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REVIEW

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Role of micro-RNAs associated with adipose-derived extracellular vesicles in metabolic disorders

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Summary

Micro-RNAs have emerged as important actors in the onset of metabolic disorders including obesity or type 2 diabetes. Particularly, several micro-RNAs are known to be key modulators of lipid metabolism, glucose homeostasis, or feeding behavior. Interestingly, the role of extracellular vesicles containing micro-RNAs, especially adipose-derived extracellular vesicles, are well-documented endocrine signals and disease biomarkers. However, the role of adipose-derived extracellular vesicles on the different tissues is different and highly related to the micro-RNA content. This review provides recent data about the potential involvement of adipose-derived extracellular vesicle-containing micro-RNAs in metabolic diseases.

KEYWORDS
adipose tissue, extracellular vesicles, metabolic syndrome, micro-RNAs

1 | INTRODUCTION

Since the first observation by Wolf in 1967,[1] the interest for extracellular vesicles (EVs) has widely increased. For a long time, they were only considered as extracellular debris but nowadays they are characterized as vectors of biological information in intercellular communication. Indeed, their capacity to contain proteins, lipids, and nucleic acids allows them to be considered as vectors of biological information.[2] Among the biological signals, it has been shown that micro-RNAs (miRNAs) are loaded into various EVs that convey miRNAs from their donor cells to the target cells in order to regulate gene expression.[3] Interestingly, intercellular communication via EV-associated miRNAs is dysregulated in some pathologies such as metabolic disorders involving various tissues including liver or adipose tissue (AT).[4–7]

In the present review, we have focused our attention on the functions of adipose tissue EV (ADEV)-derived miRNAs in different aspects of metabolic disorders such as type 2 diabetes (T2D) and obesity.

2 | EVS

2.1 | Generalities on EVs

EVs are spherical particles constituted by a phospholipid bilayer released by cells constitutively or after stimulation. It appears that every cell type can release EVs and this process has been highly conserved across the evolution from prokaryotes to eukaryotes.[8] Based on their origin and size, the International Society of Extracellular Vesicles (ISEV) classically divides those EVs into two groups, including exosomes (50–150 nm) mostly generated by endosomal compartment and microvesicles (150 nm to 1 μm) that come from the plasma membrane. To distinguish both EVs subtypes, the ISEV recommended using pragmatic

Abbreviations: ADEVs, adipose tissue extracellular vesicles; AT, adipose tissue; DIO, diet-induced obese; EVs, extracellular vesicles; HFD, high-fat diet; IR, insulin resistance; lEVs, large extracellular vesicles; miRNAs, micro-RNAs; MS, metabolic syndrome; sEVs, small extracellular vesicles; T2D, type 2 diabetes.

measurable characteristics such as size to separate both small (sEVs) and large EVs (lEVs), respectively, corresponding to exosomes and microvesicles. Furthermore, ISEV emphasizes the differences in the composition and content of EVs that could help in categorizing them.[9] Indeed, the EVs transport biological material including lipids, proteins, and nucleic acids and are involved in the communication between cells. The circulation of EVs is allowed by many biological fluids including blood, urine, cerebrospinal fluid, and sperm.[10–12]

2.2 | Biogenesis

2.2.1 | sEVs

The sEVs were first identified by Trams et al in 1981 who observed vesicles secreted in an extracellular environment by different cell lines in culture.[13] Those vesicles maintained a 5′nucleotidase activity out of their donor cell and were distinguished from cell debris. The endosomal origin of cells has been confirmed by observation of vesicles from the reticulocytes of sheep by electronic microscopy.[14] The endosomal system is a dynamic network of compartments involved in various functions from recycling elements of the plasma membrane to signalization.[15] The sEVs are generated into intraluminal vesicles (ILVs) within late endosomes, which are also called multivesicular bodies (MVB). More precisely, their biogenesis involves two steps. First, early endosomes originate from regulated or constitutive endocytosis of the plasma membrane. In the second step, ILVs emerge from membrane invagination of early endosomes consequently called MVB. This last step begins either independently through membrane micro-domains or with the interaction of the Endosomal Sorting Complex Required for Transport (ESCRT) with the endosomal membrane with its four subunits ESCRT-0, I, II, and III.[16,17] Then, the MVB will either follow lysosomal pathway or interact with the plasma membrane through cytoskeleton to release ILVs, which are then called sEVs (Figure 1). This secretion is constitutive but could also be activated by calcium-dependent mechanisms.[18]

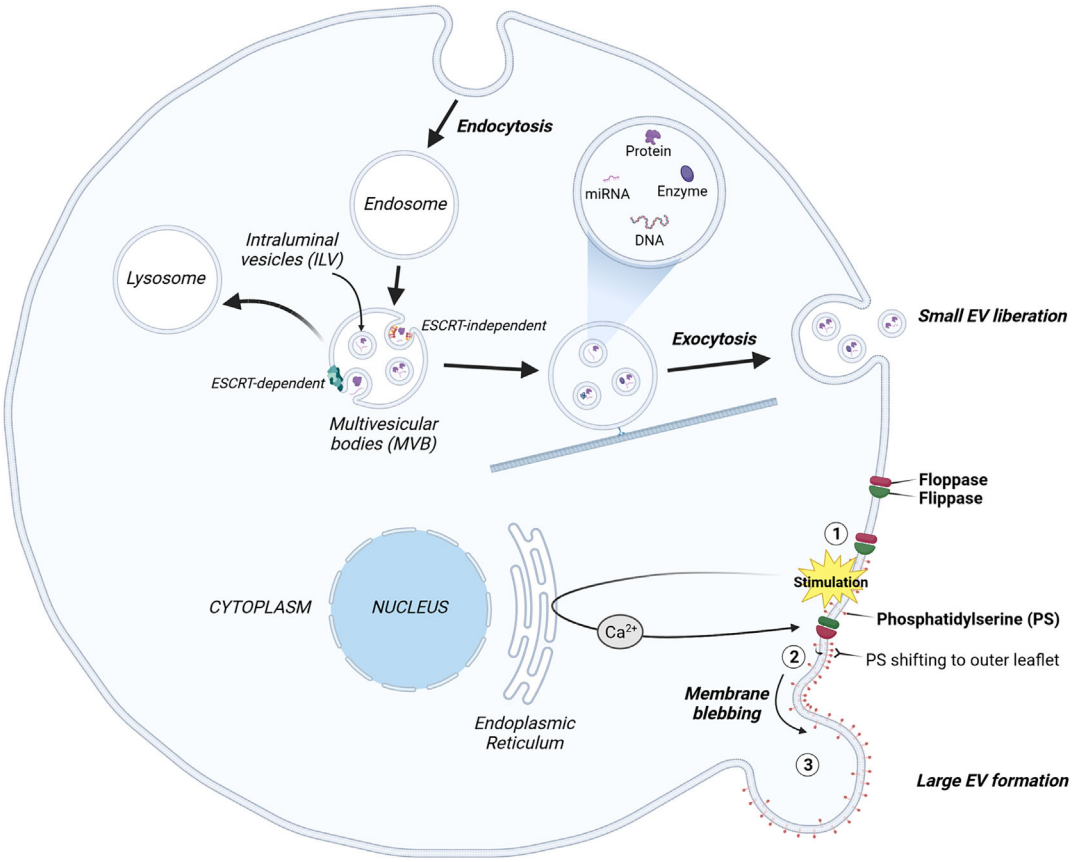

FIGURE 1 Biosynthesis of small (sEVs) and large EVs (lEVs). The sEVs are generated into intraluminal vesicles (ILV) within late endosomes and then they are called multivesicular bodies (MVB). More precisely, exosome biogenesis involves two steps. First, early endosomes originate from regulated or constitutive endocytosis of the plasma membrane. In the second step, ILVs emerge from membrane invagination of early endosomes consequently called MVB. This last step begins either independently through membrane micro-domains or with the interaction of the Endosomal Sorting Complex Required for Transport (ESCRT) with the endosomal membrane. The biogenesis of lEVs occurs only at the plasma membrane (PM). In the first step, the asymmetry of PM is maintained by enzymes like flippase or floppase (1). After stimulation of PM, some lipids like phosphatidylserine (PS) are shifted to the outer leaflet of PM and allow a little curvature of PM (2). Finally, actin network is used for the blebbing of the vesicle and the release of lEVs in the extracellular space (3).

2.2.2 | lEVs

The lEVs are produced by the blebbing of the plasma membrane with a size range between 150 nm and 1 μm (Figure 1).[19] The formation of lEVs is calcium-dependent and requires the loss of the stability of the membrane bilayer and a reorganization of the cytoskeleton. In basal conditions, the membrane stability is maintained by an asymmetric distribution of phospholipid between the two layers of the membrane with an outer membranous layer enriched in phosphatidylcholine (PC) and sphingomyelin and the inner membranous layer enriched in phosphatidylserine (PS) and phosphatidylethanolamine (PE) (Figure 1). This lipid repartition is allowed by an active process involving transporters controlling internal (flip) and external (flop) translocation of the lipids within the bilayer membrane (Figure 1). Those transporters include flippases, floppases, and scramblases. The flippases maintain the membranous asymmetry by transporting PS from the outer layer to the inner layer. In the opposite way, floppase transport actively and specifically PS from the inner layer to the outer layer. Finally, scramblase transports non-specifically lipids between the two layers (Figure 1).

After membrane stimulation by different signals as inflammation, calcium influx inhibits flippase and activates floppase and scramblase. This process results in a loss of membrane asymmetry and an accumulation of PS and PE on the outer layer allowing a positive curvature of the membrane and lEVs biogenesis.[19] In addition, calcium influx activates calpain and gelsolin, enzymes involved in cytoskeleton disruption that led to the release of the lEVs.[20]

2.3 | Adipose tissue-derived EVs

The AT including adipocytes can release both EV subtypes.[21,22] It is interesting to notice that the adipocyte-derived EVs constitute a small proportion of the total EVs in the circulation[23]; nevertheless, they can modulate the metabolism of various tissues involved in energy homeostasis.[7] Interestingly, it has been shown that ADEVs transported adipocyte markers such as adiponectin or fatty acid (FA) binding protein (Fabp4/aP2) and their expression differed in both EV subtypes based on metabolic state.[21,24] Indeed, it was observed that ADEVs from diet-induced obese (DIO) mice expressed more protein involved in FA transport, lipogenesis, and inflammation.[24] It has also been shown that ADEVs modulated macrophage polarization and adipocytes insulin sensitivity through cytokines.[25,26] They also conveyed neutral lipids to target cells in order to modulate their metabolism[27] but also carried miRNAs that target insulin signaling in pancreatic β-cells.[24,28]

3 | INTERACTION WITH TARGET CELL AND CONTENT OF EVS

3.1 | Interaction with target cells

After release, EVs interact with target cells by means of the proteins and lipids expressed at the membrane surface. This process involves integrins, tetraspanins, lactadherins, and membrane phospholipids such as PS.[29–32] These molecules are essential since the expression profile of integrin on the vesicle is correlated with its tissue organotropism.[29] Then, each EV exhibits a specific membrane signature, allowing it to interact with a specific target cell.[33] However, as demonstrated by Morelli et al, EV internalization is a necessary step for the transmission of information,[30] which was confirmed by other studies indicating that the internalized vesicles were localized in the endosomal compartment.[30,33,34] Despite studies highlighting passive mechanisms for the EVs to enter the target cell,[35–37] active mechanisms, like pinocytosis, remain the most described and accepted.[33,38] Particularly, the use of cytoskeleton inhibitors reduced vesicle uptake which is strongly in accordance with this hypothesis.[30] In addition, vesicles were also found completely intact after internalization and

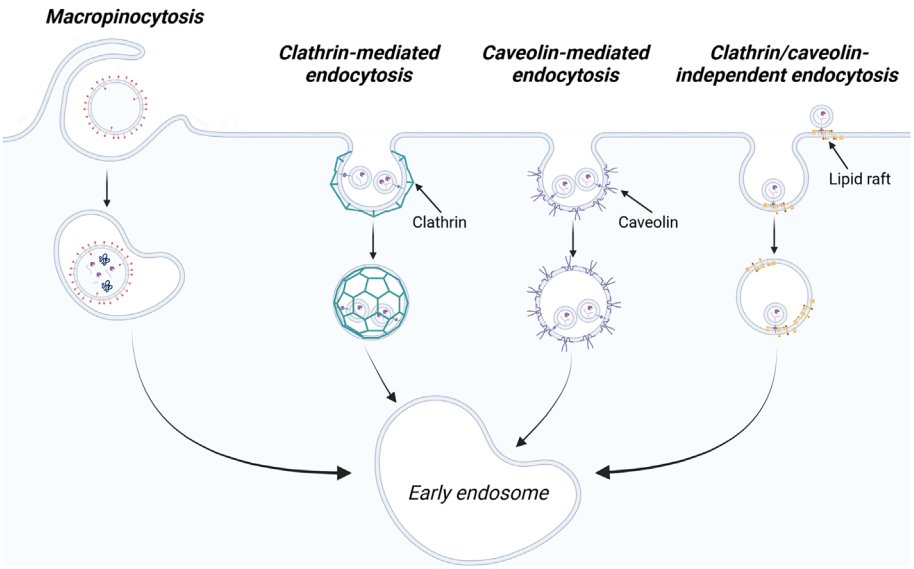

FIGURE 2 Interaction of EVs with target cells. EVs can interact with target cells with clathrin/caveolin-independent mechanisms, clathrin-mediated, or caveolin-mediated endocytosis or through macropinocytosis.

colocalized with endosomes suggesting the importance of endocytosis mechanisms.[34,39]

Pinocytosis includes two different mechanisms named micropinocytosis and macropinocytosis (Figure 2). The micropinocytosis can be subdivided into clathrin-mediated, caveolin-mediated, and clathrin/caveolin-independent endocytosis and will differ from macropinocytosis in terms of the size of EVs internalized, that is, sEVs for micro and both EVs for macro.[40,41] However, macropinocytosis is non-specific because bigger components than EVs can be internalized and micropinocytosis is more specific for EVs.[42] During micropinocytosis and before internalization, EVs need to interact mostly through surface proteins like tetraspanins or integrins.[43–45] Several studies showed that EVs could be internalized through clathrin-mediated vesicles.[46] Clathrin is a protein that allows the beginning of membrane curvature and cooperates with a large range of other proteins to produce endosomal vesicles.[47] The clathrin mechanism is the most common process involved in the continuous uptake of essential nutrients such as low-density lipoprotein cholesterol, as well as regulating the number of cell surface receptors and recycling membrane proteins of synaptic vesicles.[40] In addition, the importance of clathrin in sEV uptake has been confirmed using a cationic amphipathic drug that can deplete clathrin at the membrane.[48] However, other mechanisms take part in EV uptake as caveolin-mediated endocytosis that are similar to clathrin-mediated endocytosis. Caveolin is a protein that covers the inner layer of the plasma membrane and that induces a negative curvature of the membrane.[38] Interestingly, it has been shown that a decrease in caveolin expression reduced the internalization of sEVs.[49] Finally, other mechanisms as RhoA-dependent endocytosis or via lipid raft are also involved in pinocytosis[45] (Figure 2).

Each uptake mechanism appears to be cell-dependent and also EV-dependent. For example, it has been shown that EVs were mainly packed into cells through clathrin in PC12 and caveolin in neurons.[38,50] More interestingly, after the release, EVs exhibit a specific tropism toward their donor cells, indicating that the protein and lipid composition of the EV may influence its docking.[51]

3.2 | EV cargo

Apart from their membrane composition, EVs also contain proteins in their core, such as cytoskeleton-related proteins, enzymes, and chaperones.[21] Despite variations in EV composition,[52] certain groups of proteins are commonly found, including those involved in fusion and membrane transport (annexin and Rab GTPases), cell adhesion (integrins and tetraspanins), and antigen presentation, as well as components of the cytoskeleton (actin and tubulin).[20] The content of EVs is linked to their origin and the stimulus leading to their formation. For example, it has been evidenced that during obesity, ADEVs expressed a lower concentration of adiponectin.[53] In addition, EVs also transport bioactive lipids and miRNAs as described below.[54] Taken together, the differences in protein, lipid, and miRNA content can confer specific roles in the transmission of biological signals in the organism.

4 | MICRO-RNAS AND EVS

4.1 | Generalities

Extracellular RNAs were first described in 1978, but their function became understood after the description of the presence of extracellular ribonucleases (RNases).[55] Then, it was demonstrated that EVs derived from embryonic stem cells contained mRNAs and miRNAs.[56] These RNAs encapsulated into vesicles are protected from extracellular RNases, which improve their transport in the extracellular space.[56] Interestingly, it has been shown that miRNAs contained in EVs maintained their activity and modulated gene expression in target cells.[3,57]

4.2 | Biogenesis and action

The miRNAs are small non-coding RNAs of 21–26 nucleotides long that modulate target gene expression by increasing mRNA degradation or inhibiting gene translation.[58] They are produced from specific genes contained in clusters throughout the genome[59] (Figure 3). The transcription of these genes by RNA polymerase II leads to the formation of the precursor pri-miRNA. This pri-miRNA is then cleaved in the nucleus by a complex formed by Drosha and DiGeorge syndrome Chromosomal Region 8 (DGCR8).[60] This cleavage produced a pre-miRNA averaging 70 nucleotides with a stem-loop structure. Then, pre-miRNA interacts with exportin-5 to be transported to the cytosolic compartment. In the cytoplasm, the loop of the pre-miRNA is cleaved by an enzyme from the DICER family to obtain a double-strand miRNA.[61] Finally, the miRNA interacts with a protein Argonaut (Ago1 to 4) and Transactivation Response element RNA Binding Protein (TRBP) to form the complex RNA-induced silencing complex (RISC).[62] During the RISC complex formation, the miRNA double-strand becomes a single-strand. This mature form of miRNA interacts with the RISC complex to be guided to mRNA. RISC complex is involved in the interaction between mRNA and miRNA by recognizing a specific site of two to eight nucleotides located mainly in the 3′UTR (untranslated region) of mRNA. Finally, the mRNA can be degraded if miRNA-mRNA pairing is complete, or the translation will be repressed if miRNA-mRNA pairing is partial (Figure 3).[63]

4.3 | Loading of microRNAs in vesicles

Different studies have revealed that EVs exhibit a specific miRNA signature, suggesting that their incorporation into EVs is modulated.[64] This mechanism has not been fully clarified, but some ribonucleoproteins seem to be involved in the loading of miRNAs into vesicles (Figure 3). For instance, heterogeneous nuclear ribonucleoprotein A (hnRNPA) binds to miRNA through specific motifs named EXOmotifs.[65] In addition, deletion of the Y-Box protein-1 (YBX-1) gene reduced secretion of vesicular miR-223.[66] The knockdown of gene encoding AGO decreased miRNA expression into MVB and this incorporation was specific for let-7a but not miR-320a.[67] In another

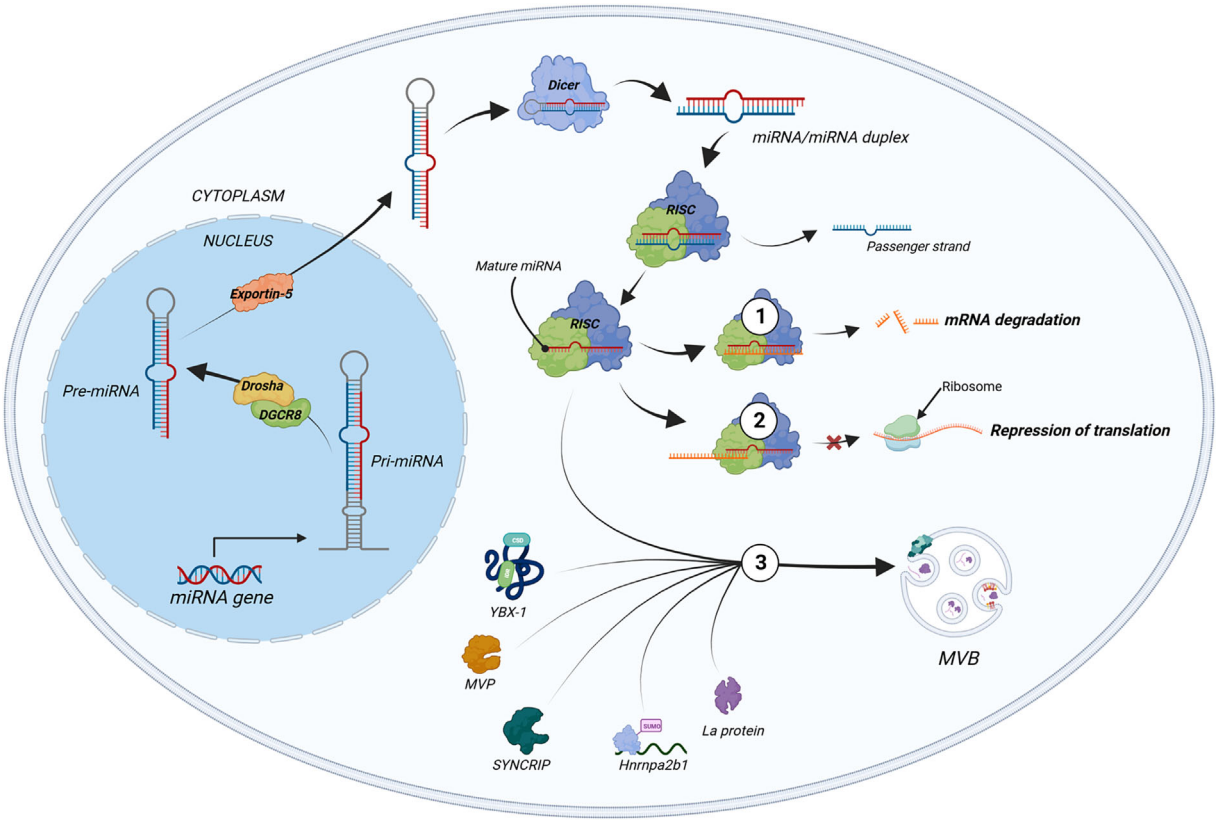

FIGURE 3 The miRNA synthesis and loading in EVs. The miRNA synthesis begins in the nucleus by the transcription of a pri-miRNA. Then, the pri-miRNA is cleaved for the production of pre-miRNA by the enzymatic complex DGCR8/DROSHA, and the pre-miRNA will be transported to the cytoplasm by Exportin-5. Then, pre-miRNA is cleaved in a double-strand RNA by the Dicer enzyme, and then, a mature miRNA will be formed. The complex RISC (result of the interaction of TBRP and Ago2) interacts with the mature miRNA and leads to the regulation of gene expression. The degradation of mRNA is induced if the interaction miRNA-mRNA is complete (1) or the translation of mRNA is repressed if the interaction is incomplete (2). Likewise, the mature miRNAs can be incorporated in EVs by means of different mechanisms but the main one involves RNA-binding proteins (RBPs) (3).

example, major vault protein (MVP) controlled the loading of miR-193a in sEVs of tumor cells.[68] Many other RNA-binding proteins (RBPs) are involved in the incorporation of miRNAs in EVs like La protein, Mex-3 RNA binding family member C (MEX3C), or neutral sphingomyelinase (NSMASE) (Figure 3).[69]

Thus, EVs exhibit a specific membrane signature and miRNA content depending on the donor cells and RBP expression. Interestingly, EV characteristics can be modulated in some pathologies such as obesity. In this context, miRNAs contained in EVs derived from the AT, which appears to be a major provider of those miRNA-enriched EVs,[11] are described as new actors in the metabolic disorders.[70]

5 | ROLE OF EV-CONTAINING MIRNAS IN OBESITY AND METABOLIC SYNDROME

5.1 | Obesity and metabolic syndrome

Obesity is characterized as a body fat mass excess resulting in an imbalance between energy intake and expenditure. Obesity is a multifactorial pathology with genetic and/or environmental factors like physical inactivity, increased energy intake, chronic stress, dysregulation of microbiota, or endocrine disruptors.[71] This pathology is associated with metabolic syndrome (MS), which is a group of various metabolic disorders including T2D, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, or arterial hypertension.[72] MS is defined as a combination of at least three of these metabolic disorders and is linked to a sedentary lifestyle but also genetic predispositions. Currently, overweight and obesity affect more than 38% of the world population with a high geographic disparity.[73] In addition, MS can be associated with metabolic inflammation in various organs such as AT, brain, gut barrier, or blood vessels. This inflammation state is involved in many diseases such as atherosclerosis.[74] Generally, metabolic disorders increase the risk of cardiovascular disease (CVD) and cancer.[75] In addition, it has been highlighted that miRNA expression in plasma is a potential biomarker for obesity.[76,77] However, since AT, especially the white AT (WAT), has a major role in obesity, it is important to better understand its role in extracellular crosstalk with other tissues. Particularly, it could be evidenced that ADEVs were involved in the development of metabolic pathologies or in the low-grade

inflammation-associated mechanisms.[78] Interestingly, the content of ADEVs appears to be modified in these pathological conditions including an enrichment of triacylglycerol content,[79] a modification of protein expression at the membrane surface, and a disruption of their miRNA content as described above.[24,80]

5.2 | Effects of EV-containing miRNAs from AT on target organs

5.2.1 | AT

As presented previously, EVs interact in a specific manner with their donor cell.[51] Thus, AT communicates with its own cells through ADEVs in order to modulate its activity and tissue homeostasis. Studies have revealed the involvement of both intracellular and extracellular miRNAs in the metabolism of this tissue.[81] For instance, miR-122, miR-192, and miR-27a/b modulated AT metabolism and inflammation by targeting genes involved in FA synthesis as Peroxisome proliferator-activated receptor-alpha (Pparα).[82] Interestingly, the effects described for miR-29a on Pparδ were also observed for AT as well as in muscles.[83] In addition, da Silva Nunes et al concluded that miR-26b transported by EVs could promote triglyceride accumulation in adipocytes by targeting F-box and leucine-rich repeat protein 19 (Fbxl19).[84,85] However, the absence of AT-specific markers could not rely on this result with an AT origin. Another study highlighted that ADEV-miR-450a-5p induced adipogenesis through the downregulation of Wisp2 (WNT1 inducible signaling pathway protein-2).[86] Interestingly, this miRNA appeared to be reduced during obesity supporting its implication in the modulation of AT metabolism.[87] Another study suggested that miR-210 could be involved in the browning of AT, a mechanism that can be used as a tool for treating obesity.[88,89] In addition, it was shown that miR-155 and miR-130b were enhanced in the plasma of subjects with obesity.[90] This observation was supported by the murine model developed by the group of Olefsky, in which those two miRNAs derived from AT macrophages (ATMs), targeted adipocytes and muscles, and reduced Pparγ and Glut4 (glucose transporter type 4) expression to consequently impair insulin sensitivity.[91] In the work of Ferrante et al, it was shown that 88 miRNAs had a different expression profile in sEVs from visceral AT of patients with obesity compared to lean subjects.[92] Among these, some miRNAs such as miR-182 or miR-23b are involved in adipogenesis regulation and energy expenditure respectively.[93,94] Therefore, miRNAs contained in ADEVs are able to modulate AT metabolism as well as other organs such as muscles. More specifically, these miRNAs can modulate insulin sensitivity and lipid metabolism and promote the development of obesity or related diseases.

5.2.2 | Liver

During obesity, circulating EVs from AT can modulate different aspects of liver metabolism.[95] For instance, AT macrophage-derived EV-containing miR-155 reduced the insulin sensitivity of liver in mice.[91] The decrease in ADEVs miR-141-3p quantity impaired glucose uptake in hepatocytes by modulating insulin sensitivity.[96] In addition, elevated levels of exosomal miR-29a in mice on a high-fat diet (HFD) increased insulin resistance (IR) by targeting Pparδ in hepatocytes[83] and could also modulate lipid metabolism through Sirtuin-1 (Sirt1).[97] Various studies also revealed that miR-15b decreased the expression of insulin receptors, which promote IR.[98] Other miRNAs, such as miR-34a, reduced macrophages M2 polarization through Kruppel-like factor 4 (Klf4) inhibition.[99] Interestingly, the phenotype of adipocyte-specific miR-34a-KO mice suggested the involvement of this miRNA in non-alcoholic fatty liver disease (NAFLD).[99] Another study showed that miR-223, reduced during obesity,[100] decreased lipid accumulation and liver fibrosis by targeting E2F transcription factor 1 (E2f1).[101] Moreover, previous studies by Castaño et al revealed that four miRNAs overexpressed in WAT-derived-EVs (miR-192, miR-122, miR-27a-3p, and miR-27b-3p) were associated with glucose intolerance, hepatic steatosis, and metabolic impairment in the WAT.[82] Some circulating miRNAs could also be related to human NAFLD and complications such as cancer. For instance, plasmatic miR-221 and 222 by targeting *DNA damage-inducible transcript 4* (Ddit4), promoted diet-induced obesity or hepatic IR. In addition, miR-222 could also be related to liver cancer and a dual effect of ADEV-containing miR-222 on liver physiopathology during obesity has been described.[102–105] Furthermore, ADEV-containing miR-27a promoted liver cancer by targeting forkhead box protein O1 (Foxo1) and extracellular miR-23a/b also amplified cancer progression by targeting the tumor suppressor Von Hippel–Lindau (VHL).[106,107] Interestingly, miR-23a was also involved in IR, by targeting phosphatase and tensin homolog (Pten) and S6 kinase (S6k),[108] which could also support a correlation between cancer development and obesity-related disease.

Conversely, while many studies have focused on the effect of ADEVs in the crosstalk between AT and the liver, it appears that the liver also talks with AT in response to metabolic changes. For instance, a recent study highlights that HFD enhances the expression of miR-210-3p, miR-31-5p, and let-7e-5p in hepatic EVs to control AT remodeling by increasing lipogenesis and adipocyte differentiation.[109] More interestingly, another study explained that hepatic miR-130a regulates the fat synthesis and IR in adipocytes in response to this HFD.[110] Thus, AT and liver crosstalk involves EV-containing miRNAs and potentiates the development of obesity. While AT sends inflammatory and metabolic signals to the liver to modulate lipid metabolism or insulin sensitivity, it appears that the signals sent by the liver act more like a sensor to promote AT plasticity and adaptation in inflammatory conditions.

5.2.3 | Pancreas

Several studies have shown that ADEVs produced in the context of obesity can modulate inflammation in pancreatic beta cells by means of miR-298-5p, miR-296-5p, miR-125a-5p, and miR-351-5p that are known to target tumor necrosis factor-alpha (Tnfα) and interferon-

gamma (Ifnγ).[111] Gao et al also revealed that miR-155 could impair insulin secretion by targeting MAF BZIP transcription factor B (Mafb), an important protein for glucose-stimulated insulin secretion through glucose transporter 2 (GLUT2).[112] Finally, three miRNAs enriched in the circulation of children with obesity (miR-486, miR-146b, and miR-15b) were associated with a higher risk of developing T2D, and more interestingly, their levels were also elevated in adulthood.[113] However, there is no direct proof that these circulating miRNAs are derived from AT, given the absence of specific markers for the identification of ADEVs, as mentioned before.

5.2.4 | Muscles

Muscles are also closely related to metabolic organs as they are involved in glucose consumption and, particularly, energy expenditure. For instance, different studies have demonstrated the role of miR-27a and miR-155 derived from adipocytes during inflammation in the development of IR through Pparγ in skeletal muscle.[91,114] It has also been highlighted that miR-130b, contained in adipocyte-derived EVs, could regulate the oxidative capacity of muscle through Pgc1α (peroxisome proliferator-activated receptor gamma coactivator 1-*alpha*).[115] However, other miRNAs could play a role in the regulation of glucose homeostasis regulation. Indeed, Katayama et al demonstrated that miR-20b-5p was enhanced in EVs and impaired glucose and insulin signaling of skeletal muscles through signal transducer and activator of transcription 3 (Stat3) and AKT interacting protein (Aktip) in the serum of patients with T2D.[116] However, the adipose origin of those EV-containing miR-20b needs to be confirmed. Additionally, a recent study showed that AT was the main source of circulating miR-222 in HFD mice that was involved in IR in muscle through repression of insulin receptor substrate 1 (IRS1).[104] Then, the muscles are also targeted by ADEV-containing miRNAs, which modulate predominantly insulin sensitivity. Interestingly, it has been observed that some miRNAs, such as miR-155, could modulate the metabolism of the liver as well as the pancreas or muscles. In addition to the pleiotropic effects of ADEVs on metabolism, further studies are needed to understand their organotropism, providing a better comprehension of their involvement during obesity.

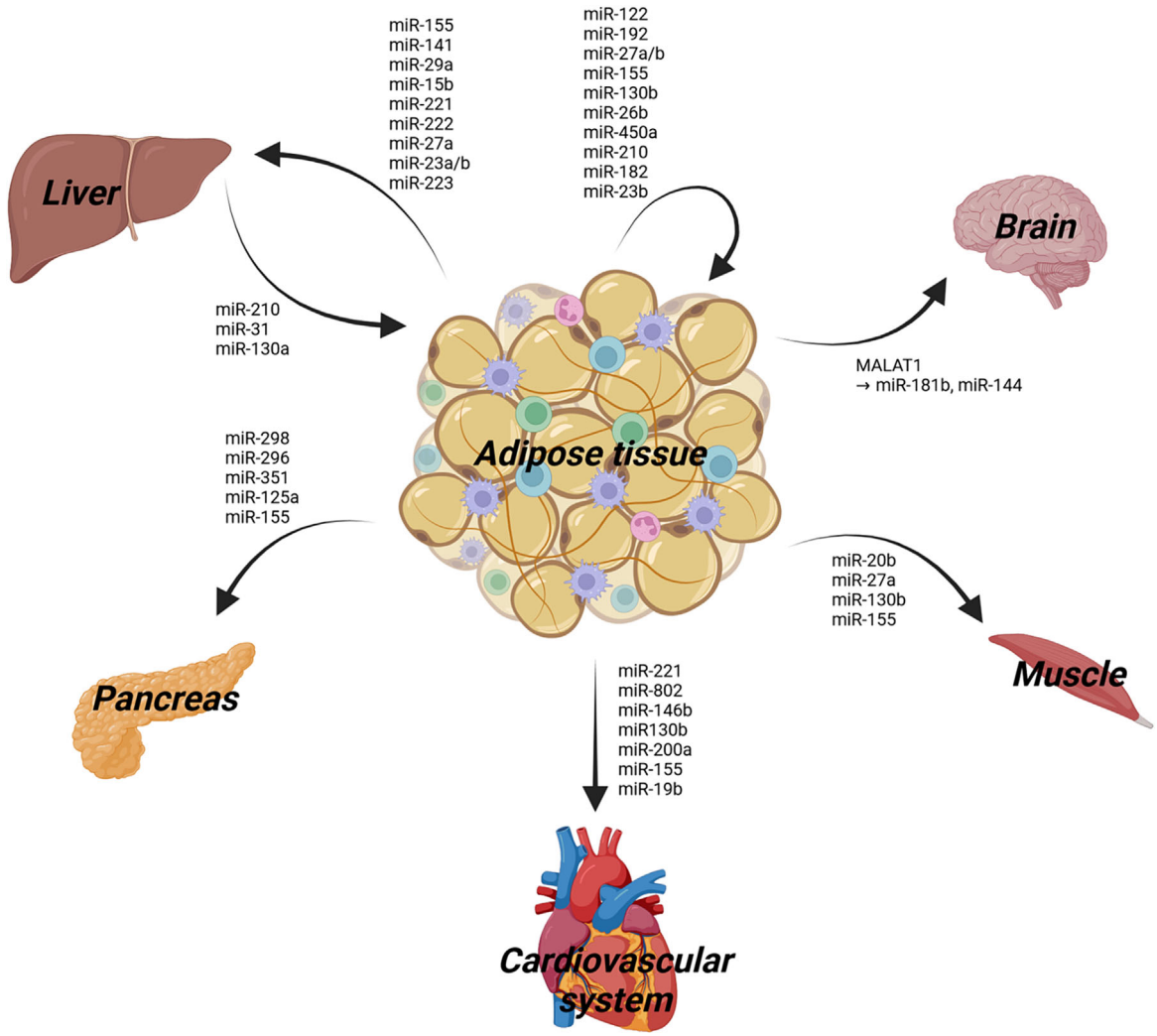

FIGURE 4 Role of ADEV-containing miRNAs in metabolic disorders.

TABLE 1 Effect of miRNAs up-regulated in ADEVs on target cells/tissues in metabolic disease.

ADEVs miRNAs	Target cell/tissue	Target gene	Effects	Reference
miR-122	Systemic	Not determined	Glucose intolerance, lipid accumulation	Castano et al, 2018
miR-130b	3T3-L1 murine adipocytes	Pparγ, Glut4	Insulin resistance	Tryggestad et al, 2019
miR-130b	Mice heart	Ampkα1/α2	Enhanced ischemia/reperfusion injuries, cardiac hypertrophy	Gan et al, 2020
miR-132	Mice stroma vascular fraction	Not determined	Lipid accumulation	da Silva Nunes et al, 2022
miR-133a	Rat heart	Tgf-β	Decrease collagen content and atrial remodeling	Shaihiv-Teper et al, 2021
miR-144	R13 rat hypothalamus cells	mTOR	Decreased POMC expression and appetite disruption	Gao et al, 2020
miR-146b	Systemic	ND	Enhanced risk of T2D	Cui et al, 2018
miR-146b	Rat heart	Timp4	Heart fibrosis	Shaihiv-Teper et al, 2021
miR-155	L6 rat skeletal myoblasts	Pparγ	Reduced insulin-stimulated glucose uptake and Glut4 translocation	Ying et al, 2017
miR-155	Primary murine hepatocytes	Pparγ	Reduced insulin-stimulated glucose uptake and Glut4 translocation	Ying et al, 2017
miR-155	Min6 murine Beta cell	Mafb	Reduced glucose-stimulated insulin secretion	Gao et al, 2021
miR-155	Human internal mammary arteries	eNOS	Endothelial dysfunction	Sun et al, 2012
miR-15b	HepG2 human hepatocytes	Insulin receptor	Insulin resistance	Yang et al, 2019
miR-15b	Systemic	Not determined	Enhanced risk of T2D	Cui et al, 2018
miR-181b	R13 rat hypothalamus cells	mTOR, P70s6k	Decreased POMC expression and appetite disruption	Gao et al, 2020
miR-192	Systemic	Not determined	Glucose intolerance, lipid accumulation	Castano et al, 2018
miR-200a	Murine primary neonatal cardiomyocytes	Pparγ	Enhanced ischemia/reperfusion injuries, cardiac hypertrophy	Fang et al, 2016
miR-20b-5p	Primary human skeletal muscle	Stat3, Aktip	Impaired glucose and insulin signaling	Katayama et al, 2019
miR-210	3T3-L1 murine adipocytes	Ndufa4	Reduced glucose uptake	Tian et al, 2020
miR-221	3T3-L1 murine adipocytes	Ddit4	Insulin resistance, diet-induced obesity	Yamaguchi et al, 2022
miR-221-3p	Mouse aortic smooth muscle cell	Contractile gene, Pgc1α	Enhanced atherosclerotic risk	Li et al, 2019
miR-222	Hepa1-6 murine hepatocytes	Ddit4, Irs1, Bbc3	Insulin resistance, diet-induced obesity	Li et al, 2020; Yamaguchi et al, 2022
miR-222	HepG2, HCC-LM3, SMCC7721 hepatocytes	Bbc3	Liver defect	Liu et al, 2018
miR-23a	BEL-7402, BEL-7402/5-Fu, Hepa1–6 hepatocytes	VHL tumor suppressor	Liver defect	Liu et al, 2019
miR-23b	BEL-7402, BEL-7402/5-Fu, Hepa1–6 hepatocytes	VHL tumor suppressor	Liver defect	Liu et al, 2019
miR-26b	Mice stroma vascular fraction	Fbxl19	Lipid accumulation	da Silva Nunes et al, 2022; Acharya et al, 2019
miR-27a	HepG2 human hepatocytes	Foxo1	Liver defect	Sun et al, 2015
miR-27a	C2C12 murine myoblasts	Pparγ	Insulin resistance	Yu et al, 2018
miR-27a-3p	Systemic	Not determined	Glucose intolerance, adipocyte function	Castano et al, 2018
miR-27b-3p	Systemic	Not determined	Glucose intolerance, adipocyte function	Castano et al, 2018
miR-29a	Primary murine hepatocytes, liver, muscles, and AT	Pparδ, Sirt1	Insulin resistance, increased lipogenesis, and circulating triglycerides	Liu et al, 2019; Hung et al, 2019
miR-34a	Murine BMDMs	Klf4	Reduced M2 polarization	Pan et al, 2019
miR-486	Systemic	Not determined	Enhanced risk of T2D	Cui et al, 2018
miR-802-5p	Neonatal rat ventricular myocytes	Hsp60	Cardiac insulin resistance	Wen et al, 2020
miR-130b	C2C12 murine myoblasts	Pgc1α	Reduced muscle oxidative capacity	Wang et al, 2013

TABLE 2 Effects of miRNAs down-regulated in ADEVs on target cells/tissues in metabolic diseases.

ADEVs miRNAs	Target cell/tissue	Target gene	Effects	Reference
miR-125a-5p	Human EndoC-βH3 Beta cell	Ifn-γ	Inflammation and β cell disruption	Gesmundo et al, 2021
miR-141-3p	AML12 murine hepatocytes	Pten	Reduced insulin-stimulated glucose uptake	Dang et al, 2019
miR-182	3T3-L1 murine adipocytes	C/ebpα	Lipid accumulation	Dong et al, 2020
miR-19b	JAR human syncytiotrophoblast-like cells	Cytokines (Il-6, Tnfα)	Cardiac development deficiency	Liu et al, 2021
miR-223	NCTC1469 murine hepatocytes	E2f1	Enhanced lipid accumulation and liver fibrosis	Niu et al, 2022
miR-296-5p	Human EndoC-βH3 Beta cell	Tnfα	Inflammation and β cell disruption	Gesmundo et al, 2021
miR-298-5p	Human EndoC-βH3 Beta cell	Tnfα	Inflammation and β cell disruption	Gesmundo et al, 2021
miR-29a	Rat heart	Not determined	Heart fibrosis	Shaihiv-Teper et al, 2021
miR-351-5p	Human EndoC-βH3 Beta cell	Tnfα	Inflammation and β cell disruption	Gesmundo et al, 2021
miR-450a-5p	Rat ADSCs	Wisp2	Reduced adipogenesis	Zhang et al, 2017

5.2.5 | Cardiovascular system

Inflammation-linked obesity has a significant impact on vessels and the heart, promoting CVDs. Interestingly, EV-containing miRNAs showed a high correlation with those CVDs. For instance, perivascular AT expresses miR-221-3p in EVs, which suppresses contractile gene expression in vascular muscle cells but also targets Pgc1α and enhances atherosclerotic risks.[117] In addition, studies focused on cardiac function during obesity have suggested a role of miR-802-5p produced by hypertrophic adipocytes in the development of IR in ventricular myocytes.[118] A more recent study showed that in patients with atrial fibrillation, epicardial AT expressed EV-containing enhanced miR-146b and reduced miR-29a, which induced heart fibrosis.[119] The enrichment of miR-130b and miR-200a in ADEVs exacerbated ischemia/reperfusion injuries in diabetic hearts of adult mice and enhanced cardiac hypertrophy through Ampkα1/α2 and Ppary, respectively.[120,121] Different studies have shown that perivascular AT released EV-containing miR-221-3p, which mediate vascular inflammation.[117] Interestingly, miR-155, as described previously, inhibits eNOS and consequently affects cardiovascular function.[122] Finally, it was evidenced that during maternal obesity, visceral AT-derived EVs contribute to cardiac deficiency through the reduction of the levels of miR-19b, which is known to reduce inflammation.[123] Since the dialogue between AT and the cardiovascular system is altered during obesity, the role of ADEV-containing miRNAs appears central in this context. Further studies would contribute to a better understanding of the role of AT on the cardiovascular system during obesity.

5.2.6 | Brain

Crosstalk between AT and the brain is well known for the regulation of feeding behavior and energy expenditure.[124] Particularly, leptin, an adipokine released by AT, can modulate the activity of the anorexigenic proopiomelanocortin (POMC) neurons located in the hypothalamus.[125,126] Recently, the importance of miRNAs in the central effects of leptin, particularly in the regulation of POMC neurons, has been reported. For instance, it has been observed that miR-200a/b, miR-429, and miR-488 were correlated with leptin levels in *ob/ob* mice, and it was also found that miRNA expression was altered in the hypothalamus of HFD mice.[62,127,128] Interestingly, EVs are known to cross the blood–brain barrier after stimulation with TNF or LPS.[129–131] In addition, these EVs contained inflammatory miRNAs such as miR-155.[132] Altogether, these different studies strongly suggest an important role of ADEV-containing miRNAs in the communication between AT and hypothalamic neurons. In accordance with this hypothesis, Gao et al suggested that the long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) could modulate appetite through miR-181b and miR-144 in POMC neurons activity in mice with obesity.[133] However, the communication of pro-/anti-inflammatory signals or modulations of metabolic pathways through EV-containing miRNAs in the brain are still to be clarified.

6 | CONCLUSION AND PERSPECTIVES

Several recent studies have highlighted the importance of the miRNAs contained in ADEVs in the onset of metabolic disorders (Figure 4). These miRNAs have been listed in Tables 1 and 2. Particularly, ADEV-containing miRNAs act on insulin sensitivity and pathway, glucose uptake, energy expenditure, and lipid accumulation. The expression of miRNAs is modified within EVs in obese or inflammatory conditions and consequently has an effect on many tissues and organ physiology involved in the control of energy homeostasis. In our opinion, the most relevant finding will be the characterization of specific markers for ADEVs to improve their detection in fluids. This technical point is

essential for the association of ADEV-derived miRNAs with different aspects of metabolic disorders.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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REFERENCES

1. Wolf P. The nature and significance of platelet products in human plasma. *Br J Haematol*. 1967;13(3):269-288. doi:10.1111/j.1365-2141.1967.tb08741.x
2. Kooijmans SAA, de Jong OG, Schiffelers RM. Exploring interactions between extracellular vesicles and cells for innovative drug delivery system design. *Adv Drug Deliv Rev*. 2021;173:252-278. doi:10.1016/j.addr.2021.03.017
3. Gao XR, Ge J, Li WY, Zhou WC, Xu L, Geng DQ. miR-34a carried by adipocyte exosomes inhibits the polarization of M1 macrophages in mouse osteolysis model. *J Biomed Mater Res A*. 2020;109(6):994-1003. doi:10.1002/jbm.a.37088
4. Cione E, Cannataro R, Gallelli L, De Sarro G, Caroleo MC. Exosome microRNAs in metabolic syndrome as tools for the early monitoring of diabetes and possible therapeutic options. *Pharmaceuticals*. 2021;14(12):1257. doi:10.3390/ph14121257
5. Xie D, Li J, Jiang P, Xue X, Wu L. Effect of adipose-derived exosome and exosomal miRNA on glycolipid metabolism. *Clin Transl Discov*. 2022;2(3):e134. doi:10.1002/ctd2.134
6. Buratta S, Shimanaka Y, Costanzi E, et al. Lipotoxic stress alters the membrane lipid profile of extracellular vesicles released by Huh-7 hepatocarcinoma cells. *Sci Rep*. 2021;11(1):4613. doi:10.1038/s41598-021-84268-9
7. Mei R, Qin W, Zheng Y, Wan Z, Liu L. Role of adipose tissue derived exosomes in metabolic disease. *Front Endocrinol*. 2022. Accessed December 15, 2022;13:873865. https://www.frontiersin.org/articles/10.3389/fendo.2022.873865
8. Kim JH, Lee J, Park J, Gho YS. Gram-negative and gram-positive bacterial extracellular vesicles. *Semin Cell Dev Biol*. 2015;40:97-104. doi:10.1016/j.semcdb.2015.02.006
9. Théry C, Witwer KW, Aikawa E, 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(1):1535750. doi:10.1080/20013078.2018.1535750
10. Barranco I, Padilla L, Parrilla I, et al. Extracellular vesicles isolated from porcine seminal plasma exhibit different tetraspanin expression profiles. *Sci Rep*. 2019;9(1):11584. doi:10.1038/s41598-019-48095-3
11. Thomou T, Mori MA, Dreyfuss JM, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature*. 2017;542(7642):450-455. doi:10.1038/nature21365
12. Lynch SF, Ludlam CA. Plasma microparticles and vascular disorders. *Br J Haematol*. 2007;137(1):36-48. doi:10.1111/j.1365-2141.2007.06514.x
13. Trams EG, Lauter CJ, Jr NS, Heine U. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles. *Biochim Biophys Acta BBA - Biomembr*. 1981;645(1):63-70. doi:10.1016/0005-2736(81)90512-5
14. Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). *J Biol Chem*. 1987;262(19):9412-9420. doi:10.1016/S0021-9258(18)48095-7
15. Klumperman J, Raposo G. The complex ultrastructure of the endolysosomal system. *Cold Spring Harb Perspect Biol*. 2014;6(10):a016857. doi:10.1101/cshperspect.a016857
16. Kim YS, Ahn JS, Kim S, Kim HJ, Kim SH, Kang JS. The potential theragnostic (diagnostic+therapeutic) application of exosomes in diverse biomedical fields. *Korean J Physiol Pharmacol*. 2018;22(2):113-125. doi:10.4196/kjpp.2018.22.2.113
17. Hurley JH. ESCRT complexes and the biogenesis of multivesicular bodies. *Curr Opin Cell Biol*. 2008;20(1):4-11. doi:10.1016/j.ceb.2007.12.002
18. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. *Nat Rev Immunol*. 2002;2(8):569-579. doi:10.1038/nri855
19. Morel O, Jesel L, Freyssinet JM, Toti F. Cellular mechanisms underlying the formation of circulating microparticles. *Arterioscler Thromb Vasc Biol*. 2011;31(1):15-26. doi:10.1161/ATVBAHA.109.200956
20. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018;19(4):213-228. doi:10.1038/nrm.2017.125
21. Durcin M, Fleury A, Taillebois E, et al. Characterisation of adipocyte-derived extracellular vesicle subtypes identifies distinct protein and lipid signatures for large and small extracellular vesicles. *J Extracell Vesicles*. 2017;6(1):1305677. doi:10.1080/20013078.2017.1305677
22. Rome S, Blandin A, Le Lay S. Adipocyte-derived extracellular vesicles: state of the art. *Int J Mol Sci*. 2021;22(4):1788. doi:10.3390/ijms22041788
23. Huang Z, Xu A. Adipose extracellular vesicles in intercellular and inter-organ crosstalk in metabolic health and diseases. *Front Immunol*. 2021;12:608680. doi:10.3389/fimmu.2021.608680
24. Kulaj K, Harger A, Bauer M, et al. Adipocyte-derived extracellular vesicles increase insulin secretion through transport of insulinotropic protein cargo. *Nat Commun*. 2023;14(1):709. doi:10.1038/s41467-023-36148-1
25. Kranendonk MEG, Visseren FLJ, van Balkom BWM, et al. Human adipocyte extracellular vesicles in reciprocal signaling between adipocytes and macrophages. *Obes Silver Spring Md*. 2014;22(5):1296-1308. doi:10.1002/oby.20679
26. Camino T, Lago-Baameiro N, Bravo SB, et al. Vesicles shed by pathological murine adipocytes spread pathology: characterization and functional role of insulin resistant/hypertrophied adiposomes. *Int J Mol Sci*. 2020;21(6):2252. doi:10.3390/ijms21062252
27. Flaherty SE, Grijalva A, Xu X, Ables E, Nomani A, Ferrante AW. A lipase-independent pathway of lipid release and immune modulation by adipocytes. *Science*. 2019;363(6430):989-993. doi:10.1126/science.aaw2586
28. Crewe C, Funcke JB, Li S, et al. Extracellular vesicle-based interorgan transport of mitochondria from energetically stressed adipocytes. *Cell Metab*. 2021;33(9):1853-1868.e11. doi:10.1016/j.cmet.2021.08.002
29. Hoshino A, Costa-Silva B, Shen TL, et al. Tumour exosome integrins determine organotropic metastasis. *Nature*. 2015;527(7578):329-335. doi:10.1038/nature15756
30. Morelli AE, Larregina AT, Shufesky WJ, et al. Endocytosis, intracellular sorting, and processing of exosomes by dendritic cells. *Blood*. 2004;104(10):3257-3266. doi:10.1182/blood-2004-03-0824

31. Matsumoto A, Takahashi Y, Nishikawa M, et al. Role of phosphatidylserine-derived negative surface charges in the recognition and uptake of intravenously injected B16BL6-derived exosomes by macrophages. *J Pharm Sci*. 2017;106(1):168-175. doi:10.1016/j.xphs.2016.07.022
32. del Conde I, Shrimpton CN, Thiagarajan P, López JA. Tissue-factor–bearing microvesicles arise from lipid rafts and fuse with activated platelets to initiate coagulation. *Blood*. 2005;106(5):1604-1611. doi:10.1182/blood-2004-03-1095
33. Fitzner D, Schnaars M, van Rossum D, et al. Selective transfer of exosomes from oligodendrocytes to microglia by macropinocytosis. *J Cell Sci*. 2011;124(Pt 3):447-458. doi:10.1242/jcs.074088
34. Heusermann W, Hean J, Trojer D, et al. Exosomes surf on filopodia to enter cells at endocytic hot spots, traffic within endosomes, and are targeted to the ER. *J Cell Biol*. 2016;213(2):173-184. doi:10.1083/jcb.201506084
35. Prada I, Meldolesi J. Binding and fusion of extracellular vesicles to the plasma membrane of their cell targets. *Int J Mol Sci*. 2016;17(8):1296. doi:10.3390/ijms17081296
36. Cullis PR, Hope MJ. Chapter 1 Physical properties and functional roles of lipids in membranes. In: Vance DE, Vance JE, eds. *New comprehensive biochemistry*. Vol. 20. Elsevier; 1991:1-41. doi:10.1016/S0167-7306(08)60329-4
37. Parolini I, Federici C, Raggi C, et al. Microenvironmental pH is a key factor for exosome traffic in tumor cells. *J Biol Chem*. 2009;284(49):34211-34222. doi:10.1074/jbc.M109.041152
38. Tian T, Zhu YL, Zhou YY, et al. Exosome uptake through Clathrin-mediated endocytosis and macropinocytosis and mediating miR-21 delivery. *J Biol Chem*. 2014;289(32):22258-22267. doi:10.1074/jbc.M114.588046
39. Joshi BS, de Beer MA, Giepmans BNG, Zuhorn IS. Endocytosis of extracellular vesicles and release of their cargo from endosomes. *ACS Nano*. 2020;14(4):4444-4455. doi:10.1021/acsnano.9b10033
40. Conner SD, Schmid SL. Regulated portals of entry into the cell. *Nature*. 2003;422(6927):37-44. doi:10.1038/nature01451
41. Pedrioli G, Paganetti P. Hijacking endocytosis and autophagy in extracellular vesicle communication: where the inside meets the outside. *Front Cell Dev Biol*. 2021;8:1540. doi:10.3389/fcell.2020.595515
42. Lin XP, Mintern JD, Gleeson PA. Macropinocytosis in different cell types: similarities and differences. *Membranes*. 2020;10(8):177. doi:10.3390/membranes10080177
43. Altei WF, Pachane BC, dos Santos PK, et al. Inhibition of αvβ3 integrin impairs adhesion and uptake of tumor-derived small extracellular vesicles. *Cell Commun Signal*. 2020;18(1):158. doi:10.1186/s12964-020-00630-w
44. Sabatier F, Roux V, Anfosso F, Camoin L, Sampol J, Dignat-George F. Interaction of endothelial microparticles with monocytic cells in vitro induces tissue factor-dependent procoagulant activity. *Blood*. 2002;99(11):3962-3970. doi:10.1182/blood.V99.11.3962
45. Svensson KJ, Christianson HC, Wittrup A, et al. Exosome uptake depends on ERK1/2-heat shock protein 27 signaling and lipid raft-mediated endocytosis negatively regulated by caveolin-1. *J Biol Chem*. 2013;288(24):17713-17724. doi:10.1074/jbc.M112.445403
46. Gurung S, Perocheau D, Touramanidou L, Baruteau J. The exosome journey: from biogenesis to uptake and intracellular signalling. *Cell Commun Signal*. 2021;19(1):47. doi:10.1186/s12964-021-00730-1
47. Kaksonen M, Roux A. Mechanisms of clathrin-mediated endocytosis. *Nat Rev Mol Cell Biol*. 2018;19(5):313-326. doi:10.1038/nrm.2017.132
48. Khalil IA, Kogure K, Akita H, Harashima H. Uptake pathways and subsequent intracellular trafficking in nonviral gene delivery. *Pharmacol Rev*. 2006;58(1):32-45. doi:10.1124/pr.58.1.8
49. Bohmer N, Jordan A. Caveolin-1 and CDC42 mediated endocytosis of silica-coated iron oxide nanoparticles in HeLa cells. *Beilstein J Nanotechnol*. 2015;6(1):167-176. doi:10.3762/bjnano.6.16
50. Yue KY, Zhang PR, Zheng MH, et al. Neurons can upregulate Cav-1 to increase intake of endothelial cells-derived extracellular vesicles that attenuate apoptosis via miR-1290. *Cell Death Dis*. 2019;10(12):869. doi:10.1038/s41419-019-2100-5
51. Longatti A, Schindler C, Collinson A, et al. High affinity single-chain variable fragments are specific and versatile targeting motifs for extracellular vesicles. *Nanoscale*. 2018;10(29):14230-14244. doi:10.1039/C8NR03970D
52. Garcia-Martin R, Brandao BB, Thomou T, Altindis E, Kahn CR. Tissue differences in the exosomal/small extracellular vesicle proteome and their potential as indicators of altered tissue metabolism. *Cell Rep*. 2022;38(3):110277. doi:10.1016/j.celrep.2021.110277
53. Phoonsawat W, Aoki-Yoshida A, Tsuruta T, Sonoyama K. Adiponectin is partially associated with exosomes in mouse serum. *Biochem Biophys Res Commun*. 2014;448(3):261-266. doi:10.1016/j.bbrc.2014.04.114
54. Subra C, Grand D, Laulagnier K, et al. Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins. *J Lipid Res*. 2010;51(8):2105-2120. doi:10.1194/jlr.M003657
55. Stroun M, Anker P, Beljanski M, et al. Presence of RNA in the nucleoprotein complex spontaneously released by human lymphocytes and frog auricles in culture. *Cancer Res*. 1978;38(10):3546-3554.
56. Ratajczak J, Miekus K, Kucia M, et al. Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery. *Leukemia*. 2006;20(5):847-856. doi:10.1038/sj.leu.2404132
57. Huang XY, Chen JX, Ren Y, Fan LC, Xiang W, He XJ. Exosomal miR-122 promotes adipogenesis and aggravates obesity through the VDR/SREBF1 axis. *Obes Silver Spring Md*. 2022;30(3):666-679. doi:10.1002/oby.23365
58. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004;116(2):281-297. doi:10.1016/s0092-8674(04)00045-5
59. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. *Science*. 2001;294(5543):853-858. doi:10.1126/science.1064921
60. Denli AM, Tops BBJ, Plasterk RHA, Ketting RF, Hannon GJ. Processing of primary microRNAs by the microprocessor complex. *Nature*. 2004;432(7014):231-235. doi:10.1038/nature03049
61. Hutvágner G, McLachlan J, Pasquinelli AE, Bálint E, Tuschl T, Zamore PD. A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. *Science*. 2001;293(5531):834-838. doi:10.1126/science.1062961
62. Derghal A, Djelloul M, Trouslard J, Mounien L. An emerging role of micro-RNA in the effect of the endocrine disruptors. *Front Neurosci*. 2016;10:318. doi:10.3389/fnins.2016.00318
63. Savagner F, Le Pennec S, Rivalin R, Eyer J. Les microARNs. *Rev Francoph Lab*. 2015;2015(473):49-54. doi:10.1016/S1773-035X(15)30159-3
64. Thamotharan S, Ghosh S, James-Allan L, Lei MYY, Janzen C, Devaskar SU. Circulating extracellular vesicles exhibit a differential miRNA profile in gestational diabetes mellitus pregnancies. *PLoS ONE*. 2022;17(5):e0267564. doi:10.1371/journal.pone.0267564
65. Villarroya-Beltri C, Gutiérrez-Vázquez C, Sánchez-Cabo F, et al. Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs. *Nat Commun*. 2013;4(1):2980. doi:10.1038/ncomms3980
66. Shurtleff MJ, Temoche-Diaz MM, Karfilis KV, Ri S, Schekman R. Y-box protein 1 is required to sort microRNAs into exosomes in cells

and in a cell-free reaction. Nilsen TW, ed. *eLife*. 2016;5:e19276. doi:10.7554/eLife.19276
67. McKenzie AJ, Hoshino D, Hong NH, et al. KRAS-MEK signaling controls Ago2 sorting into exosomes. *Cell Rep*. 2016;15(5):978-987. doi:10.1016/j.celrep.2016.03.085
68. Teng Y, Ren Y, Hu X, et al. MVP-mediated exosomal sorting of miR-193a promotes colon cancer progression. *Nat Commun*. 2017;8(1):14448. doi:10.1038/ncomms14448
69. Groot M, Lee H. Sorting mechanisms for microRNAs into extracellular vesicles and their associated diseases. *Cells*. 2020;9(4):E1044. doi:10.3390/cells9041044
70. Rovira-Llopis S, Díaz-Rúa R, Grau-del Valle C, et al. Characterization of differentially expressed circulating miRNAs in metabolically healthy versus unhealthy obesity. *Biomedicine*. 2021;9(3):321. doi:10.3390/biomedicines9030321
71. Caroline M, Apovian MD. *Obesity: definition, comorbidities, causes, and burden*. Vol. 22. Accessed January 20, 2023; 2016. https://www.ajmc.com/view/obesity-definition-comorbidities-causes-burden
72. Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech*. 2009;2(5–6):231-237. doi:10.1242/dmm.001180
73. Koliaki C, Dalamaga M, Liatis S. Update on the obesity epidemic: after the sudden rise, is the upward trajectory beginning to flatten? *Curr Obes Rep*. 2023;12(4):514-527. doi:10.1007/s13679-023-00527-y
74. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol*. 2009;6(6):399-409. doi:10.1038/nrcardio.2009.55
75. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care*. 2012;35(11):2402-2411. doi:10.2337/dc12-0336
76. Landrier JF, Derghal A, Mounien L. MicroRNAs in obesity and related metabolic disorders. *Cells*. 2019;8(8):859. doi:10.3390/cells8080859
77. Brandão-Lima PN, de Carvalho GB, Payolla TB, et al. Circulating microRNAs showed specific responses according to metabolic syndrome components and sex of adults from a population-based study. *Metabolites*. 2023;13(1):2. doi:10.3390/metabo13010002
78. Camino T, Lago-Baameiro N, Pardo M. Extracellular vesicles as carriers of adipokines and their role in obesity. *Biomedicine*. 2023;11(2):422. doi:10.3390/biomedicines11020422
79. Blandin A, Hilairet G, Ponnaiah M, et al. *Lipidomic analysis of adipose-derived extracellular vesicles reveals their potential as lipid mediators of obesity-associated metabolic complications*. Published online December 10, 2021. doi:10.1101/2021.12.10.472057
80. Kwan HY, Chen M, Xu K, Chen B. The impact of obesity on adipocyte-derived extracellular vesicles. *Cell Mol Life Sci*. 2021;78(23):7275-7288. doi:10.1007/s00018-021-03973-w
81. Karkeni E, Astier J, Tourniaire F, et al. Obesity-associated inflammation induces microRNA-155 expression in adipocytes and adipose tissue: outcome on adipocyte function. *J Clin Endocrinol Metab*. 2016;101(4):1615-1626. doi:10.1210/jc.2015-3410
82. Castaño C, Kalko S, Novials A, Párrizas M. Obesity-associated exosomal miRNAs modulate glucose and lipid metabolism in mice. *Proc Natl Acad Sci U S a*. 2018;115(48):12158-12163. doi:10.1073/pnas.1808855115
83. Liu T, Sun YC, Cheng P, Shao HG. Adipose tissue macrophage-derived exosomal miR-29a regulates obesity-associated insulin resistance. *Biochem Biophys Res Commun*. 2019;515(2):352-358. doi:10.1016/j.bbrc.2019.05.113
84. da Silva Nunes PC, Mazzarella R, da Silveira JC, Dellova DCAL. Evaluation of circulating extracellular vesicles and miRNA in neutered and obese female dogs. *Sci Rep*. 2022;12(1):16439. doi:10.1038/s41598-022-20523-x
85. Acharya A, Berry DC, Zhang H, et al. miR-26 suppresses adipocyte progenitor differentiation and fat production by targeting Fbxl19. *Genes Dev*. 2019;33(19-20):1367-1380. doi:10.1101/gad.328955.119
86. Zhang Y, Yu M, Dai M, et al. miR-450a-5p within rat adipose tissue exosome-like vesicles promotes adipogenic differentiation by targeting WISP2. *J Cell Sci*. 2017;130(6):1158-1168. doi:10.1242/jcs.197764
87. Delic D, Eisele C, Schmid R, Luippold G, Mayoux E, Grempler R. Characterization of micro-RNA changes during the progression of type 2 diabetes in Zucker diabetic fatty rats. *Int J Mol Sci*. 2016;17(5):665. doi:10.3390/ijms17050665
88. Zhang Y, Song K, Qi G, et al. Adipose-derived exosomal miR-210/92a cluster inhibits adipose browning via the FGFR-1 signaling pathway in high-altitude hypoxia. *Sci Rep*. 2020;10(1):14390. doi:10.1038/s41598-020-71345-8
89. Kim SH, Plutzky J. Brown fat and browning for the treatment of obesity and related metabolic disorders. *Diabetes Metab J*. 2016;40(1):12-21. doi:10.4093/dmj.2016.40.1.12
90. Tryggestad JB, Teague AM, Sparling DP, Jiang S, Chernausek SD. Macrophage-derived microRNA-155 increases in obesity and influences adipocyte metabolism by targeting peroxisome proliferator-activated receptor gamma. *Obes Silver Spring Md*. 2019;27(11):1856-1864. doi:10.1002/oby.22616
91. Ying W, Riopel M, Bandyopadhyay G, et al. Adipose tissue macrophage-derived exosomal miRNAs can modulate in vivo and in vitro insulin sensitivity. *Cell*. 2017;171(2):372-384.e12. doi:10.1016/j.cell.2017.08.035
92. Ferrante SC, Nadler EP, Pillai DK, et al. Adipocyte-derived exosomal miRNAs: a novel mechanism for obesity-related disease. *Pediatr Res*. 2015;77(3):447-454. doi:10.1038/pr.2014.202
93. Dong M, Ye Y, Chen Z, Xiao T, Liu W, Hu F. MicroRNA 182 is a novel negative regulator of adipogenesis by targeting CCAAT/enhancer-binding protein α. *Obes Silver Spring Md*. 2020;28(8):1467-1476. doi:10.1002/oby.22863
94. You L, Wang Y, Gao Y, et al. The role of microRNA-23b-5p in regulating brown adipogenesis and thermogenic program. *Endocr Connect*. 2020;9(5):457-470. doi:10.1530/EC-20-0124
95. Afrisham R, Sadegh-Nejadi S, Meshkani R, Emamgholipour S, Paknejad M. Effect of circulating exosomes derived from normal-weight and obese women on gluconeogenesis, glycogenesis, lipogenesis and secretion of FGF21 and fetuin A in HepG2 cells. *Diabetol Metab Syndr*. 2020;12(1):32. doi:10.1186/s13098-020-00540-4
96. Dang SY, Leng Y, Wang ZX, et al. Exosomal transfer of obesity adipose tissue for decreased miR-141-3p mediate insulin resistance of hepatocytes. *Int J Biol Sci*. 2019;15(2):351-368. doi:10.7150/ijbs.28522
97. Hung YH, Kanke M, Kurtz CL, et al. MiR-29 regulates de novo lipogenesis in the liver and circulating triglyceride levels in a Sirt1-dependent manner. *Front Physiol*. 2019;10:1367. Accessed December 19, 2022. doi:10.3389/fphys.2019.01367
98. Yang WM, Jeong HJ, Park SW, Lee W. Obesity-induced miR-15b is linked causally to the development of insulin resistance through the repression of the insulin receptor in hepatocytes. *Mol Nutr Food Res*. 2015;59(11):2303-2314. doi:10.1002/mnfr.201500107
99. Pan Y, Hui X, Hoo RLC, et al. Adipocyte-secreted exosomal microRNA-34a inhibits M2 macrophage polarization to promote obesity-induced adipose inflammation. *J Clin Invest*. 2019;129(2):834-849. doi:10.1172/JCI123069
100. Wen D, Qiao P, Wang L. Circulating microRNA-223 as a potential biomarker for obesity. *Obes Res Clin Pract*. 2015;9(4):398-404. doi:10.1016/j.orcp.2015.01.006

101. Niu Q, Wang T, Wang Z, et al. Adipose-derived mesenchymal stem cell-secreted extracellular vesicles alleviate non-alcoholic fatty liver disease via delivering miR-223-3p. *Adipocyte*. 2022;11(1):572-587. doi:10.1080/21623945.2022.2098583
102. Chan GCK, Than WH, Kwan BCH, et al. Adipose and plasma microRNAs miR-221 and 222 associate with obesity, insulin resistance, and new onset diabetes after peritoneal dialysis. *Nutrients*. 2022;14(22):4889. doi:10.3390/nu14224889
103. Yamaguchi S, Zhang D, Katayama A, et al. Adipocyte-specific inhibition of Mir221/222 ameliorates diet-induced obesity through targeting Ddit4. *Front Endocrinol*. 2022;12:750261. doi:10.3389/fendo.2021.750261
104. Li D, Song H, Shuo L, et al. Gonadal white adipose tissue-derived exosomal MiR-222 promotes obesity-associated insulin resistance. *Aging*. 2020;12(22):22719-22743. doi:10.18632/aging.103891
105. Liu Z, Sun J, Liu B, Zhao M, Xing E, Dang C. miRNA-222 promotes liver cancer cell proliferation, migration and invasion and inhibits apoptosis by targeting BBC3. *Int J Mol Med*. 2018;42(1):141-148. doi:10.3892/ijmm.2018.3637
106. Sun B, Li J, Shao D, et al. Adipose tissue-secreted miR-27a promotes liver cancer by targeting FOXO1 in obese individuals. *OncoTargets Ther*. 2015;8:735-744. doi:10.2147/OTT.S80945
107. Liu Y, Tan J, Ou S, Chen J, Chen L. Adipose-derived exosomes deliver miR-23a/b to regulate tumor growth in hepatocellular cancer by targeting the VHL/HIF axis. *J Physiol Biochem*. 2019;75(3):391-401. doi:10.1007/s13105-019-00692-6
108. Lozano-Bartolomé J, Llauradó G, Portero-Otin M, et al. Altered expression of miR-181a-5p and miR-23a-3p is associated with obesity and TNFα-induced insulin resistance. *J Clin Endocrinol Metab*. 2018;103(4):1447-1458. doi:10.1210/jc.2017-01909
109. Zhao Y, Zhao MF, Jiang S, et al. Liver governs adipose remodelling via extracellular vesicles in response to lipid overload. *Nat Commun*. 2020;11(1):719. doi:10.1038/s41467-020-14450-6
110. Wu J, Dong T, Chen T, et al. Hepatic exosome-derived miR-130a-3p attenuates glucose intolerance via suppressing PHLPP2 gene in adipocyte. *Metabolism*. 2020;103:154006. doi:10.1016/j.metabol.2019.154006
111. Gesmundo I, Pardini B, Gargantini E, et al. Adipocyte-derived extracellular vesicles regulate survival and function of pancreatic β cells. *JCI Insight*. 2021;6(5):e141962. doi:10.1172/jci.insight.141962
112. Gao H, Luo Z, Jin Z, Ji Y, Ying W. Adipose tissue macrophages modulate obesity-associated β cell adaptations through secreted miRNA-containing extracellular vesicles. *Cells*. 2021;10(9):2451. doi:10.3390/cells10092451
113. Cui X, You L, Zhu L, et al. Change in circulating microRNA profile of obese children indicates future risk of adult diabetes. *Metabolism*. 2018;78:95-105. doi:10.1016/j.metabol.2017.09.006
114. Yu Y, Du H, Wei S, et al. Adipocyte-derived exosomal MiR-27a induces insulin resistance in skeletal muscle through repression of PPARγ. *Theranostics*. 2018;8(8):2171-2188. doi:10.7150/thno.22565
115. Wang Y, Li Y, Wang X, et al. Circulating miR-130b mediates metabolic crosstalk between fat and muscle in overweight/obesity. *Diabetologia*. 2013;56(10):2275-2285. doi:10.1007/s00125-013-2996-8
116. Katayama M, Wiklander OPB, Fritz T, et al. Circulating exosomal miR-20b-5p is elevated in type 2 diabetes and could impair insulin action in human skeletal muscle. *Diabetes*. 2019;68(3):515-526. doi:10.2337/db18-0470
117. Li X, Ballantyne LL, Yu Y, Funk CD. Perivascular adipose tissue-derived extracellular vesicle miR-221-3p mediates vascular remodeling. *FASEB J*. 2019;33(11):12704-12722. doi:10.1096/fj.201901548R
118. Wen Z, Li J, Fu Y, Zheng Y, Ma M, Wang C. Hypertrophic adipocyte-derived exosomal miR-802-5p contributes to insulin resistance in cardiac myocytes through targeting HSP60. *Obes Silver Spring Md*. 2020;28(10):1932-1940. doi:10.1002/oby.22932
119. Shaihov-Teper O, Ram E, Ballan N, et al. Extracellular vesicles from epicardial fat facilitate atrial fibrillation. *Circulation*. 2021;143(25):2475-2493. doi:10.1161/CIRCULATIONAHA.120.052009
120. Gan L, Xie D, Liu J, et al. Small extracellular microvesicles mediated pathological communications between dysfunctional adipocytes and cardiomyocytes as a novel mechanism exacerbating ischemia/reperfusion injury in diabetic mice. *Circulation*. 2020;141(12):968-983. doi:10.1161/CIRCULATIONAHA.119.042640
121. Fang X, Stroud MJ, Ouyang K, et al. Adipocyte-specific loss of PPARγ attenuates cardiac hypertrophy. *JCI Insight*. 2016;1(16):e89908. doi:10.1172/jci.insight.89908
122. Sun HX, Zeng DY, Li RT, et al. Essential role of microRNA-155 in regulating endothelium-dependent vasorelaxation by targeting endothelial nitric oxide synthase. *Hypertension*. 2012;60(6):1407-1414. doi:10.1161/HYPERTENSIONAHA.112.197301
123. Liu Y, Wang Y, Wang C, et al. Maternal obesity increases the risk of fetal cardiac dysfunction via visceral adipose tissue derived exosomes. *Placenta*. 2021;105:85-93. doi:10.1016/j.placenta.2021.01.020
124. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature*. 2000;404(6778):661-671. doi:10.1038/35007534
125. Caron A, Lee S, Elmquist JK, Gautron L. Leptin and brain–adipose crosstalks. *Nat Rev Neurosci*. 2018;19(3):153-165. doi:10.1038/nrn.2018.7
126. Derghal A, Djelloul M, Azzarelli M, et al. MicroRNAs are involved in the hypothalamic leptin sensitivity. *Epigenetics*. 2018;13(10–11):1127-1140. doi:10.1080/15592294.2018.1543507
127. Crépin D, Benomar Y, Riffault L, Amine H, Gertler A, Taouis M. The over-expression of miR-200a in the hypothalamus of ob/ob mice is linked to leptin and insulin signaling impairment. *Mol Cell Endocrinol*. 2014;384(1–2):1-11. doi:10.1016/j.mce.2013.12.016
128. Sangiao-Alvarellos S, Pena-Bello L, Manfredi-Lozano M, Tena-Sempere M, Cordido F. Perturbation of hypothalamic microRNA expression patterns in male rats after metabolic distress: impact of obesity and conditions of negative energy balance. *Endocrinology*. 2014;155(5):1838-1850. doi:10.1210/en.2013-1770
129. Zhuang X, Xiang X, Grizzle W, et al. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. *Mol Ther*. 2011;19(10):1769-1779. doi:10.1038/mt.2011.164
130. Matsumoto J, Stewart T, Sheng L, et al. Transmission of α-synuclein-containing erythrocyte-derived extracellular vesicles across the blood-brain barrier via adsorptive mediated transcytosis: another mechanism for initiation and progression of Parkinson's disease? *Acta Neuropathol Commun*. 2017;5(1):71. doi:10.1186/s40478-017-0470-4
131. Chen CC, Liu L, Ma F, et al. Elucidation of exosome migration across the blood–brain barrier model in vitro. *Cell Mol Bioeng*. 2016;9(4):509-529. doi:10.1007/s12195-016-0458-3

132. Balusu S, Van Wonterghem E, De Rycke R, et al. Identification of a novel mechanism of blood–brain communication during peripheral inflammation via choroid plexus-derived extracellular vesicles. *EMBO Mol Med*. 2016;8(10):1162-1183. doi:10.15252/emmm.201606271
133. Gao J, Li X, Wang Y, et al. Adipocyte-derived extracellular vesicles modulate appetite and weight through mTOR signalling in the hypothalamus. *Acta Physiol*. 2020;228(2):e13339. doi:10.1111/apha.13339

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