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Adipose-derived extracellular vesicle miRNAs: multifunctional regulators of brain function

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Highlights:

- Adipose depot, cellular origin and metabolic state jointly shape extracellular vesicle-associated microRNA output.
- Adipose-derived extracellular vesicle-associated microRNAs may link peripheral adipose signals with hypothalamic leptin sensitivity, hippocampal synaptic plasticity, and changes in microglial functional states.
- Adipose-derived exosomal microRNAs are important regulators of central metabolic, cognitive, stress-related, and neuroimmune processes.

Abstract: Adipose tissue is increasingly recognized as a highly heterogeneous secretory organ, and the extracellular vesicle-associated microRNAs (EV-miRNAs) it releases can act as peripheral molecular signals involved in long-distance regulation. Current evidence indicates that adipose-derived EV-miRNAs exhibit pronounced adipose depot- and cell-of-origin specificity, and that their composition can be dynamically altered by metabolic state. Following biogenesis and selective sorting, these miRNAs can be transported through the circulation within EVs and, under certain conditions, gain access to the central nervous system (CNS). Functional studies have shown that adipose-derived EV-miRNAs primarily act on neurons and, in some pathological models, modulate microglial function, thereby contributing to the regulation of hypothalamic energy homeostasis, learning and memory, emotional and stress-related responses, and neuroimmune processes. Obesity further remodels the adipose-derived EV-miRNA repertoire, enhancing pathological miRNA signals while concomitantly reducing certain homeostatic miRNA signals, thereby altering their regulatory effects on the central nervous system. This review systematically summarizes the tissue and cellular origins, biogenesis and selective sorting,

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circulatory transport and central delivery of adipose-derived EV-miRNAs, as well as their regulatory effects across multiple dimensions of brain function. Collectively, adipose-derived EV-miRNAs constitute an important molecular signaling layer through which adipose tissue states influence brain function; however, their source-specific profiles under physiological conditions, mechanisms of brain region- and cell-specific targeting, and causal roles and translational potential in human disease remain to be further elucidated.

Keywords: adipose tissue; extracellular vesicles; microRNAs; adipose–brain communication; obesity; brain function

1. Introduction

Maintenance of systemic homeostasis requires the central nervous system (CNS) to continuously sense and integrate metabolic and physiological signals arising from peripheral tissues [1,2]. Among these peripheral organs, adipose tissue serves as an important source of information regarding long-term energy stores and communicates closely with the brain through humoral and neuronal pathways [3,4]. Leptin is one of the best-characterized mediators of adipose–brain communication; its circulating levels broadly reflect adiposity, and its actions on hypothalamic neural circuits contribute to the regulation of food intake and energy expenditure [5]. However, accumulating evidence indicates that adipose–brain communication extends beyond classical adipokines such as leptin and may also involve additional molecular signals capable of conveying the functional and metabolic state of adipose tissue to the CNS.

Extracellular vesicles (EVs) have emerged as important mediators of long-distance inter-organ communication by transporting bioactive molecules, including proteins, lipids, and nucleic acids, to distant recipient cells [6,7]. In recent years, EV-associated microRNAs (miRNAs) have increasingly been recognized as functionally important mediators of intercellular communication, as they can modulate gene expression in recipient cells through post-transcriptional regulation [8]. Genetic and functional studies indicate that adipose tissue is an important source of circulating miRNAs [9], whereas the miRNA composition of adipose-derived EVs does not simply mirror intracellular miRNA abundance in donor cells. Instead, it is jointly shaped by adipose depot identity, cellular origin, miRNA biogenesis, selective sorting, and metabolic state [10]. Accordingly, adipose-derived EV-miRNAs may constitute a source- and state-dependent functional signaling output through which adipose tissue conveys its physiological and metabolic status to distant organs. Of particular relevance, selected adipose-derived EV-miRNAs can act on specific recipient cells within the central nervous system and modulate neuronal and glial function through target-gene and pathway regulation, thereby providing a potential molecular mechanism linking adipose tissue status to brain function [11].

Building on this foundation, the focus of current research has gradually shifted from whether adipose-derived EV-miRNAs participate in peripheral-to-central communication to the specific functions they exert in distinct brain regions and recipient cell populations. Existing studies have linked adipose-derived EV-miRNAs to multiple central processes, including hypothalamic regulation of energy metabolism, hippocampus-related cognitive function, emotional and stress responses, and neuroimmune regulation, suggesting that these signals may help connect peripheral metabolic states with multidimensional aspects of brain function. However, the available evidence remains fragmented across studies examining different adipose sources, miRNA species, transport routes, recipient cells, and

neurological outcomes, and these findings have yet to be systematically integrated. Accordingly, this review examines the tissue and cellular origins, biogenesis and selective sorting, circulatory transport, and central delivery of adipose-derived EV-miRNAs, with particular emphasis on their emerging roles in energy homeostasis, learning and cognition, emotional and stress-related responses, and neuroimmune regulation.

2. Adipose tissue as a heterogeneous secretory organ

Historically regarded as a passive energy storage tissue, adipose tissue is now recognized as a highly dynamic endocrine and communication organ that participates in the establishment of complex systemic inter-organ signaling networks through the release of diverse bioactive molecules, including classical adipokines, inflammatory mediators, lipid-derived metabolites, and extracellular vesicle (EV)-associated nucleic acids [12–14]. Beyond its traditional role in energy storage and metabolic buffering, adipose tissue functions as an important signaling interface that integrates nutritional status, environmental cues, and inflammatory stimuli, thereby shaping the functional states of distant organs [15].

Importantly, adipose tissue is not a homogeneous entity but consists of multiple anatomically and functionally distinct adipose depots, including brown adipose tissue (BAT), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) [16,17]. In addition, adipose tissue contains diverse resident cellular populations, such as mature adipocytes, adipose tissue macrophages (ATMs), and adipose-derived stromal/stem cells (ADSCs). The unique characteristics of these depots and cellular populations collectively establish distinct secretory landscapes [18], thereby shaping the composition and functional properties of adipose-derived circulating miRNAs [19]. Understanding the source-dependent heterogeneity of adipose miRNAs provides a critical framework for elucidating their roles as systemic signaling molecules in both physiological adaptation and pathological progression.

2.1. Depot-specific identity determines distinct miRNA secretory profiles

2.1.1. Brown adipose tissue: thermogenic miRNA signals and potential central communication

BAT is a metabolically specialized thermogenic adipose depot characterized by abundant mitochondria and uncoupling protein 1 (UCP1)-dependent non-shivering thermogenesis [16,20]. Beyond its classical role in thermoregulation, BAT also functions as an endocrine organ, releasing EVs carrying functional miRNAs and thereby generating a distinct miRNA signature associated with thermogenic adaptation and systemic metabolic regulation [21].

Early studies have shown that BAT makes a substantial contribution to the circulating miRNA pool [22], with BAT-enriched miRNAs such as miR-99b-5p and miR-122-5p participating in metabolic communication between adipose tissue and the liver [9]. Its EV-miRNA profile also exhibits marked responsiveness to environmental stimuli. For example, cold stimulation promotes the enrichment of miR-378a-3p in BAT-derived EVs and regulates hepatic glucose metabolism [23], whereas circulating EV-associated miR-92a levels are inversely correlated with human BAT activity, further illustrating the relationship between BAT miRNA output and thermogenic adaptation [24]

Beyond peripheral metabolic regulation, emerging evidence suggests that BAT-derived miRNAs may participate in communication between adipose tissue and the central nervous system. Using BAT-specific RNA-tracing strategies, several BAT-derived miRNAs, including members of the let-7 family, miR-26a-5p, and miR-181-5p, have been detected in the hypothalamus [9]. Although their specific

cellular targets and functional consequences within the central nervous system remain to be fully elucidated, the presence of these BAT-derived miRNAs in the hypothalamus, a key center for metabolic regulation, suggests that BAT may convey peripheral metabolic information to the brain through circulating miRNA signals and potentially modulate neural circuits involved in energy homeostasis.

In summary, BAT-derived EV-miRNAs function as adaptive endocrine signals responsive to thermal and nutritional cues. While their presence in the hypothalamus suggests a potential central regulatory role, the identity of their functional targets and the physiological relevance of this peripheral-to-central signaling axis remain to be fully established.

2.1.2. Visceral adipose tissue: peripheral metabolic regulation and emerging brain-directed miRNA signaling

VAT is a metabolically active white adipose depot whose extracellular miRNA signals are primarily implicated in lipid and glucose metabolism, insulin responsiveness, vascular function, and immunometabolic regulation, and can mediate long-distance inter-organ signaling through EVs [6]. However, compared with the relatively well-characterized depot-specific miRNA secretory profile of BAT, the basal EV-miRNA repertoire of VAT under physiological conditions remains insufficiently characterized, and a clearly defined VAT-specific EV-miRNA landscape has yet to be established.

Nevertheless, recent functional studies have identified several VAT-derived EV-miRNAs with well-defined effects on distant tissues, providing direct evidence for their endocrine signaling potential. For example, EV-miR-27b-3p can be delivered to vascular endothelial cells and regulate PPARα-related signaling [25], whereas EV-miR-27a-5p acts on pancreatic islets to modulate β-cell insulin secretion, demonstrating the capacity of VAT-derived miRNAs to regulate distant metabolic tissues [26]. Notably, these miRNAs have been investigated primarily under obesity or metabolic stress and therefore more likely represent state-dependent remodeling rather than the basal VAT miRNA repertoire.

Emerging evidence further extends VAT-derived miRNA regulation to the central nervous system. VAT-derived EV-miR-140-5p can reach the hippocampus, where it suppresses the cyclic AMP response element-binding protein (CREB)–brain-derived neurotrophic factor (BDNF) signaling pathway and impairs synaptic plasticity under metabolic stress, providing functional evidence that VAT-derived miRNAs can directly modulate central neural function [27]. Whether a conserved, physiologically relevant VAT-to-brain EV-miRNA axis exists under non-pathological conditions, however, remains an open question.

2.1.3. Subcutaneous adipose tissue: context-dependent distal EV-miRNA regulation

SAT has a strong capacity for lipid storage and metabolic buffering and plays an important role in maintaining systemic glucose and lipid homeostasis [17]. Although the basal EV-miRNA profile of SAT under physiological conditions has not yet been systematically characterized, recent functional studies have identified SAT-derived EV-miRNAs with well-defined effects on distant tissues. SAT-derived EVs have been shown to reach the lung and be taken up by alveolar macrophages, where EV-associated miR-26a-5p targets CHUK and suppresses the NF-κB signaling pathway, thereby alleviating inflammatory responses and lung injury [28]. These findings provide direct evidence that SAT-derived EV-miRNAs can regulate the function of distant tissues. Notably, this effect has been demonstrated primarily in the

context of acute lung injury and therefore reflects the potential of SAT-derived EV-miRNAs for distal regulation rather than directly representing their basal secretory function under physiological conditions.

Compared with BAT and VAT, direct evidence for the regulation of the central nervous system by SAT-derived EV-miRNAs remains limited. Although SAT-derived EV-miRNAs have been shown to act on distant tissues, direct *in vivo* evidence is still lacking as to whether they can reach specific brain regions, be taken up by neurons or glial cells, and modulate central nervous system function. Thus, while SAT-derived EV-miRNAs have demonstrated distal regulatory capacity in peripheral disease models, direct *in vivo* evidence for their transport to, and functional impact on, specific brain regions or neural cell types is currently lacking.

2.2. Cell-specific identity determines distinct miRNA secretory profiles

2.2.1. Adipocytes: functional state-dependent EV-miRNA secretory profiles and central regulatory potential

Genetic studies have provided direct evidence that adipocytes are an important source of circulating miRNAs. For example, in adipocyte-specific Dicer knockout (ADicerKO) mice, impaired miRNA biogenesis in adipocytes was accompanied by a marked reduction in circulating exosomal miRNA levels, whereas transplantation of wild-type adipose tissue partially restored circulating miRNA levels, indicating that adipocytes actively contribute to the circulating miRNA pool and mediate long-distance molecular signaling [22]. Further small-RNA sequencing of adipocyte-derived EVs identified miR-148a-3p as one of the most abundant miRNAs and revealed marked differences in EV-miRNA composition according to adipocyte developmental stage and metabolic phenotype. Specifically, miR-98-5p was significantly enriched in EVs derived from young adipocytes with more pronounced lipolytic and thermogenic characteristics, whereas miR-365-3p was predominantly detected in EVs from adult adipocytes with greater lipogenic activity [29]. These findings indicate that adipocytes do not release a uniform pool of miRNAs but instead generate EV-miRNA output profiles associated with their functional state. Notably, recent studies have further identified adipocyte-derived EV-miRNAs with central regulatory activity, including miR-148a-3p, miR-30a-3p, and miR-181d-5p, providing direct evidence that functional miRNA signals originating from adipocytes can participate in the regulation of brain function [30].

2.2.2. Adipose tissue macrophages: a microenvironment-dependent EV-miRNA secretory phenotype

ATMs represent an important immune-cell source of extracellular miRNAs within adipose tissue and actively release small sEVs carrying functional miRNA cargos. Small-RNA sequencing identified miR-6236 as the most abundant miRNA in EVs derived from $CD9^+$ lipid-associated macrophages [31], whereas miR-690 was identified as an important functional miRNA in ATM-derived sEVs with insulin-sensitizing effects [32]. These findings indicate that ATMs generate EV-miRNA outputs associated with their cellular functional states and thereby contribute to the regulation of metabolic homeostasis. Notably, ATM-derived EV-miRNAs exhibit pronounced microenvironmental dependence. Under obesity-associated lipid-rich and hypoxic conditions, ATMs increase the release of EV-associated miR-210-3p, which can act on adipocytes, skeletal muscle cells, and hepatocytes and suppress GLUT4-mediated glucose uptake, further indicating that ATMs can generate EV-miRNA signals with distinct biological effects according to their functional state [33]. However, direct evidence for the

regulation of the central nervous system by ATM-derived EV-miRNAs remains limited, with a lack of direct *in vivo* evidence demonstrating their entry into specific brain regions or their actions on neurons or glial cells. Therefore, whether ATM-derived EV-miRNAs can serve as peripheral signals that directly participate in central neuroimmune or metabolic regulation remains to be determined.

2.2.3. Adipose-resident stem/progenitor cells: a potential EV-miRNA secretory phenotype associated with tissue repair and immunoregulation

Unlike mature adipocytes and ATMs, adipose-resident stem/progenitor cells (ASCs/APCs) exhibit a secretory phenotype more closely associated with tissue repair and immunoregulation, a functional property that is also reflected in their EV-associated miRNA repertoire. A recent study reported that miR-145-5p is enriched in EVs derived from young adipose progenitor cells and contributes to the regulation of macrophage inflammatory states [34]. The potential effects of EVs derived from adipose stromal/stem cells on CNS immune responses have been examined mainly through the therapeutic administration of EVs obtained from cultured adipose-derived mesenchymal stem/stromal cells (ADSC-EVs). In an experimental cerebral ischemia model, post-injury ADSC-EV administration was associated with altered microglial responses and improved neurological recovery, while EV profiling and *in vitro* experiments suggested candidate miRNA-mediated mechanisms [11]. However, these findings do not establish constitutive EV-miRNA signaling from native ASCs/APCs to brain-resident immune cells or the *in vivo* causal roles of individual miRNAs. Therefore, the basal EV-miRNA output of native ASCs/APCs under physiological conditions and its potential contribution to CNS regulation remain to be determined.

The pronounced heterogeneity in the cellular and depot origins of adipose-derived EV-miRNAs forms the biological basis for their diverse effects on central nervous system function. To provide a synoptic overview, Table 1 summarizes the representative EV-miRNAs discussed in this review, their adipose sources, brain targets, and functional outcomes, serving as a roadmap for the detailed mechanistic dissection presented in the following sections.

3. Biogenesis, selective sorting and secretion mechanisms of adipose-derived microRNAs

3.1. Canonical biogenesis of adipose-derived miRNAs and its metabolic regulation

Most adipose-derived miRNAs are generated through the canonical miRNA biogenesis pathway shared by mammalian cells. Primary miRNA transcripts (pri-miRNAs) are initially processed in the nucleus by the DROSHA–DGCR8 microprocessor complex to generate precursor miRNAs (pre-miRNAs), which are subsequently exported to the cytoplasm by Exportin-5 (XPO5). In the cytoplasm, pre-miRNAs are further cleaved by DICER together with its cofactor TRBP to produce miRNA duplexes. The guide strand is then selectively loaded onto an Argonaute protein to form the RNA-induced silencing complex (RISC), which mediates post-transcriptional repression of target genes [35,36]. Notably, miRNA processing in adipocytes is not a constitutively fixed process but can respond dynamically to metabolic cues. Lino *et al.* demonstrated in differentiated 3T3-L1 adipocytes that insulin stimulation increased the expression of several genes involved in miRNA biogenesis and processing, including Dgcr8, Drosha, Dicer, Trbp, and Xpo5, suggesting that the miRNA biogenesis machinery in adipocytes is metabolically regulated. However, such regulation does not translate directly into extracellular

miRNA output. Following insulin treatment, 53 miRNAs were upregulated and 66 were downregulated in small sEVs, whereas only 12 of these miRNAs exhibited concordant changes in their intracellular abundance [37]. These findings indicate that the sEV-miRNA repertoire does not simply passively mirror the intracellular miRNA pool of donor adipocytes [37]. Therefore, before mature adipose-derived miRNAs enter the EV secretory pathway, they are subject to an additional layer of selective sorting [8,38].

3.2. Sequence- and RBP-dependent selective sorting of adipocyte miRNAs into sEVs

Selective sorting is an important regulatory step that determines the extracellular miRNA repertoire of adipocytes. Garcia-Martin *et al.* found that miRNAs contain short sequence elements that influence their intracellular fate[8]. Sequences that promote incorporation into sEVs were defined as EXOmotifs, whereas those that favor retention within donor cells were termed CELLmotifs. These sequence elements exhibit marked cell-type specificity and were identified across several metabolically relevant cell types, including differentiated white and brown adipocytes. Functional insertion or mutation of these motifs further demonstrated that they can directly alter the distribution of individual miRNAs between cells and sEVs. Mechanistically, the RNA-binding proteins ALYREF and FUS were shown to participate in the selective export of miRNAs carrying the strong EXOmotif CGGGAG into sEVs; knockdown of either protein significantly reduced the sEV sorting efficiency of these miRNAs. These findings support a "miRNA sequence code–RBP recognition" model of selective sorting, in which intrinsic miRNA sequence features are recognized by specific RNA-binding proteins and thereby influence whether a miRNA is retained intracellularly or preferentially secreted into sEVs.Importantly, this sequence-dependent sorting process is not static but can be dynamically modulated by the metabolic state of adipocytes. In differentiated 3T3-L1 adipocytes, Lino *et al.* showed that insulin alters the selective distribution of miRNAs between cells and sEVs [37]. miRNAs whose secretion was enhanced by insulin were enriched in AU-rich motifs, whereas miRNAs preferentially retained within adipocytes were enriched in poly-G motifs. Mechanistically, insulin induced phosphorylation of the AU-rich motif-binding protein hnRNPA1 and enhanced its association with AU-rich miRNAs, exemplified by miR-103-3p. Mutation of the corresponding motif weakened this interaction, whereas hnRNPA1 knockdown significantly reduced insulin-stimulated secretion of miR-103-3p into sEVs. In addition, hnRNPA2B1, YBX1, SYNCRIP, and AGO2 have been reported to participate in EV-miRNA sorting in other mammalian cell systems [39–41], providing a broader mechanistic framework for understanding miRNA sorting in adipose tissue. However, whether these pathways operate similarly in adipocytes remains to be directly validated. Collectively, adipocyte sEV-miRNA output can be viewed as a dynamic process jointly shaped by intrinsic miRNA sequence codes, motif-recognizing RBPs, and metabolically regulated RBP activity.

3.3. Vesicular and non-vesicular pathways of extracellular miRNA transport

Adipose-derived microRNAs can be stably transported in the circulation through both vesicle-dependent and non-vesicular mechanisms. Among these, EVs, including exosomes and microvesicles, represent a major vehicle for adipose-derived miRNA transport [7]. In addition to EV-mediated transport, circulating miRNAs can also be stabilized in non-vesicular forms through association with RNA-binding proteins, particularly Argonaute 2 (AGO2) [42], or with circulating lipoproteins. Among the latter, HDL-associated miRNAs are the best characterized, whereas miRNA association with LDL and VLDL has

also been reported [9,43]. These carrier-associated forms protect extracellular miRNAs from RNase-mediated degradation and contribute to their stability in the circulation.

4. The pathway by which adipose-derived miRNAs enter the brain and target brain cells

4.1. Interaction with and transport across the blood–brain barrier

For adipose-derived EV-associated miRNAs to exert regulatory effects on brain function, they must achieve effective transport from the peripheral circulation to the central nervous system. The blood–brain barrier (BBB), a highly selective neurovascular interface, represents a major obstacle restricting the entry of circulating molecules into the brain. Increasing evidence indicates that EVs possess the capacity to interact with brain microvascular endothelial cells and undergo intracellular uptake and transcytotic transport across the BBB [44]. Metabolic abnormalities, including obesity, insulin resistance, and chronic low-grade inflammation, may impair BBB integrity by inducing cerebral microvascular endothelial dysfunction, increasing oxidative stress, and disrupting the stability of tight junction proteins, including claudin-5, occludin, and zonula occludens-1 (ZO-1), thereby promoting neurovascular unit remodeling [45]. Such pathological alterations of the BBB may increase the accessibility of circulating adipose-derived EV-miRNAs to the central nervous system, potentially facilitating peripheral-to-central metabolic communication [46]. Importantly, the BBB should not be regarded merely as a passive physical barrier restricting EV entry. Instead, pathological remodeling of the BBB may reshape EV–endothelial interactions by altering endothelial adhesion molecules, receptor expression, and endocytic/transcytotic pathways, thereby influencing the biodistribution, cellular targeting, and biological effects of adipose-derived EV-miRNAs within the CNS [47].

4.2. Cellular uptake and target engagement within the CNS

After reaching the brain, adipose tissue-derived EVs may exhibit cell-type-selective localization. In the animal study reported by Wang *et al.* [46], adipose tissue-derived EVs were fluorescently labeled and systemically administered to mice, and their cellular distribution was subsequently examined by immunofluorescence-based co-localization analysis. EV-associated fluorescent signals were detected predominantly in NeuN-positive neurons, with particularly prominent localization in hippocampal neurons, whereas co-localization with astrocytic and microglial markers was comparatively limited. These findings support preferential neuronal localization of experimentally administered adipose tissue-derived EVs under the conditions examined, but do not establish universal neuron-specific tropism of all adipose-derived EV populations. Moreover, fluorescent co-localization alone does not demonstrate functional delivery of EV-associated miRNAs or engagement of their intracellular targets. Although astrocytes and microglia are generally competent to internalize extracellular vesicles and may participate in neural responses to peripheral EV signals [48–50], whether adipose tissue-derived EV-miRNAs are functionally delivered to these glial populations and regulate defined molecular targets remains to be established.

5. Adipose tissue heterogeneity and metabolic state shape EV miRNA output

5.1. Obesity-driven remodeling of adipose tissue EV-miRNA secretory profiles

Obesity broadly remodels the adipose-derived EV-miRNA landscape rather than merely altering the abundance of a limited number of individual miRNAs. This remodeling involves both the increase of pathological miRNA cargos and the loss of miRNAs with homeostatic regulatory functions, thereby altering the functional molecular information carried by adipose-derived EVs. Direct miRNA profiling has demonstrated that high-fat diet (HFD)-induced obesity markedly alters the miRNA composition of visceral adipose tissue-derived EVs (VAT-EVs), with miR-140-5p further identified as a representative obesity-associated miRNA cargo with functional effects in the central nervous system [27]. Similarly, under obesity and insulin-resistant conditions, the miRNA cargo of adipose tissue-derived EVs undergoes pathological remodeling, with miR-9-3p identified as a representative functional miRNA involved in mediating the adverse effects of pathological adipose EVs on the central nervous system [46]. Conversely, obesity is also accompanied by reductions in leptin-sensitizing miRNAs, including miR-148a-3p, miR-30a-3p, and miR-181d-5p, in adipocyte-derived EVs, indicating that obesity-associated EV-miRNA remodeling involves not only the gain of detrimental signals but also the loss of homeostatic miRNA signals [30].

Obesity-induced EV-miRNA remodeling also exhibits pronounced adipose depot dependence. Comparative analyses of EVs derived from visceral white adipose tissue (vWAT), inguinal white adipose tissue (iWAT), and brown adipose tissue (BAT) have shown that diet-induced obesity (DIO) produces depot-specific alterations in EV composition and function. In particular, EVs derived from obese vWAT exhibit more pronounced pro-inflammatory and lipid-accumulating effects, accompanied by remodeling of their miRNA cargo [51]. miR-200a-3p and miR-200b-3p were further identified as representative vWAT EV-miRNAs that promote lipid accumulation, at least in part through PI3K–AKT–mTOR signaling. These findings indicate that the intrinsic anatomical and functional heterogeneity of adipose tissue further shapes depot-specific patterns of EV-miRNA remodeling during obesity [51].

Collectively, obesity remodels the adipose tissue EV-miRNA secretory profile at multiple levels, including overall cargo composition, depot-specific output, and the functional balance between homeostatic and pathological miRNAs. These alterations are not merely molecular signatures but have clear functional consequences, with the resulting EV-miRNA profiles capable of influencing both peripheral metabolism and central neural signaling. Thus, metabolic state represents an important determinant shaping the composition and functional properties of adipose-derived EV-miRNAs.

5.2. Aging-associated changes in adipose tissue EV-miRNA profiles

Adipose tissue heterogeneity is not only depot-specific but also dynamically shaped by aging [52]. Age-related adipocyte dysfunction, cellular senescence, chronic inflammation [53], and changes in stromal and immune cell composition can remodel the adipose secretory phenotype [54], leading to substantial alterations in EV-associated miRNA profiles [55]. However, a conserved aging-specific miRNA signature has not yet been established across studies.

5.3. Sex-dependent regulation of adipose miRNA expression

Sex represents another source of adipose tissue heterogeneity. Gonadal hormones and sex chromosome complement have been shown to shape adipose tissue miRNA expression profiles [56], while biological sex also influences adipose distribution, metabolic function, and inflammatory status [57]. Although sex-dependent differences in adipose tissue miRNA expression have been demonstrated, intracellular miRNA abundance does not necessarily reflect EV-associated miRNA levels because miRNAs are selectively sorted into EVs. Thus, whether sex-dependent changes in adipose miRNA expression translate into corresponding alterations in the secreted EV-miRNA profile remains to be determined.

6. Multifaceted roles of adipose-derived EV-miRNAs in regulating brain functions

6.1. Regulation of central metabolic circuits and energy homeostasis

As highlighted in Table 1, adipocyte-derived EVs enriched under healthy conditions carry a specific set of miRNAs (e.g., miR-148a-3p, miR-30a-3p, miR-181d-5p) that converge on hypothalamic circuits.

Central energy homeostasis is coordinated by a distributed neural network comprising the hypothalamus, brainstem, and higher-order cortical–limbic systems, with the hypothalamus serving as a central hub for integrating peripheral metabolic signals [58]. Within the arcuate nucleus (ARC), two distinct neuronal populations sense peripheral hormonal and nutritional cues: orexigenic AgRP/NPY neurons and anorexigenic POMC neurons. Through their projections to downstream melanocortin circuits, these neurons coordinately regulate food intake and energy expenditure [59]. Therefore, hypothalamic metabolic neurons represent the primary potential targets for investigating how adipose-derived EV-miRNAs regulate central energy homeostasis. Studies have demonstrated that, under physiological conditions, adipocyte-derived extracellular vesicles can access the central nervous system, with adipocyte-derived extracellular vesicle signals preferentially enriched in leptin receptor-expressing ($LepR^{+}$) neurons within the arcuate nucleus (ARC), suggesting that adipose tissue participates in hypothalamic metabolic regulation through EV-mediated molecular communication [30]. Further studies revealed that adipocyte-derived extracellular vesicle signaling contributes to the maintenance of leptin–melanocortin neural circuit function, thereby supporting systemic energy homeostasis. Notably, this regulatory process is not solely dependent on EVs as delivery vehicles, but is likely mediated by selectively enriched functional miRNA cargos contained within these vesicles. Therefore, obesity-associated metabolic dysfunction may not simply reflect alterations in adipose EV-miRNA composition, but rather represent the remodeling and disruption of a physiological adipose–brain EV-miRNA communication network that normally contributes to metabolic adaptation. To elucidate the functional role of AT-EVs in central metabolic regulation, researchers employed an adipose tissue-specific Rab27 deficiency model to reduce EV secretion and further performed intracerebroventricular (i.c.v.) supplementation of adipocyte-derived extracellular vesicles. The results demonstrated that impaired adipose EV secretion was associated with reduced neuronal activity in multiple hypothalamic metabolic regions and disruption of leptin–melanocortin signaling, whereas central administration of adipocyte-derived extracellular vesicles partially restored the altered neuronal activity patterns. These findings suggest that adipose-derived EVs participate in regulating the function of hypothalamic leptin-sensitive neural circuits.

Subsequent EV-miRNA profiling revealed that obesity induced substantial remodeling of the adipose EV-miRNA landscape and identified a group of candidate miRNAs involved in the regulation of leptin sensitivity. Among these, miR-148a-3p, miR-30a-3p, and miR-181d-5p were enriched in healthy adipose-derived EVs and enhanced leptin signaling responses by targeting negative regulators of the leptin pathway, including SOCS3, PIAS3, and PTEN. Clinical sample analyses further demonstrated that these leptin-sensitizing miRNAs were reduced in individuals with obesity, with circulating levels of miR-148a-3p, miR-30a-3p, and miR-181d-5p inversely correlated with body mass index (BMI) and partially restored following bariatric surgery. These findings suggest that dysregulation of adipose EV-miRNAs may contribute to the development of obesity-associated leptin resistance.

To validate the functional effects of these candidate miRNAs, researchers used adeno-associated virus (AAV)-mediated expression to selectively overexpress miR-148a-3p and miR-30a-3p in ARC neurons of diet-induced obesity mice. Overexpression of these miRNAs reduced body weight and food intake, increased energy expenditure, and enhanced leptin-induced activation of c-Fos and phosphorylated STAT3 (pSTAT3), indicating improved hypothalamic leptin sensitivity. Furthermore, adipose tissue-specific overexpression of these miRNAs similarly ameliorated obesity-related metabolic phenotypes, suggesting their potential therapeutic relevance in metabolic disorders and further supporting the critical role of adipose-derived EV-miRNAs in regulating central leptin sensitivity and energy homeostasis.

Collectively, the hypothalamic actions of adipose-derived EV-miRNAs exemplify a bidirectional equilibrium model: under physiological conditions, EV-miRNAs such as miR-148a-3p and miR-30a-3p actively sustain leptin sensitivity, whereas obesity simultaneously augments pathogenic signals (e.g., miR-140-5p) and depletes these homeostatic signals. This dual disruption-a gain of detrimental signals coupled with a loss of beneficial ones-likely represents a critical molecular mechanism driving the transition from metabolic adaptation to maladaptation in the central regulation of energy balance. This “yin-yang” remodeling may be a general principle extending to cognitive and affective domains.

6.2. Regulation of learning, memory and cognitive functions

The cognitive domain includes experimentally investigated pathological EV-miRNAs, such as adipose tissue-derived miR-9-3p, as well as human biomarker candidates, such as circulating exosomal miR-125a-5p (Table 1).

Learning, memory, and cognition rely on coordinated neural networks involving the hippocampus, prefrontal cortex, and amygdala, which primarily contribute to memory encoding and consolidation, executive control, and emotional memory, respectively [60,61]. Their coordinated activity provides a neural substrate through which peripheral signals, including adipose-derived miRNAs, may influence cognitive function.

Table 1. Representative adipose-derived EV-miRNAs implicated in the regulation of brain function.

miRNA	Adipose source and metabolic context	Brain region/ recipient cell	Molecular targets and pathways	CNS effects	Evidence type	Key outcomes	Reference
miR-148a-3p, miR-30a-3p, miR-181d-5p	Adipocyte-derived EVs; enriched under healthy conditions and reduced in obesity; inversely associated with BMI	ARC/LepR$^+$ neurons	Candidate negative regulators of leptin signaling; enhanced leptin–STAT3 responsiveness	Enhanced leptin responsiveness and energy homeostasis; direct ARC functional validation strongest for miR-148a-3p and miR-30a-3p	Rodent DIO models; AAV-based functional studies; human observational validation	Loss of these miRNAs in obesity may contribute to central leptin resistance	[30]
miR-9-3p	Pathological adipose tissue EVs; identified under HFD, insulin-resistant, and diabetic conditions	Hippocampal neurons	BDNF suppression → impaired neurotrophic signaling and synaptic homeostasis; SLC7A11 inhibition → impaired antioxidant defense, oxidative stress, iron accumulation, and ferroptosis	Synaptic dysfunction, impaired neurotrophic signaling, oxidative stress, iron accumulation, neuronal ferroptosis, and cognitive impairment	Rodent HFD and diabetes models, including transfer experiments using EVs isolated from patients with diabetes; adipose-specific miR-9-3p inhibition.	Promotes hippocampal injury and cognitive impairment	[46,62]
miR-125a-5p	Adipose-associated exosomal miRNA; elevated in individuals with T2DM and cognitive vulnerability	Direct CNS delivery and recipient brain cell not established; left hippocampal body volume assessed by structural neuroimaging	Mechanism not yet defined	Increased susceptibility to amnestic mild cognitive impairment; a smaller left hippocampal body volume	Human adipose-tissue and serum exosomal miRNA profiling; Mendelian randomization; multicenter human cohorts; neuroimaging analysis	Candidate circulating biomarker of cognitive vulnerability in T2DM	[63]

Table 1. *Cont.*

miRNA	Adipose source and metabolic context	Brain region/ recipient cell	Molecular targets and pathways	CNS effects	Evidence type	Key outcomes	Reference
miR-6760-3p, miR-6798-3p	FABP4-enriched adipocyte-associated sEVs in serum and CSF from patients with AD	Direct CNS delivery, neuronal uptake, and recipient brain cell identity not established	Targeting of neuronal CREB-related signaling components predicted by bioinformatic pathway analysis; direct molecular targets and target engagement in recipient neurons not experimentally validated	Adipocyte-associated sEV-miRNA modules were inversely correlated with MMSE scores; effects on neuronal plasticity and cognitive function were not directly tested	Human AD serum/CSF sEV profiling; weighted gene co-expression network analysis; bioinformatic pathway prediction	Candidate AD-associated adipocyte-associated sEV-miRNA signature	[64,65]
miR-140-5p	VAT-derived EVs; increased in HFD-induced obesity	Hippocampus, preferentially pyramidal neurons	CREB (direct target); suppression of downstream CREB–BDNF signaling → impaired hippocampal synaptic plasticity	Impaired hippocampal synaptic plasticity; increased susceptibility to subthreshold stress and depression-like behavioral responses	Rodent HFD models; EV tracing and RNA scope; gain- and loss-of-function studies; CREB/BDNF pathway validation	Increases stress susceptibility in obesity	[27]
miR-93-3p, miR-128-3p, miR-144-3p, miR-146a-5p, miR-223-3p, miR-106b-5p, miR-200a-3p, miR-363-3p	EVs from cultured ADSCs (ADSC-EVs); post-injury therapeutic administration in a mouse tMCAO model	Brain (tMCAO model)/Iba1^{+} microglia	STAT1 and PTEN identified as candidate regulatory nodes by bioinformatic analysis; selected miRNA mimics reduced STAT1 or PTEN expression in cultured cells	ADSC-EV treatment was associated with reduced pro-inflammatory and increased repair-associated microglial marker profiles, together with improved neurological recovery	Mouse tMCAO model with post-injury ADSC-EV administration; EV localization in Iba1-positive microglia; EV-miRNA profiling; bioinformatic target analysis; *in vitro* miRNA-mimic assays	Supports therapeutic modulation of post-ischemic microglial responses by administered ADSC-EVs	[11]

Studies have demonstrated that AT-EVs can enter the brain through a membrane protein-dependent mechanism and exhibit a pronounced preference for neuronal uptake, with particularly prominent accumulation in hippocampal neurons [46]. Pathological AT-EVs derived from HFD-fed mice or patients with diabetes can induce synaptic loss and cognitive dysfunction. Further studies showed that reducing the overall miRNA content of AT-EVs markedly attenuated these neurological and cognitive abnormalities, indicating that EV-associated miRNAs constitute important functional cargo mediating pathological adipose–brain communication. Building on these findings, further profiling of the miRNA repertoire of AT-EVs identified miR-9-3p as a potential key pathogenic miRNA. Subsequent selective inhibition of miR-9-3p in adipose tissue markedly alleviated the associated synaptic damage and cognitive dysfunction, further supporting a causal role for miR-9-3p in metabolic dysfunction-associated cognitive impairment. Mechanistic studies demonstrated that AT-EV-carried miR-9-3p, following delivery to hippocampal neurons, suppresses the expression of brain-derived neurotrophic factor (BDNF), a critical neurotrophic factor required for neuronal survival, synapse formation, and synaptic plasticity. Thus, pathological adipose tissue may disrupt BDNF-related neurotrophic signaling and synaptic homeostasis in the hippocampus through EV-mediated delivery of miR-9-3p, ultimately leading to cognitive dysfunction. More recently, the pathogenic role of adipose-derived miR-9-3p was further validated in diabetic mice: visceral adipose tissue-derived extracellular vesicles delivered miR-9-3p to the hippocampus and suppressed its direct target, SLC7A11, thereby impairing antioxidant defenses and promoting oxidative stress, iron accumulation, and ferroptotic injury [62]. Collectively, these findings indicate that pathological EV-associated miRNAs can disrupt multiple physiological processes in the hippocampus, including synapse formation, neurotrophic signaling, and redox homeostasis, ultimately leading to impaired learning and memory.

Recent human studies have provided clinical evidence linking adipose-associated EV-miRNAs to cognitive impairment. Yang *et al.* combined adipose-tissue miRNA sequencing, Mendelian randomization, and multicenter cohort validation to investigate EV-associated miRNAs related to cognitive vulnerability in individuals with type 2 diabetes mellitus [63]. The study identified exosomal miR-125a-5p as a candidate circulating biomarker of cognitive impairment. In the human cohorts, higher circulating exosomal miR-125a-5p levels were associated with an increased risk of amnestic mild cognitive impairment and reduced left hippocampal body volume. Mendelian randomization further supported a putative genetically inferred association between increased miR-125a-5p and Alzheimer's disease (AD) risk. These findings suggest that adipose-associated EV-miRNA alterations may serve as early molecular indicators of cognitive vulnerability in metabolic disease. However, unlike miR-9-3p, for which neuronal delivery, molecular targets, and functional effects have been experimentally examined, the available human data do not demonstrate that circulating EV-associated miR-125a-5p is delivered to neurons or contributes to cognitive decline through a defined neuronal pathway. Thus, the current evidence for miR-125a-5p is primarily epidemiological and genetic rather than a directly validated EV-mediated neuronal mechanism.

Alterations in adipocyte-associated sEV-miRNA profiles may be linked not only to metabolic cognitive impairment but also to neurodegenerative disorders such as Alzheimer's disease. Batabyal *et al.* isolated FABP4-enriched, adipocyte-associated small extracellular vesicles from the serum and cerebrospinal fluid (CSF) of patients with AD and cognitively normal controls and identified significant differences in their miRNA profiles [64]. Weighted gene co-expression network analysis further

revealed coordinated miRNA modules in both serum- and CSF-derived sEVs that were negatively correlated with Mini-Mental State Examination (MMSE) scores, linking EV-miRNA dysregulation to the severity of cognitive impairment [64]. However, the detection of these sEV populations in serum or cerebrospinal fluid does not, by itself, demonstrate the delivery of their miRNA cargo to neurons. Bioinformatic pathway analysis in the same study predicted that the cognition-associated miRNA modules could target components of neuronal cAMP response element-binding protein (CREB) signaling [64]. Among the miRNAs upregulated in adipocyte-associated sEV fractions from both serum and CSF, miR-6760-3p and miR-6798-3p were highlighted in the original sEV study [64]. A separate bioinformatic analysis of AD brain datasets reported that these miRNAs were also elevated in the cerebral cortex of patients with AD [65]. Although this cross-study concordance is potentially informative, it does not establish that the miRNAs detected in brain tissue originated from circulating adipocyte-associated sEVs. CREB is an important transcriptional regulator of BDNF and other plasticity-related genes [66]; therefore, the predicted suppression of CREB signaling by these EV-associated miRNAs may compromise BDNF-dependent neurotrophic support, activity-dependent synaptic remodeling, and memory-related neuronal plasticity. Nevertheless, neuronal uptake of miR-6760-3p and miR-6798-3p, engagement of their predicted intracellular targets, suppression of CREB signaling, and corresponding functional effects have not been experimentally tested in recipient brain cells. Their proposed regulation of CREB signaling should therefore be regarded as a bioinformatically predicted mechanism rather than an experimentally established pathway.

Overall, the available evidence suggests that dysregulation of adipose-associated EV-miRNA networks under metabolic or pathological conditions may be linked to impaired neuronal homeostasis and increased cognitive vulnerability. In experimental models, miR-9-3p has been functionally shown to regulate defined neuronal targets and cognitive phenotypes. In contrast, the available human findings concerning miR-125a-5p, miR-6760-3p, and miR-6798-3p currently provide biomarker, epidemiological, genetic, or bioinformatic evidence but do not establish direct EV-mediated delivery or molecular target engagement in the human brain. Therefore, the contributions of these miRNAs to human cognitive decline and neurodegenerative disease remain to be determined.

6.3. Modulation of emotional and stress-related neural circuits

Emotional regulation relies on multiple interconnected neural networks, including the corticolimbic system centered on the hippocampus, amygdala, and prefrontal cortex, as well as the mesolimbic dopaminergic system involved in reward and motivation processing [67–69]. Among these regions, the hippocampus not only participates in contextual memory encoding but also plays a critical role in stress adaptation and emotional regulation [70,71]. Recent studies suggest that adipose-derived EV-miRNAs may serve as molecular mediators linking peripheral metabolic states with emotion-related neural circuits. Through modulation of neuroplasticity and stress-related signaling pathways, adipose EV-miRNAs may influence central emotional homeostasis and individual susceptibility to stress.

Obesity remodels the miRNA profile of adipose tissue-derived EVs, providing a potential molecular route through which peripheral metabolic dysfunction influences affective regulation. In HFD-induced obese mice, miRNA profiling revealed substantial alterations in VAT-EVs, with miR-140-5p markedly increased in both VAT-EVs and the hippocampus. EV-tracing and RNAscope analyses further indicated preferential targeting of VAT-EVs and miR-140-5p to hippocampal pyramidal neurons.

Mechanistically, miR-140-5p directly binds to the 3′ untranslated region of CREB, suppressing CREB expression and downstream BDNF signaling, thereby impairing hippocampal synaptic plasticity. Multilevel gain- and loss-of-function experiments further supported a causal role for miR-140-5p in obesity-associated stress susceptibility, while manipulation of CREB and BDNF demonstrated that these effects were largely dependent on the CREB–BDNF signaling cascade. Collectively, obesity-associated elevation of VAT-EV miR-140-5p may reduce stress resilience by disrupting hippocampal CREB–BDNF signaling and synaptic plasticity, thereby increasing susceptibility to subthreshold stress and facilitating depression-like behavioral responses [27]. These findings identify impaired hippocampal neuroplasticity as a key mechanism through which obesity-associated adipose EV-miRNA dysregulation may increase vulnerability to affective disturbances.

Although direct evidence for the affective effects of adipose-derived miRNAs currently centers on the hippocampus, their influence may not be restricted to a single brain region but may extend to interconnected corticolimbic and mesolimbic networks. Supporting this possibility, independent circuit-level studies have shown that HFD-induced metabolic dysfunction remodels emotion- and reward-related neural circuits, including glutamatergic projections from the ventral hippocampus (vHPC) to the NAc, whose hyperactivation contributes to depression-like behaviors [72]. Moreover, obesity and anxiety- and depression-like states can be reciprocally regulated through defined neural circuits, highlighting functional integration between metabolic and affective regulation at the circuit level [73]. Consistent with these experimental findings, human neuroimaging studies have identified obesity-associated structural and functional alterations within fronto-mesolimbic networks [74]. Collectively, these observations provide a circuit-level framework for the possibility that the affective consequences of adipose-derived miRNA signaling extend beyond the hippocampus; however, whether adipose-derived miRNAs directly target these brain regions or defined neural circuits remains to be established.

6.4. Potential modulation of neuroimmune homeostasis

Neuroimmune homeostasis is maintained through coordinated interactions among microglia, astrocytes, neurons, and the neurovascular unit. Among these components, microglia serve as key immune-responsive cells in the central nervous system [75], integrating metabolic and inflammatory signals to regulate synaptic integrity and tissue homeostasis [76,77]. However, chronic metabolic disturbances such as obesity and insulin resistance can disrupt microglial homeostasis, leading to persistent inflammatory activation and neuronal dysfunction [78]. Therefore, microglia represent a critical cellular interface linking peripheral metabolic alterations with CNS inflammatory responses, providing a potential target through which adipose-derived EV-miRNAs may modulate brain function.

In peripheral immune regulation, adipose tissue-derived EV-miRNAs have been demonstrated to mediate intercellular communication between adipocytes and macrophages and reshape obesity-associated inflammatory microenvironments. Zhang *et al.* reported that obesity-associated adipocyte-derived exosomal miR-1224 suppresses MSI2/Wnt/β-catenin signaling in macrophages, thereby limiting M2-associated polarization and promoting adipose tissue inflammation.These findings support a pro-inflammatory role for adipocyte-derived EV miR-1224 in obesity-associated adipose tissue inflammation [79]. Furthermore, Pan *et al.* demonstrated that, under obese conditions, miR-34a was significantly enriched in adipocyte-derived EVs and transferred to adipose tissue macrophages. By directly binding to and suppressing the expression of Krüppel-like factor 4 (KLF4), an essential

transcriptional regulator of M2 macrophage polarization, EV-associated miR-34a impaired M2 macrophage differentiation, promoted the transition of macrophages toward a pro-inflammatory M1-like phenotype, and ultimately exacerbated adipose tissue inflammation and systemic metabolic dysfunction [80].

Direct evidence that endogenous adipose tissue-derived EV-miRNAs regulate CNS immune cells remains limited. Current insights are derived primarily from a therapeutic intervention study using exogenously administered extracellular vesicles derived from cultured adipose-derived mesenchymal stem/stromal cells, rather than from evidence of constitutive EV-mediated signaling between native adipose tissue and brain-resident immune cells [11]. In a transient middle cerebral artery occlusion (tMCAO) mouse model, ADSC-EVs administered after ischemic injury were detected in Iba1-positive microglia. ADSC-EV treatment was accompanied by a reduced proportion of CD16/Iba1 double-positive pro-inflammatory microglia and an increased proportion of Arg-1/Iba1 double-positive repair-associated microglia, together with improved neurological recovery. These findings support the capacity of therapeutically administered ADSC-EVs to modulate post-ischemic microglial responses but do not establish constitutive signaling from native adipose tissue to brain microglia. To investigate potential miRNA mediators of this immunomodulatory effect, the authors performed miRNA sequencing of ADSC-EVs and identified a distinct miRNA profile relative to fibroblast-derived EVs. Integrated bioinformatic analyses identified STAT1 and PTEN as candidate inflammation-related regulatory nodes potentially targeted by ADSC-EV-enriched miRNAs. In cultured cells, mimics of miR-93-3p, miR-128-3p, miR-144-3p, miR-146a-5p, and miR-223-3p reduced STAT1 expression, whereas mimics of miR-106b-5p, miR-200a-3p, miR-223-3p, and miR-363-3p decreased PTEN expression. Given the involvement of STAT1 in pro-inflammatory microglial responses and the association of the PTEN/Akt pathway with repair-related microglial states, these findings identify candidate miRNA–target relationships that might contribute to the effects of ADSC-EV treatment. However, because the miRNA mimics were tested in cultured cells outside the intact EV-delivery context, these experiments demonstrate target-regulatory potential but do not establish that the corresponding miRNAs were delivered by ADSC-EVs to microglia or engaged STAT1 or PTEN *in vivo*. Moreover, the study did not determine whether depletion of any individual miRNA from ADSC-EVs abolished the microglial or neurological effects of the intervention. The miRNA-specific mechanisms should therefore be regarded as candidate mechanisms supported by bioinformatic analysis and *in vitro* experiments rather than as established *in vivo* causal pathways.

Collectively, the available evidence indicates that adipocyte-derived EV-miRNAs can modulate peripheral macrophage functions, whereas evidence for CNS immune regulation currently relies mainly on therapeutic administration of ADSC-EVs after experimental cerebral ischaemia. The latter demonstrates that exogenously administered ADSC-EVs can influence post-injury microglial responses and that selected EV-enriched miRNAs possess target-regulatory activity *in vitro*; however, it does not establish a constitutive EV-miRNA signaling pathway from native adipose tissue to brain microglia. Further studies incorporating adipose-cell-specific EV tracing, miRNA-specific loss-of-function and rescue experiments, and direct assessment of miRNA delivery and target engagement in recipient microglia are required to determine whether EV-miRNAs released from mature adipocytes or adipose tissue macrophages contribute to neuroimmune homeostasis under physiological conditions or to its disruption in metabolic disorders such as obesity.

7. Conclusion and perspectives

Current evidence supports adipose-derived extracellular vesicle-associated microRNAs (EV-miRNAs) as a potential molecular component of communication between adipose tissue and the central nervous system, with possible involvement in the regulation of brain function under specific physiological or pathological conditions. These signals do not arise from a single adipose cell population; rather, their composition and biological activity vary according to adipose depot, cellular origin, and metabolic state, and are jointly shaped by multiple regulatory processes, including miRNA biogenesis, selective sorting, and metabolic cues. The lipid bilayer of EVs contributes to the stability of miRNAs in the circulation and provides a structural basis for long-distance transport. However, the mechanisms by which adipose-derived EV-miRNAs cross or interact with the blood–brain barrier, reach specific brain regions, and achieve selective delivery to recipient cell populations remain incompletely understood.

From a functional perspective, current evidence has established relatively clear links between adipose-derived EV-miRNAs and several specific central nervous system processes. Within hypothalamic metabolic circuits, candidate miRNAs enriched in adipocyte-derived EVs, including miR-148a-3p and miR-30a-3p, have been associated with the regulation of leptin sensitivity and energy homeostasis and have received functional validation in animal models. In the hippocampus, adipose-derived EV-associated miR-9-3p has been implicated in BDNF-related signaling, synaptic injury, and cognitive dysfunction. In diabetic models, miR-9-3p has also been linked to SLC7A11 downregulation and ferroptosis-related hippocampal injury. Separately, visceral adipose tissue-derived EV-associated miR-140-5p targets CREB and disrupts CREB–BDNF signaling and synaptic plasticity, thereby increasing susceptibility to subthreshold stress. Meanwhile, post-injury administration of ADSC-EVs was associated with altered microglial responses and improved neurological recovery, whereas STAT1- and PTEN-related effects of selected miRNA mimics were demonstrated only in cultured cells. Therefore, the extent of in vivo validation varies across miRNA-specific pathways. Taken together, these observations suggest that adipose-derived EV-miRNAs should not be regarded merely as isolated disease-associated biomarkers, but rather as biologically active regulatory factors with potential roles across metabolic, cognitive, affective, and neuroimmune domains.

However, the current evidence remains concentrated on a limited number of miRNAs, specific adipose sources, selected brain regions, and animal disease models. The baseline EV-miRNA profiles of different adipose depots and cell types under physiological conditions have not yet been sufficiently characterized, and systematic evidence regarding the regional distribution and recipient-cell specificity of adipose-derived EV-miRNAs in the brain is still lacking. In human studies, a complete causal chain linking adipose origin, central delivery, target-gene engagement, and functional phenotype has likewise not been established. Future studies should therefore integrate adipose depot- and cell type-specific genetic tracing, quantitative EV-miRNA profiling, spatial mapping of recipient cells within the brain, and miRNA-specific functional perturbation to establish a more complete source–EV–recipient cell–target gene–phenotype causal framework. In parallel, longitudinal and multicenter human studies will be needed to determine whether specific adipose-derived EV-miRNA signatures can reproducibly reflect central metabolic dysfunction, cognitive decline, or other neurological alterations, and to further evaluate their robustness and clinical utility as biomarkers. Only on this basis can strategies aimed at inhibiting

detrimental EV-miRNAs, restoring beneficial miRNAs, or using engineered EVs for targeted delivery gain stronger support for translational development.

Technologically, future work should leverage single-cell RNA sequencing of brain recipient cells coupled with multiplexed EV-miRNA tracing to deconvolute the precise cell-type specificity of EV uptake and downstream transcriptional responses. Furthermore, the emerging toolkit for engineered EVs-including cell-type-specific surface functionalization and miRNA-loading systems-offers a promising avenue not only for validating causal miRNA functions *in vivo* but also for developing targeted therapeutic interventions that either ablate pathogenic signals or restore protective miRNA pools in specific neural circuits.

Overall, adipose-derived EV-miRNAs provide a promising mechanistic framework linking adipose tissue heterogeneity and metabolic state to the multidimensional regulation of brain function.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. Specifically, the authors used ChatGPT for language polishing only. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Conceptualization, H.Y. and J.W.; methodology, H.Y., M.T. and X.C.; validation, H.Y. and K.W.; formal analysis, H.Y.; investigation, H.Y.; resources, Y.B. and J.W.; data curation, H.Y. and X.C.; writing—original draft preparation, H.Y.; writing—review and editing, H.Y., M.T., Y.B. and J.W.; visualization, H.Y. and K.W.; supervision, H.Y., M.T. and J.W.; project administration, Y.B. and J.W.; funding acquisition, Y.B. and J.W. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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