

Review

Adipocyte-Derived Extracellular Vesicles: Small Vesicles with Big Impact

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Abstract

While increasing numbers of studies have established that adipose tissue plays a vital role in balancing energy intake and energy expenditure as both an energy and an endocrine organ, the detailed functions of adipose tissue remain unclear. Adipose tissues are complex, with multiple resident cell populations that communicate to diverse cells and organs via local and systemic metabolic, thermal, and inflammatory signaling. In normal physiology, adipose tissue-derived extracellular vesicles mediate the regulation of energy storage/consumption in adipose tissue, liver, and muscle. In a pathological sense, fat-derived extracellular vesicles can promote the progression of obesity, endocrine diseases, cancer, and reproductive system disorders. In this review, we demonstrate that adipocyte-derived extracellular vesicles function not only in physiological balance but also in the pathological process. We aim to illustrate the impact of adipocyte-derived extracellular vesicles and their value in understanding both homeostasis and disorders.

Keywords: adipose; extracellular vesicles; insulin resistance; obesity; endocrine

1. Background

Obesity is a significant health problem worldwide as it is currently viewed as a major driving factor in circulation disorders [1,2], insulin resistance, metabolic syndrome [3], and even some malignancies such as liver and breast cancer [4]. Adipose tissue is an endocrine organ with high metabolic activity [5]. With a better appreciation of adipose tissue comes an increased understanding of adipose tissue-secreted adipokines and lipoxins, as well as peptides and extracellular vesicles with biological activity [6]. By delivering encapsulated cargos, extracellular vesicles mediate communication between diverse cell, tissue, and organ types [7]. Extracellular vesicles derived from adipose tissues have been studied by several groups in recent years; however, the function of adipose tissue-derived extracellular vesicles, as well as the detailed mechanisms they control, remain unclear. In the present review, we explore these relationships, focusing on some of the newest studies that link adipose tissue-derived extracellular vesicles to both normal physiological balance and pathological processes.

2. Adipose Tissue

2.1 Composition of Adipose Tissues

Adipose tissue can be classified into three major types: (i) white adipose tissue [8] (WAT); (ii) brown adipose tis-

sue [9] (BAT); and (iii) beige adipose tissue [10]. In general, white adipose tissue represents more than 95% of adipose tissue mass, while brown adipose tissue represents just 1% to 2% of total adipose mass [11]. Beige adipose tissue, which is not clearly quantifiable, is able to switch into brown-like adipocyte tissue under cold exposure or adrenergic stimulation.

2.2 White and Brown Adipose Tissues

Over the past 20 years, it has become well-acknowledged that homeostasis depends not only on a balance between energy intake [12] and consumption [13] but also depends on a balance between white fat, the primary site of energy storage, and brown adipose tissue, the site for energy consumption. In general, white adipose tissue is the most variable and dynamic tissue in the human body. The percentage of white adipose tissue ranges from less than 10% to more than 65% of body weight [14]. Adipocyte hypertrophy through lipid accumulation [15], in addition to adipocyte hyperplasia through preadipocyte proliferation, leads to the increase of fat mass in obesity. Numerous studies report that the total number of fat cells is established during childhood and remains in balance into adulthood [16]. For example, Zhou *et al.* [6] reported that adipocyte-derived extracellular vesicles contribute to both the menstrual cycle and fertilization. However, overfeeding



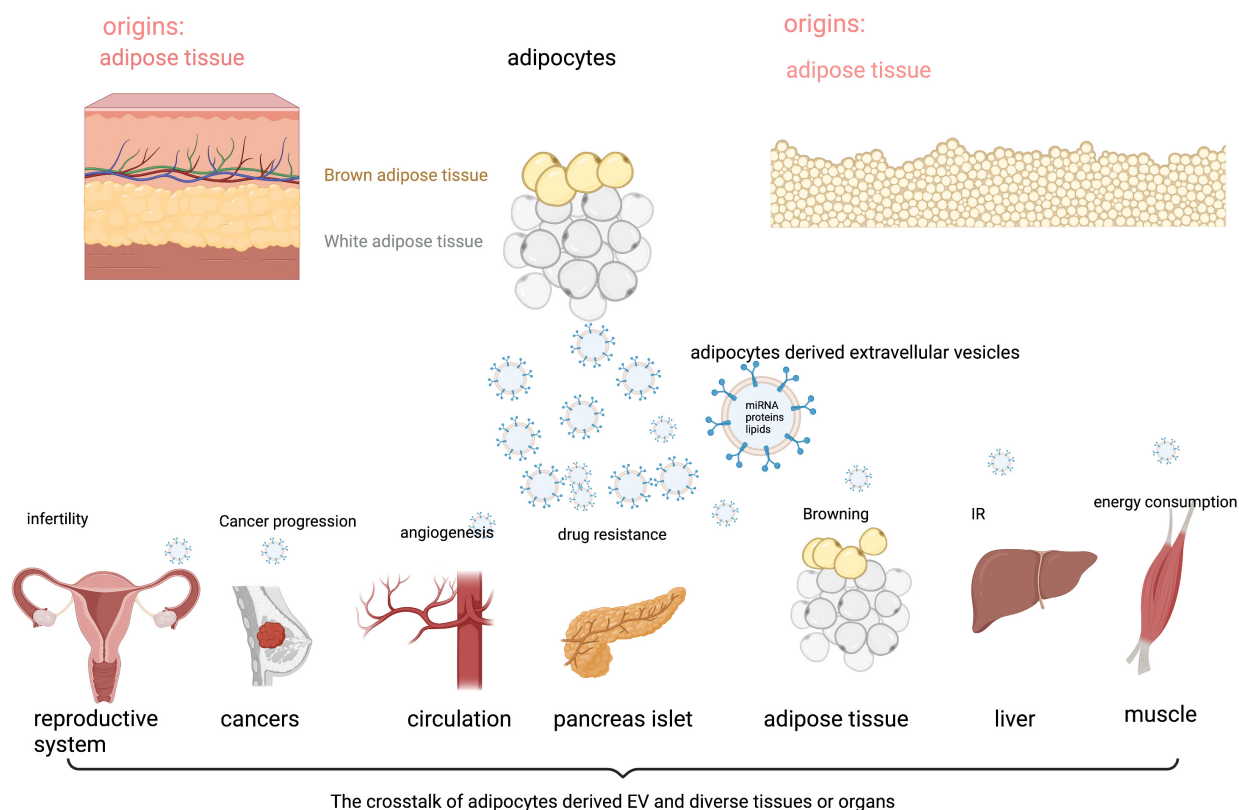


Fig. 1. Schematic diagram showing the genesis and targets of extracellular vesicles derived from adipocytes. EV, extracellular vesicles; IR, insulin resistance.

or other non-healthy lifestyles might induce an increase in white adipose tissue [17]. White adipocytes contain a large unilocular lipid droplet in the cytoplasm for the storage of energy [18]. In contrast, brown [18] and beige adipocytes contain multilocular droplets and high mitochondrial density for the consumption of energy [19], which can inhibit the development of obesity.

2.3 Adipose Tissue and Endocrine Regulation

Recently, several studies reported that adipose tissue, beyond its role as an energy storage organ, also functions as an endocrine organ [20]. Adipose tissues secrete a variety of adipokines, including leptin [21] and adiponectin [22]. Leptin [23] is a 16 kDa protein produced by white adipocytes and binds to leptin receptors in the hypothalamus resulting in the inhibition of feeding behavior. Adiponectin [24] is a 30 kDa protein produced in both white and brown adipocytes and is associated with insulin resistance as adiponectin levels increase in patients with severe insulin resistance due to anti-insulin receptor antibodies or insulin receptor mutations. In addition to leptin and adiponectin, adipose tissue also produces numerous hormones that regulate insulin balance and metabolic homeostasis.

3. Extracellular Vesicles

Extracellular vehicles (EVs) are small, membrane-bound vesicular structures derived from diverse cell types [25] and include exosomes, macrovesicles (MVs), and apoptotic bodies. EVs are released during cell activation, senescence, or programmed cell death, including apoptosis, necroptosis, and pyroptosis.

Extracellular vesicles can deliver cargos, including miRNAs, long non-coding RNAs, proteins, DNA fragments, lipids, and mRNAs, from producing cells to recipient cells/tissues [26]. Recently, increasing numbers of studies have focused on the emerging roles of adipocyte-derived extracellular vesicles in regulating obesity and metabolic homeostasis [27]. Extracellular vesicles have historically been viewed as conveyors of cellular waste; however, increasing evidence indicates that extracellular vesicles can, in addition to cargo delivery, convey information between diverse cells and tissues [28]. Extracellular vesicles derived from cancer cells, or cancer-associated cells, can mediate cancer progression [28,29], wound healing [30], and macrophage polarization. Extracellular vesicles derived from a primary site could dictate cell behavior at distant sites, including immunosuppression. Furthermore, extracellular vesicles have been viewed as potential disease biomarker candidates [31], as well as potential therapeutic carriers for drug delivery [32].

4. Extracellular Vesicles and Functions

4.1 Adipose Tissue Extracellular Vesicles and Physiological Balance

Adipose tissue can secrete extracellular vesicles into the microenvironment and circulation, resulting in disbursement throughout the body. As depicted in Fig. 1, adipose tissue-derived extracellular vesicles play important roles in regulating energy consumption, circulation homeostasis, and metabolic balance.

4.1.1 Adipose Tissue-Extracellular Vesicles and Energy Consumption

Considering that adipose tissue represents the largest energy storage and secretory organ in the human body, adipose tissue-derived extracellular vesicles play important roles in regulating energy consumption by communicating with adipose tissue, liver [33], and skeletal muscle cells [34]. As adipose tissues contain diverse types of cells, the crosstalk between extracellular vesicles and adipose tissue depends on cell heterogeneity within adipose tissue [35]. Adipose tissue-extracellular vesicles derived from obese mice can promote the activation of adipose tissue macrophages. This, in turn, can lead to increased expression of pro-inflammatory cytokines, which further promote the development of insulin resistance. The adipocyte-derived extracellular vesicle miRNA-34a was reported to inhibit M2 macrophage polarization [36] and subsequent induction of fat-associated inflammation [37]. Furthermore, adipose tissue macrophage-derived extracellular vesicles contain diverse miRNA species that can mediate metabolic homeostasis through interplay with adipocytes, hepatocytes, and skeletal muscle cells [38]. For example, EVs released by brown adipose tissue (BAT) containing miR-99b can target Fgf21 in the liver, and EVs released by brown adipose tissue containing miR-92a are a potential biomarker for BAT [39].

4.1.2 Adipose Tissue-Extracellular Vesicles and Circulation

Extracellular vesicles derived from adipose tissue are tightly associated with vascular health and circulatory balance. In general, adipose tissue-derived extracellular vesicles can influence the regulation of vascular homeostasis through neovascularization and angiogenesis. Human adipose stem cell (ADSC)-derived extracellular vesicles are rich in miRNA-125a and miRNA-31, which can be transferred to vascular endothelial cells to stimulate proliferation and promote angiogenesis [40]. ADSC-derived extracellular vesicles can induce vascular endothelial cell migration and vascular endothelial cell proliferation [41] and mediate neo-vessel formation. Previous reports indicated that extracellular vesicles released by adipocytes express high levels of glycosylphosphatidylinositol (GPI)-anchored proteins [22] and CD73 [42]. These proteins are viewed as mediators of triacylglycerol esterification as well as

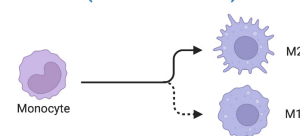
lipolysis—both processes involved in vascular health. In addition, other studies reported that adipocyte-derived extracellular vesicles could carry various miRNAs, including miR-221 [43], miR-26 [6], and miR-143 to regulate cell proliferation and apoptosis, as well as to mediate inflammation and control angiogenesis in vascular tissues. Recent studies indicate that extracellular vesicles can transport mitochondria from energetically stressed adipocytes to protect cardiomyocytes from acute oxidative stress by inhibiting the release of Reactive Oxygen Species (ROS) production [44]. Adipocytes can also release extracellular vesicles during mitochondrial stress, and these adipocyte EVs would promote protection from ischemic stresses that result from obesity.

4.1.3 Adipose Tissue-Extracellular Vesicles and Endocrine Regulation

The endocrine function of adipose tissue is partially mediated by adipose tissue-derived extracellular vesicles by affecting various aspects of metabolic homeostasis, including insulin signaling, lipolysis [45], and inflammation. Increasing evidence has shown that the composition of adipose-derived extracellular vesicles fluctuates during microenvironmental changes. For example, when the proteomic profiles of adipocyte-derived extracellular vesicles from obese diabetic rats and obese non-diabetic rats are analyzed, different results are obtained. Levels of caveolin 1, lipoprotein lipase, and aquaporin 7 were significantly higher in exosomes and cells of Otsuka Long-Evans Tokushima Fatty (OLETF) rats than in those of Long-Evans Tokushima Otsuka (LETO) rats. In contrast, AK2, catalase, and liver carboxylesterase were expressed at lower levels in OLETF rats when compared to LETO rats [46]. Brown adipose tissue (BAT) generates heat during adaptive thermogenesis in response to cold temperatures and in profound hypothyroidism [47]. Circulating TGF- β 1 might be available to monitor type 2 diabetes status in obese patients, and EV may be useful to track adiposity [48], according to studies that qualitatively and quantitatively characterized EV subpopulations secreted by fat cells, large extracellular vesicles (IEVs) were found to possess high levels of externalized phosphatidylserine. Exposure to a chronic low-grade inflammation state associated with obesity could increase the secretion of IEVs and small EVs (sEVs) [49]. In obesity, adipose tissue and placenta-derived EVs are related to the development of gestational diabetes mellitus (GDM) [50]. Extracellular vesicles derived from the obese diabetic group expressed high levels of proteins and enzymes involved in lipolysis and glycerol export, which can lead to the subsequent development of insulin resistance. Moreover, it was reported that adipocyte-derived extracellular vesicles could mediate the survival and function of pancreatic β cells [51], and adipocytes and macrophages within adipose tissue use exosomes to interact with each other to maintain metabolic homeostasis (Fig. 1).

metabolic functions:
energy expenditure
insulin sensitive (miR-3075)

other functions:
inhibit M2 polarization (miRNA-34a)



Disorders:

Adipocyte derived extracellular vesicles in physiological processes and pathological processes

Lipogenic enhancement (miR-132-3p)
adipocyte metabolism (LncRNA-ADIPINT)
NASH (CD36)



Diabetes (TSP5)



Insulin resistance (miR-27a)



vascular diseases:
Atherosclerosis development
(High fat diet visceral ATEV)

macrophage foam cell formation
(promot inflammation)

Cancer progression

Hepatocellular carcinoma (circRNA-DB)



Breast cancer (promoting EMT)



infertility (miR-26b)



Fig. 2. Overview of adipose-derived extracellular vesicles in health and disease.

4.2 Adipose Tissue-Extracellular Vesicles and Pathological Process

Increasing evidence has demonstrated that adipose tissue can secrete diverse types of extracellular vesicles that contain numerous cargos and hormone-like functions into the microenvironment and circulation. These EVs can, in turn, communicate with cells or tissues to regulate metabolic homeostasis and energy balance. When these system balances are disturbed, adipose tissue-derived extracellular vesicles could participate in pathophysiological processes such as obesity development, metabolic syndrome, cancer progression, and other diverse disease types.

4.2.1 Adipose Tissue-Derived Extracellular Vesicles and Metabolic Diseases

It has been demonstrated that adipose tissue-extracellular vesicles contribute to diabetes, nonalcoholic fatty liver disease, and insulin resistance-related cardiovascular disease. For example, adipocyte-derived extracellular vesicles may mediate crosstalk between adipose tissue and insulin-sensitive organs such as the liver and skeletal muscle. A consensus view has developed that adipose tissue-derived extracellular vesicles are linked to insulin resistance. Studies have reported that adipocyte-derived extracellular vesicles containing miR-27a may induce insulin resistance in skeletal muscle by suppressing PPAR γ expression [52]. It has also been reported that adipose tissue-derived extracellular vesicles can mediate insulin resistance by inducing adipose tissue

macrophage polarization [38]. Additionally, microRNA-34a in adipocyte-secreted extracellular vesicles inhibits M2 macrophage polarization and promotes obesity-induced adipose inflammation. It was also discovered that adipose tissue macrophage-derived extracellular vesicles contain miRNAs that can regulate insulin sensitivity [36]. Furthermore, extracellular vesicles derived from adipocytes undergoing hypoxic stress can inhibit the uptake of 2-deoxyglucose in adipocytes, indicating that hypoxic adipocytes can control hypoxic status through extracellular vesicles [53]. Other studies have reported that a high-fat diet can reduce the expression of AMPK- α 1, a critical molecule that regulates extracellular vesicle synthesis, content, and shedding in white adipose tissues. AMPK α 1 deficiency promoted CD36 sorting into extracellular vesicles. CD36 is responsible for nonalcoholic fatty liver disease (NASH), and CD36 silencing has been found to attenuate lipid accumulation in liver tissue. While CD36 silencing did not affect extracellular vesicle secretion, extracellular vesicle internalization by hepatocytes, as well as hepatocyte damage, was significantly mitigated [5]. Adipose tissue-extracellular vesicles are also linked to the development of diabetes. ADSC-derived extracellular vesicles can activate M2 macrophage polarization and reduce inflammation in white adipose tissue (WAT) of diet-induced obese mice [54]. Further, adipose tissue-derived-extracellular vesicles are associated with cardiovascular disease. A significant increase in extracellular vesicle-associated gene expression is significantly

associated with cardiac fibrosis and implicating these vesicles as a likely adipose-to-cardiac paracrine signaling mechanism [55]. Human adipose tissue-derived extracellular vesicles help form a reciprocal pro-inflammatory signaling loop between adipocytes and macrophages, and this signaling has the potential to aggravate local and systemic insulin resistance [56]. Adipocyte-derived exosomes are linked to lipid metabolism and obesity-related insulin resistance, and exosomes secreted by adipose stromal cells are involved in angiogenesis as well as immunomodulation [57,58]. In addition, atrophied adipocytes shed EVs that promote macrophage inflammation by stimulating IL-6 and TNF α expression [59]. Brown adipose tissue (BAT) was also reported to contribute to metabolic disorders as BAT-derived extracellular vesicle miR-132-3p suppresses hepatic Srebf1 expression and thereby attenuates the expression of lipogenic genes [60]. Similarly, long non-coding RNAs, such as lncRNA-ADIPINT, were reported to regulate human adipocyte metabolism through pyruvate carboxylase [61] (Fig. 2).

4.2.2 Adipose Tissue-Extracellular Vesicles and Vascular Diseases

Obesity is causally associated with atherosclerosis, and adipose tissue-derived extracellular vesicles may be implicated in metabolic complications of obesity beyond their role in regulating whole-body energy metabolism through its storage function in white adipocytes and its energy dissipating function in brown and beige adipocytes. High-fat diet visceral adipose tissue-derived extracellular vesicles could significantly induce M1 phenotype transition and pro-inflammatory cytokines such as tumor necrosis factor α and interleukin 6 secretion. These are markers of macrophage foam cell formation and polarization, as well as the subsequent atherosclerosis development [62]. Additionally, others have reported that endothelial cells could transfer Caveolin1-containing EVs to adipocytes *in vivo*, which reciprocate by releasing EVs to target endothelial cells. Adipose tissue-derived EVs contain proteins and lipids capable of modulating numerous cellular signaling pathways [63], suggesting that EVs could participate in tissue response to changes in systemic nutrient state (Fig. 2).

4.2.3 Adipose Tissue-Derived Extracellular Vesicles and Cancer

It is acknowledged that obesity is associated with some malignancies, such as liver and breast cancer. Adipocytes within the cancer microenvironment not only surround the tumor but also communicate with cancer cells through both local and systemic effects [64]. Increasing evidence indicates that extracellular vesicles derived from adipose tissue function in the growth and migration of liver, ovarian, breast, and other cancer types. Communication between adipocytes and cancer cells can occur directly through the microenvironment or systemically through EV-

mediated cell-to-cell communication [65]. Adipose tissue-derived extracellular vesicle circRNA-DB (circular RNA related to deubiquitylation) can promote the growth of hepatocellular carcinoma by suppressing miR-34a and activating the USP7/Cyclin A2 signaling pathway [66]. Extracellular vesicles derived from human adipose tissue can promote the migration of breast cancer through epithelial-mesenchymal transition (EMT) signaling [67]. Furthermore, breast cancer-derived extracellular vesicles induce adipose tissue-derived mesenchymal stem cells to adopt a tumor-associated myofibroblast phenotype with high levels of α -SMA expression [68]. Some studies reported that extracellular vesicles collected from multiple myeloma patient adipocytes could protect multiple myeloma cells from chemotherapy-induced apoptosis by enhancing METTL7A activity. Recently, studies determined that adipocyte-derived extracellular vesicles might induce breast cancer progression in patients with type 2 diabetes by regulating the EMT. This suggests that extracellular vesicles can mediate crosstalk between metabolically abnormal adipose tissues and breast cancer to promote tumor progression in type 2 diabetes patients. Transcription of targeted genes was further increased in cells exposed to exosomes shed from type 2 diabetes patient-derived adipocytes or insulin-resistant adipocytes, and these events required the epigenetic reader proteins BRD2 and BRD4 within the recipient cells. The thrombospondin family protein TSP5, which is associated with cancer, was more abundant in exosomes from type 2 diabetes or insulin-resistant adipocytes and partially contributed to EMT activation in recipient cells [67] (Fig. 2).

4.2.4 Adipose Tissue-Derived Extracellular Vesicles and Infertility

Infertility has drawn the attention of many doctors and scientists as increased infertility affects more than 10 percent of reproductive-age couples. It was reported that obesity is associated with dysregulation of the reproductive system, not only through polycystic ovary syndrome and paramenia but also asthenospermia. It has been demonstrated that a high-fat diet can enhance the expression of phosphatidylcholine in extracellular vesicle-derived adipose tissue [69], and adipose tissue-derived extracellular vesicles can lead to insulin resistance and polycystic ovary syndrome [25]. Hepatocyte-derived extracellular vesicles from early-onset obese mice promote insulin sensitivity through miR-3075. Additionally, a previous study from our group showed that extracellular vesicles derived from adipocytes could deliver encapsulated miR-26b into cumulus cells and promote their apoptosis. This had the effect of further inducing ovulation failure and subsequent polycystic ovary syndrome [32]. Mechanistically, increasing findings suggest that adipose tissue-derived extracellular vesicle-mediated insulin resistance may be a prominent reason for subsequent infertility.

Table 1. The effect of adipose tissue-derived EV on various pathologies.

Disorders	EV or EV-related cargoes
Metabolic disorders:	
a. Insulin resistance	EV miR-27a
b. Diabetes	EV-TSP5
c. NASH	EV-CD36
Vascular disorders:	
d. Atherosclerosis	High-fat diet AT-EV
e. Macrophage foam cell formation	Pro-inflammation EV
Cancer progression:	
f. Hepatoma carcinoma cell	EV circRNA-DB
g. Breast cancer progression	Promoting EMT EV
Other disorders:	
h. Infertility	miR-26b

NASH, non-alcoholic fatty liver disease; AT, adipose tissues; EV, extracellular Vesicles; EMT, epithelial-mesenchymal transition.

5. Summary and Perspectives

Herein, we reviewed the literature concerning adipose tissue-derived extracellular vesicles and their function in maintaining physiological balance as well as promoting pathophysiological processes (Table 1). Adipose tissue function not only in energy storage but also play a prominent role in endocrine function through extracellular vesicle activity. EVs may influence energy consumption in adipose tissues, liver, and muscle, and through insulin sensitivity, circulation, and effects on the reproductive system. Although various functions of adipose tissue-derived extracellular vesicles have been reported, more studies are required to fully understand the underlying mechanisms and signaling pathways that control response to these response mediators. It is well acknowledged that adipose tissue-derived extracellular vesicles are of significance and act as small vesicles with a big impact.

Author Contributions

YL: Substantial contributions to the conception of the manuscript, and literature research, manuscript writing, as well as reviewing. XT: Analysis of data, interpretation of data and manuscript polishing. YG: Analysis of data, drafting the figures and reviewing the manuscript. GZ: Design of the conception, interpretation of data, drafting the manuscript and final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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