age-related VEGF signaling insufficiency promotes healthy aging and extends life span**. *Science* 2021, **373**:6554.
Progressive vascular deterioration is a founding factor of organismal aging. The authors demonstrate that VEGF signaling decreases with aging, at least in part, due to the increased production of sVEGFR1. sVEGFR1 is a decoy receptor that restricts VEGF pro-angiogenic signaling. Importantly, VEGF supplementation, and thus enhanced angiogenesis, was shown to alleviate aging-related metabolic impairment, endothelial cell senescence, and inflammation.

17. An YA, Sun K, Joffin N, Zhang F, Deng Y, Donze O, *et al*.: **Angiopoietin-2 in white adipose tissue improves metabolic homeostasis through enhanced angiogenesis**. *Elife* 2017, **6**:e24071.

18. Vijay J, Gauthier M-F, Biswell RL, Louiselle DA, Johnston JJ, Cheung WA, *et al*.: **Single-cell analysis of human adipose tissue identifies depot-and disease-specific cell types**. *Nat Metab* 2020, **2**:97-109.

19. Harms MJ, Ishibashi J, Wang W, Lim H-W, Goyama S, Sato T, *et al*.: **Prdm16 is required for the maintenance of brown adipocyte identity and function in adult mice**. *Cell Metab* 2014, **19**:593-604.

20. Aranguren XL, Agirre X, Beerens M, Coppiello G, Uriz M, Vandersmissen I, *et al*.: **Unraveling a novel transcription factor code determining the human arterial-specific endothelial cell signature**. *Blood J Am Soc Hematol* 2013, **122**:3982-3992.

21. Min SY, Kady J, Nam M, Rojas-Rodriguez R, Berkenwald A, Kim JH, *et al*.: **Human'brite/beige'adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice**. *Nat Med* 2016, **22**:312-318.

22. Bailin SS, Kropski JA, Gangula RD, Hannah L, Simmons JD, Mashayekhi M, *et al*.: **A single-cell molecular atlas of white adipose tissue shows differences in myeloid and lymphoid cell polarization in type 2 diabetes and HIV infection**. *bioRxiv* 2022, https://www.biorxiv.org/content/10.1101/2022.03.21.484794v2.

23. Piera-Velazquez S, Jimenez SA: **Endothelial to mesenchymal transition: role in physiology and in the pathogenesis of human diseases**. *Physiol Rev* 2019, **99**:1281-1324.

24. Wang F, Ding P, Liang X, Ding X, Brandt CB, Sjöstedt E, *et al*.: **Endothelial cell heterogeneity and microglia regulons revealed by a pig cell landscape at single-cell level**. *Nat Commun* 2022, **13**:1-18.

25. Corvera S, Solivan-Rivera J, Yang Loureiro Z: **Angiogenesis in adipose tissue and obesity**. *Angiogenesis* 2022, **25**:439-453.

26. Hildreth AD, Ma F, Wong YY, Sun R, Pellegrini M, O'Sullivan TE: **Single-cell sequencing of human white adipose tissue identifies new cell states in health and obesity**. *Nat Immunol* 2021, **22**:639-653.

27. Ioannidou A, Alatar S, Schipper R, Baganha F, Åhlander M, Hornell A, *et al*.: **Hypertrophied human adipocyte spheroids as in vitro model of weight gain and adipose tissue dysfunction**. *J Physiol* 2022, **600**:869-883.

28. Sárvári AK, Van Hauwaert EL, Markussen LK, Gammelmark E, Marcher A-B, Ebbesen MF, *et al*.: **Plasticity of epididymal adipose**

tissue in response to diet-induced obesity at single-nucleus resolution. *Cell Metab* 2021, **33**:437-453 e5.

29. Abumrad NA, Cabodevilla AG, Samovski D, Pietka T, Basu D, Goldberg IJ: **Endothelial cell receptors in tissue lipid uptake and metabolism**. *Circ Res* 2021, **128**:433-450.

30. • Fischer AW, Jaeckstein MY, Gottschling K, Heine M, Sass F, Mangels N, *et al*.: **Lysosomal lipoprotein processing in endothelial cells stimulates adipose tissue thermogenic adaptation**. *Cell Metab* 2021, **33**:547-564 e7.

Thermogenic adipocytes internalize large amounts of fatty acids after LPL-mediated hydrolysis of TGRLs in the capillary lumen of brown and white adipose tissue. The authors demonstrate, in cold-exposed mice, that vascular ECs in the adipose tissue endocytose substantial amounts of entire TGRL particles, which determines thermogenic function and browning of the adipose tissue.

31. Crewe C, Joffin N, Rutkowski JM, Kim M, Zhang F, Towler DA, *et al*.: **An endothelial-to-adipocyte extracellular vesicle axis governed by metabolic state**. *Cell* 2018, **175**:695-708 e13.

32. Kanda T, Brown JD, Orasanu G, Vogel S, Gonzalez FJ, Sartoretto J, *et al*.: **PPARγ in the endothelium regulates metabolic responses to high-fat diet in mice**. *J Clin Investig* 2008, **119**:110-124.

33. Gogg S, Nerstedt A, Boren J, Smith U: **Human adipose tissue microvascular endothelial cells secrete PPARγ ligands and regulate adipose tissue lipid uptake**. *JCI Insight* 2019, **4**:e125914.

34. Briot A, Decaunes P, Volat F, Belles C, Coupaye M, Ledoux S, *et al*.: **Senescence alters PPARγ (Peroxisome Proliferator–Activated Receptor Gamma)-dependent fatty acid handling in human adipose tissue microvascular endothelial cells and favors inflammation**. *Arterioscler Thromb Vasc Biol* 2018, **38**:1134-1146.

35. Barinda AJ, Ikeda K, Nugroho DB, Wardhana DA, Sasaki N, Honda S, *et al*.: **Endothelial progeria induces adipose tissue senescence and impairs insulin sensitivity through senescence associated secretory phenotype**. *Nat Commun* 2020, **11**:1-13.

36. Li X, Sun X, Carmeliet P: **Hallmarks of endothelial cell metabolism in health and disease**. *Cell Metab* 2019, **30**:414-433.

37. Bae H, Hong KY, Lee C-K, Jang C, Lee S-J, Choe K, *et al*.: **Angiopoietin-2–integrin α5β1 signaling enhances vascular fatty acid transport and prevents ectopic lipid-induced insulin resistance**. *Nat Commun* 2020, **11**:1-17.

38. Son N-H, Basu D, Samovski D, Pietka TA, Peche VS, Willecke F, *et al*.: **Endothelial cell CD36 optimizes tissue fatty acid uptake**. *J Clin Investig* 2018, **128**:4329-4342.

39. Ibrahim A, Yucel N, Kim B, Arany Z: **Local mitochondrial ATP production regulates endothelial fatty acid uptake and transport**. *Cell Metab* 2020, **32**:309-319 e7.

40. •• Monelli E, Villacampa P, Zabala-Letona A, Martinez-Romero A, Llena J, Beiroa D, *et al*.: **Angiocrine polyamine production regulates adiposity**. *Nat Metab* 2022, **4**:327-343.

The authors demonstrate that *Pten*-deficient mice are resistant to diet-induced weight gain. This phenotype is, at least in part, due to a newly described axis of adipocyte–endothelial cell crosstalk. The authors demonstrate that AdECs produce, via an akt–mTOR pathway, angiocrine polyamines that promote adipocyte lipolysis. Adipocyte-derived FFAs then feed into endothelial cell FAO to sustain endothelial cell proliferation and to promote vascular growth.

41. Théry C, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, *et al*.: **Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines**. *J Extracell Vesicles* 2018, **7**:1535750.

42. Thomou T, Mori MA, Dreyfuss JM, Konishi M, Sakaguchi M, Wolfrum C, *et al*.: **Adipose-derived circulating miRNAs regulate gene expression in other tissues**. *Nature* 2017, **542**:450-455.

43. Becker-Greene D, Li H, Perez-Cremades D, Wu W, Bestepe F, Ozdemir D, *et al*.: **MiR-409-3p targets a MAP4K3-ZEB1-PLGF signaling axis and controls brown adipose tissue angiogenesis and insulin resistance**. *Cell Mol Life Sci* 2021, **78**:7663-7679.

44. Sun X, Lin J, Zhang Y, Kang S, Belkin N, Wara AK, *et al*.: **MicroRNA-181b improves glucose homeostasis and insulin sensitivity by regulating endothelial function in white adipose tissue**. *Circ Res* 2016, **118**:810-821.

45. Karki S, Farb MG, Ngo DT, Myers S, Puri V, Hamburg NM, *et al*.: **Forkhead box O-1 modulation improves endothelial insulin resistance in human obesity**. *Arterioscler Thromb Vasc Biol* 2015, **35**:1498-1506.

46. Bartel DP: **MicroRNAs: target recognition and regulatory functions**. *Cell* 2009, **136**:215-233.

47. Tang X, Miao Y, Luo Y, Sriram K, Qi Z, Lin F-M, *et al*.: **Suppression of endothelial AGO1 promotes adipose tissue browning and improves metabolic dysfunction**. *Circulation* 2020, **142**:365-379.

48. Yang J, Vamvini M, Nigro P, Ho L-L, Galani K, Alvarez M, *et al*.: **Single-cell dissection of the obesity-exercise axis in adipose-muscle tissues implies a critical role for mesenchymal stem cells**. *Cell Metab* 2022, **34**:1578-1593 e6.

49. Crewe C, Funcke J-B, Li S, Joffin N, Gliniak CM, Ghaben AL, *et al*.: **Extracellular vesicle-based interorgan transport of mitochondria from energetically stressed adipocytes**. *Cell Metab* 2021, **33**:1853-1868 e11.

50. Brestoff JR, Wilen CB, Moley JR, Li Y, Zou W, Malvin NP, *et al*.: **Intercellular mitochondria transfer to macrophages regulates white adipose tissue homeostasis and is impaired in obesity**. *Cell Metab* 2021, **33**:270-282 e8.

51. Rosina M, Ceci V, Turchi R, Chuan L, Borcherding N, Sciarretta F, *et al*.: **Ejection of damaged mitochondria and their removal by macrophages ensure efficient thermogenesis in brown adipose tissue**. *Cell Metab* 2022, **34**:533-548 e12.

52. • Borcherding N, Jia W, Giwa R, Field RL, Moley JR, Kopecky BJ, *et al*.: **Dietary lipids inhibit mitochondria transfer to macrophages to divert adipocyte-derived mitochondria into the blood**. *Cell Metab* 2022, **34**:1499-1513 e8.

Intercellular mitochondrial transfer occurs between adipocytes and adipose tissue-resident cells. The authors demonstrate that ECs represent a major recipient of adipocyte-derived mitochondria, particularly in BAT. This axis of organellar transfer between adipocytes and ECs is dysregulated in aging and DIO.

53. Ji C, Guo X: **The clinical potential of circulating microRNAs in obesity**. *Nat Rev Endocrinol* 2019, **15**:731-743.

54. Norreen-Thorsen M, Struck EC, Öling S, Zwahlen M, Von Feilitzen K, Odeberg J, *et al*.: **A human adipose tissue cell-type transcriptome atlas**. *Cell Rep* 2022, **40**:111046.

55. Oo JA, Pálfi K, Warwick T, Wittig I, Prieto-Garcia C, Matkovic V, *et al*.: **Long non-coding RNA PCAT19 safeguards DNA in quiescent endothelial cells by preventing uncontrolled phosphorylation of RPA2**. *Cell Rep* 2022, **41**:111670.

56. Pradas-Juni M, Hansmeier NR, Link JC, Schmidt E, Larsen BD, Klemm P, *et al*.: **A MAFG-lncRNA axis links systemic nutrient abundance to hepatic glucose metabolism**. *Nat Commun* 2020, **11**:1-17.

57. Schmidt E, Dhaouadi I, Gaziano I, Oliverio M, Klemm P, Awazawa M, *et al*.: **LincRNA H19 protects from dietary obesity by constraining expression of monoallelic genes in brown fat**. *Nat Commun* 2018, **9**:1-16.

58. Tran K-V, Brown EL, DeSouza T, Jespersen NZ, Nandrup-Bus C, Yang Q, *et al*.: **Human thermogenic adipocyte regulation by the long noncoding RNA LINC00473**. *Nat Metab* 2020, **2**:397-412.