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Review

Obesity and Adipose-Derived Extracellular Vesicles: Implications for Metabolic Regulation and Disease

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Abstract: Obesity, a global epidemic, is a major risk factor for chronic diseases such as type 2 diabetes, cardiovascular disorders, and metabolic syndrome. Adipose tissue, once viewed as a passive fat storage site, is now recognized as an active endocrine organ involved in metabolic regulation and inflammation. In obesity, adipose tissue dysfunction disrupts metabolic balance, leading to insulin resistance and increased production of adipose-derived extracellular vesicles (AdEVs). These vesicles play a key role in intercellular communication and contribute to metabolic dysregulation, affecting organs such as the heart, liver, and brain. AdEVs carry bioactive molecules, including microRNAs, which influence inflammation, insulin sensitivity, and tissue remodeling. In the cardiovascular system, AdEVs can promote atherosclerosis and vascular dysfunction, while those derived from brown adipose tissue offer cardioprotective effects. In type 2 diabetes, AdEVs exacerbate insulin resistance and contribute to complications such as diabetic cardiomyopathy and cognitive decline. Additionally, AdEVs are implicated in metabolic liver diseases, including fatty liver disease, by transferring inflammatory molecules and lipotoxic microRNAs to hepatocytes. These findings highlight the role of AdEVs in obesity-related metabolic disorders and their promise as therapeutic targets for related diseases.

Keywords: obesity; extracellular vesicles; adipose-derived extracellular vesicles; type 2 diabetes; cardiovascular system; MAFLD; metabolic syndrome

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1. Introduction

Obesity has become one of the most critical public health challenges of the 21st century, recognized as a global epidemic projected to affect 51% of the world's population within the next decade [1]. Defined by the excessive accumulation of body fat, obesity is a major risk factor for numerous chronic diseases, including type 2 diabetes, cardiovascular disorders, cognitive impairment, certain cancers, and metabolic syndrome. Metabolic syndrome is characterized by elevated blood glucose levels, reduced high-density lipoprotein cholesterol, increased triglycerides, and high blood pressure [2]. The prevalence of obesity continues to rise at an alarming rate, driven by complex interactions among genetic, environmental, and behavioral factors. In addition to its systemic effects, obesity also induces alterations at the cellular and molecular levels, such as chronic inflammation, insulin resistance, and lipid dysregulation [3,4].

Adipocytes, once considered inert fat storage cells, are now recognized as active regulators of inflammatory balance, metabolic health, and nutrient homeostasis [5,6].

Adipose tissue functions as an endocrine organ, engaging in intricate communication with other organs, including the gut, liver, pancreas, and brain, to regulate processes such as appetite, thermogenesis, and overall body weight [7–9]. This communication is closely tied to the inflammatory state of adipose tissue, which plays a pivotal role in obesity-related complications.

In recent years, extracellular particles (EPs), including extracellular vesicles (EVs) and non-vesicular extracellular particles [10,11], have garnered significant attention for their roles in intercellular and inter-organ communication [12], as well as in the regulation of metabolic processes. These nanostructures, released by all cell types, carry bioactive cargoes such as proteins, lipids, and nucleic acids, which can modulate the function of recipient cells [12,13]. In the context of obesity, EVs have emerged as critical mediators of tissue crosstalk, contributing to metabolic dysregulation and the progression of associated diseases [14].

Adipose tissue (AT), categorized into white adipose tissue (WAT) and brown adipose tissue (BAT), plays a central role in energy storage, metabolic regulation, and endocrine signaling [15]. WAT, the predominant form of adipose tissue, functions as a primary energy reservoir and serves as an endocrine organ by secreting adipokines, cytokines, fatty acids, and EPs. It is distributed throughout the body, with major depots in the subcutaneous and visceral regions. In contrast, BAT, which is found in specific regions of the body, is specialized in thermogenesis and energy expenditure, processes stimulated by the sympathetic release of noradrenaline, which activates the β3-adrenergic receptor (β3-AR) on brown adipocytes [16]. BAT's role in glucose homeostasis and insulin sensitivity further underscores its importance in metabolic health [17,18].

In obesity, WAT undergoes adaptations, including hyperplasia (increased cell proliferation) and hypertrophy (cell enlargement), which contribute to elevated inflammation. This inflammation is driven by immune cell infiltration, particularly macrophages, and is a key factor in the development of insulin resistance and type 2 diabetes [19]. Under negative energy balance, sympathetic release of noradrenaline stimulates lipolysis in WAT, mobilizing free fatty acids to meet the body's energy demands [20]. On the other hand, BAT has a protective effect on metabolism by promoting energy expenditure and improving insulin sensitivity. BAT is typically reduced in individuals who are obese or elderly and is also associated with cardiovascular health [21,22].

EVs originating from adipocytes are suggested to contribute significantly to the pathophysiology of obesity and its associated comorbid conditions [23]. Recent studies have highlighted the role of adipose-derived EVs (AdEVs), secreted by both white and brown adipocytes, in regulating distant tissues such as the heart, liver or gut. AdEVs, which constitute approximately 80% of circulating EVs in human blood, are a crucial component of the human adipose secretome and carry bioactive molecules that influence the inflammatory state and metabolic function of recipient cells, as observed in both a healthy and pathological heart [24,25]. In obesity, AdEVs have been shown to contribute to gut inflammation by delivering proinflammatory microRNAs (miRNAs) to the intestinal lamina propria, promoting macrophage polarization and aggravating colitis [26]. Furthermore, beige adipocytes, found within WAT but with morphological, functional, and metabolic characteristics of brown adipocytes [27], exhibit thermogenic properties that improve metabolic health and glucose metabolism. Other findings indicate that EVs derived from beige adipocytes can enhance hepatic steatosis and glucose tolerance in diet-induced obese mice [28].

This review explores the intricate relationship between obesity and EVs, focusing on their roles in metabolic regulation, disease pathogenesis and associated-comorbidities. By examining the current evidence, we also aim to highlight the potential of EVs as therapeutic targets for

addressing obesity-related disorders such as cardiovascular alterations, type 2 diabetes, and metabolic dysfunction-associated fatty liver disease.

2. Influence of EVs in Metabolic Regulation and Obesity-Related Disease

AT is a dynamic organ that adapts its physiological and functional characteristics to regulate metabolic balance during variations in caloric intake. However, chronic or excessive caloric intake can lead to AT dysfunction, characterized by insulin resistance, impaired energy storage, dysregulated lipolysis, and inflammation [29]. Such dysfunction is a key contributor to the onset of metabolic diseases, including type 2 diabetes mellitus, steatohepatitis, and cardiovascular conditions [30,31]. Decades of research underscore the pivotal role of AT health in maintaining overall metabolic stability. The behavior of AT during obesity is partly influenced by dynamic interactions between adipocytes and adipose tissue macrophages (ATMs) [32]. Previous research has identified EVs as a critical mechanism facilitating this communication by serving as carriers of bioactive molecules [33–37]. EVs enable the transfer of molecular signals that regulate inflammation, metabolism, and tissue remodeling, playing a pivotal role in the crosstalk between these cell types and shaping AT function under obese conditions. Studies using high-fat diet-induced or genetically modified rodent models have shown increased AdEV production in obesity [38,39]. Similarly, human studies report elevated circulating EV levels in obese individuals compared to lean subjects, suggesting a role for adipose tissue-derived EVs in these processes [38,40,41]. Altered AdEV profiles have also been observed in obese patients with type 2 diabetes through ex vivo and in vitro studies [40,42].

MicroRNAs (miRNAs) are a class of short noncoding RNAs with a length of about 18–22 nucleotides that are widely produced by all eukaryotic cells [43]. A large number of these miRNAs exist in body fluids [44,45]. Circulating miRNAs are stable in body fluids and can be protected by binding to Argonaute proteins, high-density lipoprotein (HDL), or microRNA protein expression and/or by being encapsulated in EVs [46,47]. The microRNA can control protein expression by binding to mRNA [48,49]. The EVs from diseased sources have been proven to have unique miRNA expression profiles [46]. Recent research indicates that miRNAs are key contributors to the effects of EVs in obesity and metabolic regulation [50–53]. The miRNA profiles of EVs are influenced by the originating cell type and its physiological state. Importantly, the process of miRNA packaging into EVs is non-random, as specific miRNA sequences are recognized by sorting proteins for selective inclusion [54–56]. This regulated secretion of miRNAs via EVs appears to be an evolutionary mechanism for facilitating intercellular and interorgan communication, supporting the maintenance of metabolic homeostasis [38].

2.1. Influence of Adipose-Derived EVs on Cardiovascular System

Obesity is a risk factor for cardiovascular diseases. AdEVs appears to play a role in the physiology and pathophysiology of the heart (Figure 1) as they can be taken up by cardiac tissues, as observed many times using the fluorescent labeling of adipose-derived EVs [57,58].

Significant progress has been made in understanding the role of AdEVs secreted by BAT in maintaining cardiovascular health. It has been shown that AdEVs released by BAT play a crucial role in exercise-induced cardioprotection [59]. A 4-week exercise regimen was sufficient to promote BAT expansion, and the resulting EVs effectively reduced reperfusion injury following myocardial infarction. Moreover, comparative RNA sequencing (RNAseq) of circulating EVs and BAT-derived EVs from sedentary and exercised rodents identified miR-125-5p, miR-128-3p, and miR-30d-5p as key mediators of this cardioprotective effect by mitigating apoptosis through inhibition of the MAPK pathway [59]. Other authors also demonstrated that EVs' communication from BAT to cardiac myocytes and fibroblasts has

cardioprotective effects [58]. Their study showed that EVs from β3-AR-activated brown adipocytes protected against AngII-induced cardiac remodeling. The study identified inducible nitric oxide synthase as a key EV cargo contributing to cardiac fibroblast dysfunction and remodeling when BAT was not activated [58]. Additionally, the identification of over 500 differentially expressed lncRNAs in EVs from white and brown adipose tissues may further reveal lncRNAs involved in BAT-mediated cardioprotection in future studies [60]. While brown adipocyte-derived EVs have shown cardioprotective effects, treatment with rosiglitazone, a peroxisome proliferator-activated receptor-gamma (PPARγ) activator used for type II diabetes, has revealed harmful effects. PPARγ is essential for brown adipocyte differentiation [61]. Rosiglitazone induces the release of EVs containing miR-200a, which promotes cardiac hypertrophy by activating mTOR signaling [62]. This mechanism may explain the cardiac hypertrophy and increased heart failure risk observed in preclinical models and clinical trials, leading to restrictions on rosiglitazone use [63].

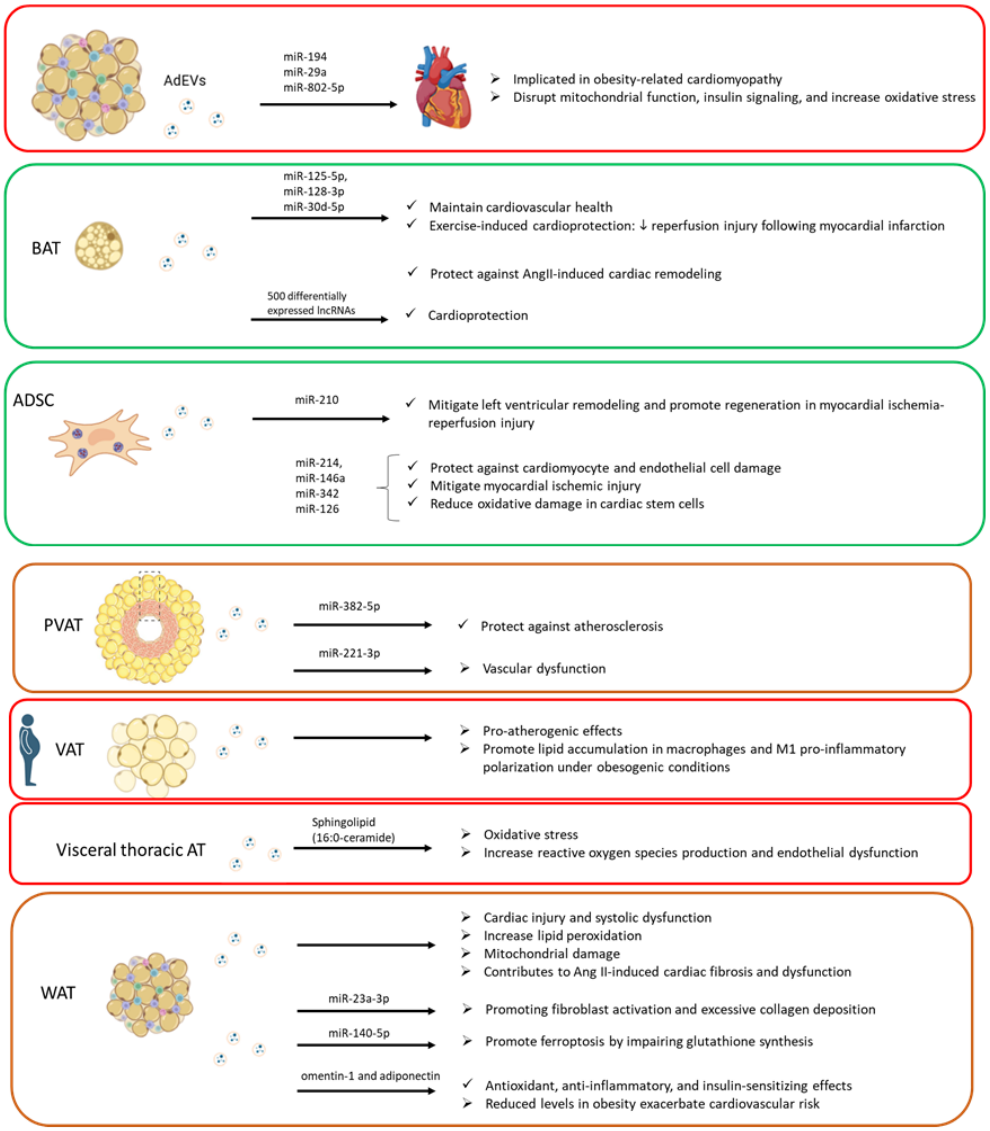

Figure 1. Summary of different types of adipose-derived EVs in the physiology and pathophysiology of the heart (original artwork). AdEVs: adipose-derived extracellular vesicles; AT: adipose tissue; BAT: brown adipose tissue; ADSC: adipose tissue-derived stem cells; PVAT: perivascular adipose tissue; VAT: visceral adipose tissue; WAT: white adipose tissue; Ang II: angiotensin II.

Other authors demonstrated that EVs derived from adipose tissue-derived stem cells, when transfected with miR-210, mitigated left ventricular remodeling and promoted regeneration in a rat model of myocardial ischemia-reperfusion injury [64]. EVs derived from adipose-derived regenerative cells carrying miR-214, as well as those from adipose-derived mesenchymal stem cells (MSCs) enriched with miR-146a, miR-342, and miR-126, were shown to protect against cardiomyocyte and endothelial cell damage, mitigate myocardial ischemic injury, and reduce oxidative damage in cardiac stem cells, respectively [65–68].

It has also been shown that EVs derived from perivascular adipose tissue (PVAT) play key roles in regulating vascular physiology and pathology. Several studies reveal that EVs from PVAT protect against atherosclerosis by preventing the formation of macrophages with lipid accumulation through mechanisms such as miR-382-5p, which promotes cholesterol transport and limits lipid accumulation in macrophages [68–70]. Interestingly, lower miR-382-5p levels are observed in PVAT-derived EVs from coronary atherosclerosis patients compared to healthy individuals [69]. In contrast, EVs from visceral adipose tissue (VAT) have pro-atherogenic effects, including promoting lipid accumulation in macrophages and M1 pro-inflammatory polarization under obesogenic conditions [71]. Additionally, visceral thoracic adipose tissue has been linked to oxidative stress via EVs secretion containing sphingolipids like C16:0-ceramide, which increases reactive oxygen species production and endothelial dysfunction. Targeting C16:0-ceramide with glucagon-like peptide-1 analog liraglutide shows therapeutic potential, as it reduces plasma levels of this ceramide, which has been associated with increased cardiovascular risk [72]. Other miRNAs in PVAT-derived EVs, such as miR-221-3p, contribute to vascular dysfunction. For instance, under inflammatory conditions, miR-221-3p induces vascular smooth muscle cell phenotypic switching, contributing to early vascular remodeling and dysfunction [73]. However, the exact PVAT cell sources of miR-221-3p in obesity remain unclear.

Obesity drives hyperplastic and hypertrophic remodeling of WAT. This leads to inflammation and long-lasting disruptions in WAT's endocrine signaling. Notably, WAT-derived EVs are altered in the context of metabolic diseases [41,74], highlighting their potential role in disease progression. Long-term consumption of high-fat diets (HFDs) has been linked to cardiac injury and systolic dysfunction [75,76], with recent evidence implicating EVs derived from adipose tissue macrophages [77]. In obese mice on HFDs, these EVs were associated with increased lipid peroxidation, mitochondrial damage, and an enrichment of miR-140-5p, a microRNA that promotes ferroptosis in cardiomyocytes by impairing glutathione synthesis [77]. Other miRNAs in EVs, such as miR-194, miR-29a, and miR-802-5p, have also been implicated in obesity-related cardiomyopathy, disrupting mitochondrial function, insulin signaling, and increasing oxidative stress [78–80]. However, the origins of these EVs—whether from WAT, BAT, macrophages, or hepatocytes—remain unclear. Interestingly, while adipocyte-derived EVs can transport mitochondrial components that impact systemic metabolism [81–83], stressed mitochondrial particles in EVs from adipocytes may also activate cardiomyocyte antioxidant defenses, potentially reducing ischemia/reperfusion injury in obesogenic conditions [57]. In obesity, BAT is significantly reduced, leading to the loss of cardioprotective effects [18,21,84]. However, BAT-derived EVs have shown promise; their administration improved cardiac function and metabolic syndrome in mice on HFDs, possibly through direct effects on the heart and enhanced glucose metabolism [85]. Furthermore, EVs from WAT enclose key adipocytokines like omentin-1 and adiponectin, which exert antioxidant, anti-inflammatory, and insulin-sensitizing effects. Omentin-1 was predominantly found in EVs from visceral AT, while high- and medium-molecular-weight adiponectin was present in EVs from subcutaneous AT [86]. Reduced levels of these adipocytokines in obesity likely exacerbate cardiovascular risk [87]. It could be interesting to explore the role of EVs in adipocytokine-mediated

protection and their contribution to cardiac damage caused by obesity. The regulatory role of human antigen R, an RNA-binding protein linked to WAT function, may also play a part in EV formation and its association with cardiac fibrosis and inflammation [88,89]. Other authors demonstrated that WAT contributes to angiotensin II (Ang II)-induced cardiac fibrosis and dysfunction through an EV-mediated mechanism [90]. EVs from Ang II-stimulated adipocytes delivered miR-23a-3p to cardiac fibroblasts, promoting their activation and excessive collagen deposition by targeting RAP1, while interventions targeting WAT or miR-23a-3p effectively attenuated these pathological changes [90].

These findings highlight the dual roles of EVs in both mediating cardiac dysfunction in obesity and offering potential therapeutic strategies for mitigating cardiac injury.

2.2. Influence of Adipose-Derived EVs on Type 2 Diabetes

EVs play a pivotal role in regulating glucose homeostasis, and their dysregulation in obesity significantly contributes to the onset and progression of type 2 diabetes (T2D).

In obese individuals, AdEVs carry microRNAs, such as miR-155 and miR-29a, which impair insulin signaling by targeting insulin receptor substrates [34,91]. Obesity-induced systemic insulin resistance and chronic inflammation are closely linked, with macrophages playing a critical role in amplifying inflammatory responses though EV-mediated signaling. Recent findings demonstrate that 3T3-L1 adipocytes secrete AdEVs with angiogenic properties, containing approximately 7000 mRNAs and 140 microRNAs [92]. Most adipocyte-specific transcripts and microRNAs were abundant in AdEVs, mirroring donor cell expression. Notably, AdEVs facilitated the transfer of adiponectin and resistin transcripts to RAW264.7 macrophages, while adipocyte-specific genes such as PPARγ2 were detected in serum-derived EVs. Other authors demonstrated that EVs miR-500a-5p derived from adipose tissue macrophages, which is elevated under high-glucose conditions, promoted adipocyte inflammation by suppressing Nrf2 expression [93]. This suppression activated the NLRP3 inflammasome, establishing a connection between macrophage-derived EVs and adipose tissue inflammation [93]. It has also been demonstrated that adipose tissue macrophages release EVs enriched with miR-210-3p, which are delivered to neighboring adipocytes, skeletal muscle cells, and hepatocytes through paracrine and endocrine pathways, thereby affecting insulin sensitivity [94]. Mechanistically, miR-210-3p suppresses glucose transporter type 4 (GLUT4) expression by silencing its mRNA, thereby impairing glucose uptake and reducing insulin sensitivity. Studies have demonstrated that macrophage EVs overexpressing miR-210-3p induce glucose intolerance and insulin resistance in lean mice, while therapeutic inhibition of miR-210-3p in visceral adipose tissue restores glucose tolerance in obese mice, underscoring its potential as a therapeutic target [94]. These findings suggest that targeting adipose tissue macrophage-specific miR-210-3p during obesity could be a promising strategy for managing insulin resistance and T2D.

AdEVs also modulate macrophage polarization through paracrine signaling, with outcomes depending on their miRNA content. For instance, elevated levels of miR-155 in these EVs promote M1 macrophage polarization by targeting the suppressor of the cytokine signaling 1 gene [95]. Conversely, high levels of miR-34a and miR-1224 suppress M2 macrophage polarization by targeting the Krüppel-like factor 4 and Musashi RNA-binding protein 2 (MSI2) genes, respectively [37,96]. This M1 macrophage accumulation leads to the release of pro-inflammatory cytokines in adipose tissue, contributing to insulin resistance.

Other findings highlight the significance of adipocyte EVs as mediators of palmitic acid (PA)-induced metabolic disturbances [97]. Elevated levels of PA, a key factor associated with obesity, have been shown to activate the NF-κB and endoplasmic reticulum (ER) stress pathways in adipocytes, leading to an increased release of miRNAs via EVs. Specifically, obesity-induced increases in PA levels trigger ER stress through NF-κB activation, resulting

in elevated levels of EVs miR-4431, miR-548ab/ag, and miR-450a-5p [97]. These miRNAs exacerbate inflammation and metabolic dysfunction, suggesting their utility as biomarkers and therapeutic targets in obesity-related conditions.

In addition, adipose-derived stem cells (ADSC) secrete EVs with anti-inflammatory and metabolic benefits associated with obesity. A study by Zhao, H. et al. [98] showed that ADSC-derived EVs improved metabolic balance in obese mice, enhancing insulin sensitivity by 27.8%, reducing obesity, and alleviating hepatic steatosis. These EVs promoted M2 macrophage polarization, reduced inflammation, and induced the beiging of white adipose tissue (WAT) in diet-induced obese mice. Mechanistically, ADSC-derived EVs activated M2 macrophages through the transfer of active STAT3, which transactivated arginase-1 and fostered anti-inflammatory phenotypes. Furthermore, M2 macrophages increased tyrosine hydroxylase expression and supported ADSC proliferation and lactate production, thereby promoting WAT beiging and restoring metabolic homeostasis in response to high-fat diets [98]. These findings highlight a novel EV-mediated mechanism of ADSC–macrophage interaction that promotes immune and metabolic balance in WAT, offering promising therapeutic avenues for the treatment of obesity and T2D.

A study employing fluorescence AdEV-tracing, SILAC labeling, and (phospho)proteomics investigated the role of AdEVs in glucose regulation [92]. AdEVs were shown to influence glucose regulation by delivering insulinotropic proteins to pancreatic β-cells, where they enhanced first-phase glucose-stimulated insulin secretion (GSIS) through GPCR/cAMP/PKA signaling in murine islets. Interestingly, these insulinotropic effects were specific to AdEVs derived from obese, insulin-resistant mice, reflecting their unique protein cargo and structural characteristics. In vivo, these AdEVs improved insulin secretion and glucose tolerance, highlighting their role in β-cell adaptation to insulin resistance and suggesting their therapeutic potential for improving glucose tolerance [92].

Furthermore, a recent study suggested that phosphotyrosine 1 phosphatase (PTP1B) and protein phosphatase 2 (PP2A), carried by EVs from insulin-resistant individuals, may serve as potential therapeutic targets against insulin resistance in adipose tissue and liver, as well as for preventing the development of obesity [99]. Researchers isolated EVs from individuals with (IR group) and without insulin resistance (n-IR group), and they found that EVs from the IR group were enriched with active PTP1B and PP2A. When these EVs were administered to mice, they impaired systemic, adipose tissue, and liver insulin signaling, and increased adipocyte size and adipogenic gene expression. Inhibition of PTP1B and PP2A activity in IR EVs restored insulin signaling in adipocytes and hepatocytes [99].

Adipocytes are recognized as a major source of EVs miRNA production [100]. miRNA-enriched EVs from adipocytes are not confined to adipose tissue but are also transported to distant insulin-responsive tissues. AdEVs miRNAs influence adipogenesis and adipocyte differentiation through autocrine signaling. For example, miR-122, enriched in adipocyte EVs, promotes adipogenesis by targeting the vitamin D3 receptor gene, which serves as a negative regulator of the sterol regulatory element-binding transcription factor 1 [101]. Research by Ojima et al. [102] revealed that during adipocyte differentiation, EVs enriched with miRNAs support their own differentiation while inhibiting skeletal muscle differentiation.

Furthermore, AdEVs influence gene expression in recipient cells across various organs via endocrine signaling, with effects dependent on the miRNA content and the physiological state of the adipocytes [103–105]. For β cells, EVs from healthy adipocytes promote cell survival and insulin secretion, whereas EVs from inflamed adipocytes cause β-cell death and insulin resistance [106]. In skeletal muscle cells, miR-27a-enriched EVs induce insulin resistance by targeting the peroxisome proliferator-activated receptor gamma gene [100]. Animal studies confirmed elevated serum EVs miR-27a levels in obese mice, which were

reduced following exercise-induced browning of WAT [107]. Similarly, EVs miR-222 inhibits the insulin receptor substrate 1 (IRS1) gene, impairing glucose uptake in skeletal muscle and hepatocytes, suggesting its potential as a therapeutic target for obesity-induced metabolic syndrome and T2D [108,109].

In hepatocytes, miR-99b-enriched EVs suppress the fibroblast growth factor 21 gene, reducing insulin sensitivity [110]. Conversely, EVs deficient in miR-141-3p impair insulin signaling by upregulating phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K/Akt pathway critical for glucose uptake [111].

It was demonstrated that miR-27a-5p, delivered to pancreatic β-cells via EVs from visceral adipocytes, impaired insulin secretion by downregulating the CaV1.2 calcium channel in β-cells [112]. This led to glucose intolerance in obesity, and blocking miR-27a-5p improved β-cell function and glucose regulation, suggesting it as a therapeutic target for obesity-related type 2 diabetes [112].

Insulin plays a crucial role in regulating miRNA expression and its secretion into EVs from adipocytes [113]. It stimulated the release of miRNAs, such as miR-103-3p and let-7f-5p, which were associated with obesity and disrupted insulin signaling in the liver. The sorting of miRNAs by insulin was driven by specific sequence motifs within the miRNAs and involved RNA-binding proteins that recognized these sequences [113]. This highlights how hormonal control of EV cargo sorting influences inter-organ communication through EVs miRNAs, underscoring its potential as a therapeutic target for conditions like insulin resistance, obesity, type 2 diabetes, and metabolic syndrome (Table 1).

Influence of Adipose-Derived EVs on Type 2 Diabetes-Associated Comorbidities

Emerging research has unveiled novel communication mechanisms between adipose tissue and various organs, including the heart and brain, that contribute to the development of comorbidities associated with type 2 diabetes (T2D) and their progression. EVs derived from adipocytes, macrophages, and other adipose cell types can exacerbate systemic metabolic dysfunction and contribute to the development of cardiovascular and cognitive complications. Dysfunctional and senescent white adipocytes have been strongly implicated in the development of T2D and its associated complications [114]. Obesity-induced inflammation and metabolic dysregulation contribute to impaired glucose metabolism and systemic metabolic alterations. Long-term complications induced by diabetes type 2, frequently associated with obesity, have been related to changes in EVs [115] as reported for cardiovascular comorbidities [116,117], diabetic-induced retinopathy [118], or neuropathy [119].

EVs derived from dysfunctional visceral white adipocytes under obesogenic conditions, such as high-fat diets, exacerbate myocardial ischemia/reperfusion (MI/R) injury in diabetic patients compared to healthy individuals [120]. Elevated levels of miR-130b-3p in adipose-derived EVs from diabetic rats and in the plasma of diabetic patients were shown to promote myocardial injury by inducing pro-apoptotic responses in cardiac myocytes [120]. Furthermore, senescent and dysfunctional adipocytes are linked to the development of diabetic cardiomyopathy [114]. A study demonstrated that removal of epididymal visceral WAT alleviated diastolic dysfunction in streptozotocin-induced diabetic mouse models. The findings revealed that EVs from visceral WAT contributed to contractile and mitochondrial dysfunction in isolated cardiac myocytes, with miR-326-3p enrichment in these EVs suppressing Rictor expression and driving cardiac impairments. In addition, miR-802-5p, carried in EVs from hypertrophic adipocytes, has been implicated in cardiac insulin resistance [80]. This microRNA downregulates HSP60, a regulator of insulin-like growth factor-1 receptor (IGF-1R) signaling, which is inversely associated with the progression of diabetic cardiomyopathy [121]. Collectively, these studies emphasize the central role of

AdEVs in mediating systemic metabolic dysfunction and cardiac-specific complications in obesity and T2D, while highlighting their potential as therapeutic targets to mitigate disease progression.

EVs also play a dual role in metabolic and cognitive health. In the crosstalk between adipocytes and the brain, a study by Gao et al. [122] showed that EVs secreted by adipocytes from obese mice can be internalized by POMC-like neurons in vitro. When these EVs were transferred to lean mice, they induced increased appetite and body weight gain, likely through the transfer of miRNAs and lncRNAs to POMC neurons, which activated the mTORC1 signaling pathway. Conversely, EVs from adipocytes of lean mice suppressed appetite and attenuated weight gain in mice fed a high-fat diet (HFD) by downregulating mTORC1 signaling. A study revealed that an enzyme involved in NAD+ biosynthesis, the extracellular nicotinamide phosphoribosyltransferase (eNAMPT), is transported via EVs through systemic circulation and significantly declines with age in mice and humans [123]. Increasing circulating eNAMPT levels in aged mice by adipose-specific overexpression of eNAMPT increased NAD+ levels in various tissues, including the hypothalamus, leading to anti-aging effects in female mice. Furthermore, neurons from the hypothalamus were shown to regulate aging and lifespan by promoting adipose eNAMPT release through the sympathetic nervous system [124]. These findings highlight a bidirectional communication between the brain and adipose tissue to sustain NAD+ levels and promote healthy aging.

In the context of obesity, T2D has been linked to cognitive decline [125]. EVs derived from adipose tissue also play a crucial role in cognitive decline associated with T2D. In a recent study, control mice treated with EVs derived from the adipose tissue of HFD-fed mice or diabetic patients displayed hippocampal synaptic loss and cognitive impairments [126]. These effects were attributed to an altered miRNA cargo in the EVs, particularly the enrichment of miR-9-3p, which suppressed hippocampal BDNF expression, a critical factor for synaptic function. Elevated serum levels of EV miR-9-3p have been linked to obesity-related insulin resistance and cognitive decline in diabetes, suggesting that targeting adipose tissue EVs or their miRNA cargo may offer therapeutic strategies for treating cognitive deficits associated with T2DM and insulin resistance [126] (Table 1).

Given their ability to mediate systemic effects on both the heart and brain, adipose-derived EVs represent a critical mechanism through which T2D contributes to the development of comorbidities, such as diabetic cardiomyopathy and cognitive decline. These particles offer potential as therapeutic targets to prevent or mitigate the progression of these complications, providing new avenues for intervention in patients with T2D.

Table 1. Effects of cargo in adipose-derived EVs on obesity and type 2 diabetes.

Identified Cargo from AdEVs	Effect on Obesity and T2D	References
miR-155 and miR-29a	Impairs insulin signaling by targeting insulin receptor substrates	[34,91]
140 microRNAs	Angiogenic properties	[92]
Adiponectin and Resistin	Facilitate the transfer of their transcripts to macrophages	[92]
miR-500a-5p	Promotes adipocyte inflammation by suppressing Nrf2 expression	[93]
miR-210-3p	Delivered to neighboring adipocytes, skeletal muscle cells, and hepatocytes, it reduces insulin sensitivity and suppresses glucose transporter type 4 expression	[94]
miR-155	Promotes M1 macrophage polarization by targeting the suppressor of cytokine signaling 1 gene	[95]

Table 1. *Cont.*

Identified Cargo from AdEVs	Effect on Obesity and T2D	References
miR-34a and miR-1224	Suppress M2 macrophage polarization by targeting the Krüppel-like factor 4 and Musashi RNA-binding protein 2 genes M1 macrophage accumulation leads to the release of pro-inflammatory cytokines in adipose tissue, contributing to insulin resistance	[127–129]
miR-4431, miR-548ab/ag, and miR-450a-5p	Exacerbate inflammation and metabolic dysfunction	[97]
STAT3	Anti-inflammatory and metabolic benefits associated with obesity Activates M2 macrophages	[98]
Insulinotropic proteins	Glucose regulation Improve insulin secretion and glucose tolerance, highlighting their role in β-cell adaptation to insulin resistance	[92]
PTP1B and PP2A	Inhibition of PTP1B and PP2A activity in EVs from individuals with insulin resistance restores insulin signaling in adipocytes and hepatocytes	[99]
miR-122	Promotes adipogenesis by targeting the vitamin D3 receptor gene, which serves as a negative regulator of the sterol regulatory element-binding transcription factor 1	[101]
miR-27a	Induces insulin resistance by targeting the peroxisome proliferator-activated receptor gamma gene	[100]
miR-27a-5p	Delivered to pancreatic β-cells, impairs insulin secretion by downregulating the CaV1.2 calcium channel in β-cells. This led to glucose intolerance.	[112]
miR-222	Inhibits the insulin receptor substrate 1 (IRS1) gene, impairing glucose uptake in skeletal muscle and hepatocytes	[108,109]
miR-99b	In hepatocytes, suppress the fibroblast growth factor 21 gene, reducing insulin sensitivity	[110]
miR-141-3p	Deficiency in miR-141-3p impairs insulin signaling by upregulating phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K/Akt pathway, which is critical for glucose uptake	[111]
miR-103-3p and let-7f-5p	Disrupts insulin signaling in the liver	[113]
miR-130b-3p	Promotes myocardial injury	[120]
miR-326-3p	Suppresses Rictor expression and contributes to cardiac impairments	[114]
miR-802-5p	Cardiac insulin resistance Downregulates HSP60, a regulator of insulin-like growth factor-1 receptor (IGF-1R) signaling, which is inversely associated with the progression of diabetic cardiomyopathy	[80]
miR-9-3p	Hippocampal synaptic loss and cognitive impairment Suppresses hippocampal BDNF expression, a critical factor for synaptic function	[126]

A crucial role of the immunological dysregulation leading to systemic inflammation has been suggested as being at the basis of the pathophysiological mechanisms leading to long-term complications in obese patients [130]. EVs' release from immune cells appear to modulate inflammation and metabolic responses in obesity [3,4] being the macrophages the cells of the immune system those most studied [52,130–132]. The macrophages from patients experiencing obesity-associated disorders also release EVs. In atherosclerosis, macrophages stimulated by oxidized low-density lipid (LDL) release EVs that contain regulatory miRNAs or other non-coding RNAs. The adipose tissue macrophages release EVs carrying miR-29a and miR-155 that inhibit activation of adipogenic transcription factor PPAR-γ, resulting in increased insulin resistance and predisposition to type 2 diabetes [130]. Of note, classically activated pro-inflammatory M1 macrophages and adipocytes in the inflammatory environment preferentially release miR-155 [133]. EVs derived from T cells, pro-inflammatory macrophages, B cells, and dendritic cells can release miRNAs that could promote islet β-cell dysfunction and apoptosis [134].

2.3. Influence of Adipose-Derived EVs on Liver Lipid Metabolism and Inflammation: Metabolic-Associated Fatty Liver Disease

Hepatic steatosis, defined as fat accumulation in liver cells, represents the initial stage of liver diseases such as non-alcoholic fatty liver disease (NAFLD), metabolic-associated fatty liver disease (MAFLD), and alcoholic liver disease. These conditions differ in their causes and associated comorbidities. NAFLD is diagnosed when hepatic steatosis occurs without significant alcohol intake, secondary causes, or other chronic liver diseases. In contrast, MAFLD, a newer term, emphasizes the metabolic origins of the disease, requiring evidence of hepatic steatosis alongside metabolic dysfunctions, such as overweight/obesity, type 2 diabetes, or metabolic dysregulation [135]. Although the damage in fatty liver disease is multifactorial, a significant contribution arises from fat accumulation in the adipose tissue. Once the adipose tissue's storage capacity is exceeded, excess lipids are redirected, leading to ectopic fat deposition in the liver [136,137]. This redirection is mediated by free fatty acids released from adipose tissue, which are transported to the liver, bound to albumin, as well as dietary triglycerides delivered via chylomicrons.

AdEVs contribute to MAFLD progression by transferring lipotoxic molecules and inflammatory miRNAs to hepatocytes, further exacerbating metabolic stress [138–140]. The inflammatory cargo of these vesicles exacerbates hepatic inflammation and insulin resistance, further driving lipid accumulation and potentially transitioning steatosis to metabolic associated steatohepatitis (MASH) [138].

As highlighted in the previous paragraphs, WAT expands significantly during obesity through hypertrophy and hyperplasia. Human WAT-derived EVs are primarily enriched with cytokines and adipokines, including interleukin (IL)-6, migration inhibitory factor (MIF), MCP-1, adiponectin, resistin, and retinol-binding protein-4 (RBP-4) [141]. These molecules have been shown to inhibit the insulin-induced increase in the pAkt/Akt ratio in HepG2 hepatocytes following treatment with WAT EVs [142].

Other researchers have shown that melatonin can reduce AdEVs containing the adipokine resistin, which helps mitigate hepatic steatosis [143]. AdEVs induced by endoplasmic reticulum stress in adipocytes, collected from mouse models of MASH induced by a HFD or a methionine- and choline-deficient diet, are enriched with Aldo-ketoreductase 1B7, a critical enzyme involved in liver lipid metabolism [144].

Treatment with EVs derived from BAT can partially alleviate HFD-induced hepatic steatosis and reduce serum ALT levels [85]. Using DiR fluorescent dye tracing, Zhou et al. [85] demonstrated that BAT-derived EVs predominantly accumulate in the liver, significantly enhancing hepatocyte oxygen consumption and energy expenditure. Consistent with these findings, proteins in BAT EVs are enriched in mitochondrial components

associated with metabolic pathways, likely contributing to their positive effects on liver metabolism [85]. Moreover, it has been demonstrated that EVs derived from BAT significantly improved metabolic syndrome in HFD-fed mice. After intravenous injection, BAT EVs preferentially targeted the liver, reducing the expression of two inflammatory genes (TNFα and IL1β), serum ALT levels, and hepatic lipid accumulation. BAT EVs are capable of delivering functional proteins to the liver, suggesting their potential as a promising therapeutic approach for MAFLD [145]. Additionally, AdEVs have been shown to directly impair hepatic insulin sensitivity through mechanisms involving either miRNAs or proteins. For instance, EVs miR-99b from BAT facilitates communication between AT and the liver by modulating glucose metabolism [110]. It does so by downregulating FGF21 expression in hepatocytes, leading to glucose intolerance and the development of fatty liver [110]. Furthermore, BAT EVs have been shown to promote the browning of WAT, presenting new therapeutic strategies for treating obesity-related metabolic disorders [146]. Additionally, studies indicate that EVs miR-222 derived from WAT is elevated in the livers of obese mice fed an HFD. This miRNA reduces insulin sensitivity in hepatocytes by inhibiting insulin receptor substrate 1 and phospho-AKT, thereby exacerbating hepatic steatosis [147]. Furthermore, EVs miR-155 from ATMs has been found to impair insulin signaling in hepatocytes by targeting PPARγ [34]. Several other miRNAs, such as miR-29, miR-103, miR-223, miR-23a, miR-197, miR-27a, miR-320a, and miR-509-5p, derived from AT EVs have also been linked to metabolic disorders and dyslipidemia through their actions on hepatocytes [148]. Moreover, EVs from obese adipose tissue have been shown to promote liver fibrosis by regulating the expression of fibrosis-associated proteins. This includes the suppression of matrix metalloproteinase-7 in hepatocytes and matrix metalloproteinase-9 in hepatic stellate cells, along with the upregulation of the tissue inhibitor of matrix metalloproteinase-1 and integrin αvβ-5 in both cell types, leading to excessive extracellular matrix production [149]. Interestingly, not all effects of AT EVs are detrimental. EVs enriched with miR-690 from M2 macrophages have been shown to enhance insulin sensitivity in primary hepatocytes when compared to control hepatocytes from obese individuals in vitro [52]. These findings highlight the critical role of AT EVs as regulators of hepatic glucose metabolism and insulin sensitivity.

Endoplasmic reticulum (ER) stress-induced AdEVs have been shown to elevate serum levels of AST, ALT, total cholesterol, triglycerides, and free fatty acids [144]. These AT EVs released under conditions of ER stress also trigger ER stress in the liver, as evidenced by increased expression of markers such as GPR78, CHOP, and IRE1α [144]. Hepatic ER stress is known to exacerbate insulin resistance and promote inflammation through activation of the NF-κB and JNK pathways [150]. In obese mice, the presence of ER stress-induced AT EVs correlates with elevated levels of pro-inflammatory cytokines TNF-α and IL-1β in the liver [144]. Additionally, AT releases EVs containing miR-103, which are internalized by hepatocytes. MiR-103 interacts with PTEN, inhibiting autophagy and contributing to the progression of MASH [151]. These findings highlight the significant impact of ER stress-induced AT EVs on liver dysfunction and inflammation.

AT EVs also play a role in fibrogenesis, the advanced stage of MAFLD. Transforming growth factor beta (TGF-β) is the key pro-fibrogenic growth factor responsible for the activation of hepatic stellate cells into myofibroblast-like cells and for promoting collagen synthesis [152]. Research by Koeck et al. [153] demonstrated that EVs derived from the AT of obese individuals dysregulate the TGF-β signaling pathway in HepG2 cells. This dysregulation is characterized by increased expression of integrin αvβ-5 and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) and reduced expression of PAI-1 and matrix metalloproteinase-7 (MMP-7). Furthermore, hepatic stellate cells, which are central to liver fibrogenesis, exhibited elevated Smad-3 expression, along with upregulation of TIMP-1,

TIMP-4, MMP-9, and integrins [153]. Interestingly, among the MMPs and TIMPs studied, mRNA levels for MMP-2, MMP-3, MMP-12, MMP-14, MMP-19, and TIMP-1 are strongly induced in obese adipose tissues compared with lean tissues [154]. EVs derived from macrophages carry bioactive MMP-14, which has gelatinolytic and collagenolytic activities, thus influencing the development of adipose tissue [155,156]. Other proteins with MMP activity have been implicated in obesity, such as ADAM 10/17. A recent work reported that adipose tissue-selective ablation of ADAM10 results in divergent metabolic phenotypes following long-term dietary manipulation [156], and knocking out ADAM17 in mice leads to extremely lean animals [157]. Interestingly, ADAM10/17 have also been found to be released with EVs [157], which can contribute to adipocytes differentiation and growth of adipose tissue. Another study by Gu et al. [144] linked an increased release of AdEVs under ER stress conditions to higher liver expression of TGF-β1, collagen 4α1, and collagen 1α2. These findings underscore the role of AT EVs in promoting liver fibrosis through multiple molecular mechanisms.

Understanding the molecular composition of these EVs and their liver-targeting mechanisms offers promising avenues for therapeutic intervention to mitigate obesity-induced liver disease. Recently, it has been shown that lifestyle interventions can influence EVs' profiles, potentially mediating metabolic improvements. A study analyzed 18 Latino adolescents with obesity and hepatic steatosis who underwent a six-month intervention, and results showed a 23% reduction in hepatic fat fraction and smaller EV sizes post-intervention [158]. Moreover, proteomic profiling identified 462 EV proteins, with 113 significantly altered post-intervention, enriched in complementary cascade pathways. Hepatocyte-specific analysis revealed 40 proteins with suggestive changes [158]. These findings suggest EV-derived proteins may contribute to hepatic fat reduction through complement-related mechanisms.

3. Conclusions

AdEVs play a central role in the pathogenesis of metabolic diseases, particularly in obesity and its associated complications, such as T2D, cardiovascular dysfunction, and liver diseases. In obesity, the dysregulation of AT metabolism leads to an overproduction of AdEVs, which facilitate communication between adipocytes and macrophages, modulating inflammatory responses, metabolism, and tissue remodeling. These vesicles, enriched with specific microRNAs, regulate glucose homeostasis, insulin sensitivity, and lipid metabolism, contributing to the onset and progression of insulin resistance, hepatic steatosis, and systemic metabolic dysfunction.

The impact of AdEVs extends beyond metabolic regulation to cardiovascular health, where they can either promote or protect against cardiac dysfunction. EVs derived from BAT show cardioprotective properties, reducing myocardial injury and promoting exercise-induced cardioprotection. In contrast, EVs from WAT and perivascular adipose tissue may exacerbate cardiovascular disease by promoting inflammation and vascular remodeling. However, AdEVs from ADSCs have demonstrated therapeutic potential, improving cardiac regeneration and mitigating myocardial injury, highlighting their promise in treating obesity-related cardiovascular conditions.

In liver diseases, AdEVs contribute to the progression of MAFLD by transferring inflammatory molecules and lipotoxic miRNAs to hepatocytes, exacerbating hepatic inflammation, insulin resistance, and lipid accumulation. These processes drive the progression from simple steatosis to more severe forms of liver disease, such as steatohepatitis and fibrosis. AdEVs also play a role in liver fibrosis by dysregulating key pathways, such as TGF-β signaling, and activating hepatic stellate cells, further promoting excessive extracellular matrix production.

Moreover, AdEVs contribute to the systemic effects of obesity-related diseases, influencing organs such as the brain, liver, and heart. In diabetic conditions, the altered miRNA cargo of AdEVs exacerbates insulin resistance and organ-specific damage, including diabetic cardiomyopathy and cognitive decline. These findings underscore the multifaceted roles of AdEVs in mediating inflammation, metabolic dysfunction, and tissue-specific damage.

Importantly, lifestyle interventions, including dietary changes, can influence the profile of AdEVs, potentially mitigating metabolic dysfunction and improving clinical outcomes in individuals with obesity-related conditions. This suggests that targeting AdEVs and their miRNA cargo could offer novel therapeutic strategies to address obesity, type 2 diabetes, cardiovascular diseases, and liver diseases, marking a promising area for future research and clinical application.

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References

1. Mahase, E. Global Cost of Overweight and Obesity Will Hit $4.32tn a Year by 2035, Report Warns. *BMJ* **2023**, *380*, 523. [CrossRef]
2. Sakers, A.; De Siqueira, M.K.; Seale, P.; Villanueva, C.J. Adipose-Tissue Plasticity in Health and Disease. *Cell* **2022**, *185*, 419–446. [CrossRef]
3. Codoñer-Franch, P.; Valls-Bellés, V.; Arilla-Codoñer, A.; Alonso-Iglesias, E. Oxidant Mechanisms in Childhood Obesity: The Link between Inflammation and Oxidative Stress. *Transl. Res.* **2011**, *158*, 369–384. [CrossRef] [PubMed]
4. Gasmi, A.; Noor, S.; Menzel, A.; Doşa, A.; Pivina, L.; Bjørklund, G. Obesity and Insulin Resistance: Associations with Chronic Inflammation, Genetic and Epigenetic Factors. *Curr. Med. Chem.* **2021**, *28*, 800–826. [CrossRef]
5. Baldelli, S.; Aiello, G.; Mansilla Di Martino, E.; Campaci, D.; Muthanna, F.M.S.; Lombardo, M. The Role of Adipose Tissue and Nutrition in the Regulation of Adiponectin. *Nutrients* **2024**, *16*, 2436. [CrossRef]
6. Harvey, I.; Boudreau, A.; Stephens, J.M. Adipose Tissue in Health and Disease. *Open Biol.* **2020**, *10*, 1281–1306. [CrossRef] [PubMed]
7. Díaz-Castro, F.; Morselli, E.; Claret, M. Interplay between the Brain and Adipose Tissue: A Metabolic Conversation. *EMBO Rep.* **2024**, *25*, 5277–5293. [CrossRef]
8. Kershaw, E.E.; Flier, J.S. Adipose Tissue as an Endocrine Organ. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2548–2556. [CrossRef]
9. Wang, S.; Liu, Y.; Chen, J.; He, Y.; Ma, W.; Liu, X.; Sun, X. Effects of Multi-Organ Crosstalk on the Physiology and Pathology of Adipose Tissue. *Front. Endocrinol.* **2023**, *14*, 1198984. [CrossRef] [PubMed]
10. Welsh, J.A.; Goberdhan, D.C.I.; O'Driscoll, L.; Buzas, E.I.; Blenkiron, C.; Bussolati, B.; Cai, H.; Di Vizio, D.; Driedonks, T.A.P.; Erdbrügger, U.; et al. Minimal Information for Studies of Extracellular Vesicles (MISEV2023): From Basic to Advanced Approaches. *J. Extracell. Vesicles* **2024**, *13*, e12404. [CrossRef] [PubMed]
11. Sun, S.; Cox-Vázquez, S.J.; Cho, N.J.; Bazan, G.C.; Groves, J.T. Direct Imaging with Multidimensional Labelling and High-Content Analysis Allows Quantitative Categorization and Characterizations of Individual Small Extracellular Vesicles and Nanoparticles (SEVPs). *J. Extracell. Vesicles* **2024**, *13*, e12520. [CrossRef] [PubMed]
12. Cabrera-Pastor, A. Extracellular Vesicles as Mediators of Neuroinflammation in Intercellular and Inter-Organ Crosstalk. *Int. J. Mol. Sci.* **2024**, *25*, 7041. [CrossRef]

13. Malaguarnera, M.; Cabrera-Pastor, A. Emerging Role of Extracellular Vesicles as Biomarkers in Neurodegenerative Diseases and Their Clinical and Therapeutic Potential in Central Nervous System Pathologies. *Int. J. Mol. Sci.* **2024**, *25*, 10068. [CrossRef] [PubMed]
14. Bond, S.T.; Calkin, A.C.; Drew, B.G. Adipose-Derived Extracellular Vesicles: Systemic Messengers and Metabolic Regulators in Health and Disease. *Front. Physiol.* **2022**, *13*, 837001. [CrossRef] [PubMed]
15. Corvera, S. Cellular Heterogeneity in Adipose Tissues. *Annu. Rev. Physiol.* **2021**, *83*, 257–278. [CrossRef]
16. Emorine, L.J.; Marullo, S.; Briend-Sutren, M.M.; Patey, G.; Tate, K.; Delavier-Klutchko, C.; Strosberg, A.D. Molecular Characterization of the Human Beta 3-Adrenergic Receptor. *Science* **1989**, *245*, 1118–1121. [CrossRef]
17. Lowell, B.B.; S-Susulic, V.; Hamann, A.; Lawitts, J.A.; Himms-Hagen, J.; Boyer, B.B.; Kozak, L.P.; Flier, J.S. Development of Obesity in Transgenic Mice after Genetic Ablation of Brown Adipose Tissue. *Nature* **1993**, *366*, 740–742. [CrossRef]
18. Cypess, A.M.; Lehman, S.; Williams, G.; Tal, I.; Rodman, D.; Goldfine, A.B.; Kuo, F.C.; Palmer, E.L.; Tseng, Y.-H.; Doria, A.; et al. Identification and Importance of Brown Adipose Tissue in Adult Humans. *New Engl. J. Med.* **2009**, *360*, 1509–1517. [CrossRef]
19. Freedland, E.S. Role of a Critical Visceral Adipose Tissue Threshold (CVATT) in Metabolic Syndrome: Implications for Controlling Dietary Carbohydrates: A Review. *Nutr. Metab.* **2004**, *1*, 12. [CrossRef]
20. Muzzin, P.; Revelli, J.P.; Kuhne, F.; Gocayne, J.D.; McCombie, W.R.; Venter, J.C.; Giacobino, J.P.; Fraser, C.M. An Adipose Tissue-Specific Beta-Adrenergic Receptor. Molecular Cloning and down-Regulation in Obesity. *J. Biol. Chem.* **1991**, *266*, 24053–24058. [CrossRef] [PubMed]
21. Becher, T.; Palanisamy, S.; Kramer, D.J.; Eljalby, M.; Marx, S.J.; Wibmer, A.G.; Butler, S.D.; Jiang, C.S.; Vaughan, R.; Schöder, H.; et al. Brown Adipose Tissue Is Associated with Cardiometabolic Health. *Nat. Med.* **2021**, *27*, 58–65. [CrossRef]
22. Leitner, B.P.; Huang, S.; Brychta, R.J.; Duckworth, C.J.; Baskin, A.S.; McGehee, S.; Tal, I.; Dieckmann, W.; Gupta, G.; Kolodny, G.M.; et al. Mapping of Human Brown Adipose Tissue in Lean and Obese Young Men. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 8649–8654. [CrossRef] [PubMed]
23. Kwan, H.Y.; Chen, M.; Xu, K.; Chen, B. The Impact of Obesity on Adipocyte-Derived Extracellular Vesicles. *Cell Mol. Life Sci.* **2021**, *78*, 7275–7288. [CrossRef]
24. Hartwig, S.; De Filippo, E.; Göddeke, S.; Knebel, B.; Kotzka, J.; Al-Hasani, H.; Roden, M.; Lehr, S.; Sell, H. Exosomal Proteins Constitute an Essential Part of the Human Adipose Tissue Secretome. *Biochim. Biophys. Acta Proteins Proteom.* **2019**, *1867*, 140172. [CrossRef]
25. Michel, L.Y.M. Extracellular Vesicles in Adipose Tissue Communication with the Healthy and Pathological Heart. *Int. J. Mol. Sci.* **2023**, *24*, 7745. [CrossRef] [PubMed]
26. Wei, M.; Gao, X.; Liu, L.; Li, Z.; Wan, Z.; Dong, Y.; Chen, X.; Niu, Y.; Zhang, J.; Yang, G. Visceral Adipose Tissue Derived Exosomes Exacerbate Colitis Severity via Pro-Inflammatory MiRNAs in High Fat Diet Fed Mice. *ACS Nano* **2020**, *14*, 5099–5110. [CrossRef] [PubMed]
27. Wu, J.; Boström, P.; Sparks, L.M.; Ye, L.; Choi, J.H.; Giang, A.H.; Khandekar, M.; Virtanen, K.A.; Nuutila, P.; Schaart, G.; et al. Beige Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human. *Cell* **2012**, *150*, 366–376. [CrossRef]
28. Jung, Y.J.; Kim, H.K.; Cho, Y.; Choi, J.S.; Woo, C.H.; Lee, K.S.; Sul, J.H.; Lee, C.M.; Han, J.; Park, J.H.; et al. Cell Reprogramming Using Extracellular Vesicles from Differentiating Stem Cells into White/Beige Adipocytes. *Sci. Adv.* **2020**, *6*, eaay6721. [CrossRef]
29. Crewe, C.; An, Y.A.; Scherer, P.E. The Ominous Triad of Adipose Tissue Dysfunction: Inflammation, Fibrosis, and Impaired Angiogenesis. *J. Clin. Investig.* **2017**, *127*, 74–82. [CrossRef] [PubMed]
30. Blüher, M. Adipose Tissue Dysfunction Contributes to Obesity Related Metabolic Diseases. *Best. Pract. Res. Clin. Endocrinol. Metab.* **2013**, *27*, 163–177. [CrossRef] [PubMed]
31. Longo, M.; Zatterale, F.; Naderi, J.; Parrillo, L.; Formisano, P.; Raciti, G.A.; Beguinot, F.; Miele, C. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. *Int. J. Mol. Sci.* **2019**, *20*, 2358. [CrossRef] [PubMed]
32. Engin, A.B. Adipocyte-Macrophage Cross-Talk in Obesity. *Adv. Exp. Med. Biol.* **2017**, *960*, 327–343. [CrossRef] [PubMed]
33. Ying, W.; Gao, H.; Dos Reis, F.C.G.; Bandyopadhyay, G.; Ofrecio, J.M.; Luo, Z.; Ji, Y.; Jin, Z.; Ly, C.; Olefsky, J.M. MiR-690, an Exosomal-Derived MiRNA from M2-Polarized Macrophages, Improves Insulin Sensitivity in Obese Mice. *Cell Metab.* **2021**, *33*, 781–790.e5. [CrossRef]
34. Ying, W.; Riopel, M.; Bandyopadhyay, G.; Dong, Y.; Birmingham, A.; Seo, J.B.; Ofrecio, J.M.; Wollam, J.; Hernandez-Carretero, A.; Fu, W.; et al. Adipose Tissue Macrophage-Derived Exosomal MiRNAs Can Modulate In Vivo and In Vitro Insulin Sensitivity. *Cell* **2017**, *171*, 372–384.e12. [CrossRef] [PubMed]
35. Tryggestad, J.B.; Teague, A.M.; Sparling, D.P.; Jiang, S.; Chernausek, S.D. Macrophage-Derived MicroRNA-155 Increases in Obesity and Influences Adipocyte Metabolism by Targeting Peroxisome Proliferator-Activated Receptor Gamma. *Obesity* **2019**, *27*, 1856–1864. [CrossRef]
36. Tian, F.; Tang, P.; Sun, Z.; Zhang, R.; Zhu, D.; He, J.; Liao, J.; Wan, Q.; Shen, J. MiR-210 in Exosomes Derived from Macrophages under High Glucose Promotes Mouse Diabetic Obesity Pathogenesis by Suppressing NDUFA4 Expression. *J. Diabetes Res.* **2020**, *2020*, 6894684. [CrossRef]

37. Paneru, B.D.; Hill, D.A. The role of extracellular vesicle-derived miRNAs in adipose tissue function and metabolic health. *Immunometabolism* **2023**, *5*, e00027. [CrossRef]
38. Le Lay, S.; Rome, S.; Loyer, X.; Nieto, L. Adipocyte-Derived Extracellular Vesicles in Health and Diseases: Nano-Packages with Vast Biological Properties. *FASEB Bioadv.* **2021**, *3*, 407–419. [CrossRef]
39. Lazar, I.; Clement, E.; Dauvillier, S.; Milhas, D.; Ducoux-Petit, M.; LeGonidec, S.; Moro, C.; Soldan, V.; Dalle, S.; Balor, S.; et al. Adipocyte Exosomes Promote Melanoma Aggressiveness through Fatty Acid Oxidation: A Novel Mechanism Linking Obesity and Cancer. *Cancer Res.* **2016**, *76*, 4051–4057. [CrossRef] [PubMed]
40. Camino, T.; Lago-Baameiro, N.; Bravo, S.B.; Molares-Vila, A.; Sueiro, A.; Couto, I.; Baltar, J.; Casanueva, E.F.; Pardo, M. Human Obese White Adipose Tissue Sheds Depot-Specific Extracellular Vesicles and Reveals Candidate Biomarkers for Monitoring Obesity and Its Comorbidities. *Transl. Res.* **2022**, *239*, 85–102. [CrossRef] [PubMed]
41. Eguchi, A.; Lazic, M.; Armando, A.M.; Phillips, S.A.; Katebian, R.; Maraka, S.; Quehenberger, O.; Sears, D.D.; Feldstein, A.E. Circulating Adipocyte-Derived Extracellular Vesicles Are Novel Markers of Metabolic Stress. *J. Mol. Med.* **2016**, *94*, 1241–1253. [CrossRef]
42. Mleczko, J.; Ortega, F.J.; Falcon-Perez, J.M.; Wabitsch, M.; Fernandez-Real, J.M.; Mora, S. Extracellular Vesicles from Hypoxic Adipocytes and Obese Subjects Reduce Insulin-Stimulated Glucose Uptake. *Mol. Nutr. Food Res.* **2018**, *62*, 1700917. [CrossRef]
43. Friedman, R.C.; Farh, K.K.H.; Burge, C.B.; Bartel, D.P. Most Mammalian MRNAs Are Conserved Targets of MicroRNAs. *Genome Res.* **2009**, *19*, 92–105. [CrossRef]
44. Teoh, S.L.; Das, S. MicroRNAs in Various Body Fluids and Their Importance in Forensic Medicine. *Mini Rev. Med. Chem.* **2022**, *22*, 2332–2343. [CrossRef]
45. Cortez, M.A.; Bueso-Ramos, C.; Ferdin, J.; Lopez-Berestein, G.; Sood, A.K.; Calin, G.A. MicroRNAs in Body Fluids--the Mix of Hormones and Biomarkers. *Nat. Rev. Clin. Oncol.* **2011**, *8*, 467–477. [CrossRef] [PubMed]
46. Groot, M.; Lee, H. Sorting Mechanisms for MicroRNAs into Extracellular Vesicles and Their Associated Diseases. *Cells* **2020**, *9*, 1044. [CrossRef]
47. Cui, H.; Lv, K.; Yang, N. HDL and MicroRNAs. *Adv. Exp. Med. Biol.* **2022**, *1377*, 153–161. [CrossRef] [PubMed]
48. Schmiedel, J.M.; Klemm, S.L.; Zheng, Y.; Sahay, A.; Blüthgen, N.; Marks, D.S.; Van Oudenaarden, A. Gene Expression. MicroRNA Control of Protein Expression Noise. *Science* **2015**, *348*, 128–131. [CrossRef]
49. Fan, R.; Hilfinger, A. The Effect of MicroRNA on Protein Variability and Gene Expression Fidelity. *Biophys. J.* **2023**, *122*, 905–923. [CrossRef]
50. Thomou, T.; Mori, M.A.; Dreyfuss, J.M.; Konishi, M.; Sakaguchi, M.; Wolfrum, C.; Rao, T.N.; Winnay, J.N.; Garcia-Martin, R.; Grinspoon, S.K.; et al. Adipose-Derived Circulating MiRNAs Regulate Gene Expression in Other Tissues. *Nature* **2017**, *542*, 450. [CrossRef]
51. Wang, J.; Zhang, T.; Gu, R.; Ke, Y.; Zhang, S.; Su, X.; Pan, X.; He, Q.; Li, G.; Zhang, Z.; et al. Development and Evaluation of Reconstructed Nanovesicles from Turmeric for Multifaceted Obesity Intervention. *ACS Nano* **2024**, *18*, 23117–23135. [CrossRef] [PubMed]
52. Castaño, C.; Meza-Ramos, A.; Batlle, M.; Guasch, E.; Novials, A.; Párrizas, M. Treatment with EV-miRNAs Alleviates Obesity-Associated Metabolic Dysfunction in Mice. *Int. J. Mol. Sci.* **2022**, *23*, 14920. [CrossRef]
53. Duisenbek, A.; Lopez-Armas, G.C.; Pérez, M.; Avilés Pérez, M.D.; Aguilar Benitez, J.M.; Pereira Pérez, V.R.; Gorts Ortega, J.; Yessenbekova, A.; Ablaikhanova, N.; Escames, G.; et al. Insights into the Role of Plasmatic and Exosomal microRNAs in Oxidative Stress-Related Metabolic Diseases. *Antioxidants* **2023**, *12*, 1290. [CrossRef] [PubMed]
54. Garcia-Martin, R.; Wang, G.; Brandão, B.B.; Zanotto, T.M.; Shah, S.; Kumar Patel, S.; Schilling, B.; Kahn, C.R. MicroRNA Sequence Codes for Small Extracellular Vesicle Release and Cellular Retention. *Nature* **2022**, *601*, 446–451. [CrossRef]
55. Villarroya-Beltri, C.; Gutiérrez-Vázquez, C.; Sánchez-Cabo, F.; Pérez-Hernández, D.; Vázquez, J.; Martin-Cofreces, N.; Martinez-Herrera, D.J.; Pascual-Montano, A.; Mittelbrunn, M.; Sánchez-Madrid, F. Sumoylated HnRNPA2B1 Controls the Sorting of MiRNAs into Exosomes through Binding to Specific Motifs. *Nat. Commun.* **2013**, *4*, 2980. [CrossRef] [PubMed]
56. Temoche-Diaz, M.M.; Shurtleff, M.J.; Nottingham, R.M.; Yao, J.; Fadadu, R.P.; Lambowitz, A.M.; Schekman, R. Distinct Mechanisms of MicroRNA Sorting into Cancer Cell-Derived Extracellular Vesicle Subtypes. *Elife* **2019**, *8*, e47544. [CrossRef] [PubMed]
57. Crewe, C.; Funcke, J.B.; Li, S.; Joffin, N.; Gliniak, C.M.; Ghaben, A.L.; An, Y.A.; Sadek, H.A.; Gordillo, R.; Akgul, Y.; et al. Extracellular Vesicle-Based Interorgan Transport of Mitochondria from Energetically Stressed Adipocytes. *Cell Metab.* **2021**, *33*, 1853–1868.e11. [CrossRef] [PubMed]
58. Lin, J.R.; Ding, L.L.Q.; Xu, L.; Huang, J.; Zhang, Z.B.; Chen, X.H.; Cheng, Y.W.; Ruan, C.C.; Gao, P.J. Brown Adipocyte ADRB3 Mediates Cardioprotection via Suppressing Exosomal INOS. *Circ. Res.* **2022**, *131*, 133–147. [CrossRef]
59. Zhao, H.; Chen, X.; Hu, G.; Li, C.; Guo, L.; Zhang, L.; Sun, F.; Xia, Y.; Yan, W.; Cui, Z.; et al. Small Extracellular Vesicles From Brown Adipose Tissue Mediate Exercise Cardioprotection. *Circ. Res.* **2022**, *130*, 1490–1506. [CrossRef] [PubMed]
60. Hong, P.; Wu, Y.; Zhang, Q.; Liu, P.; Zhang, S.; Yu, M.; Tian, W. Identification of Thermogenesis-Related LncRNAs in Small Extracellular Vesicles Derived from Adipose Tissue. *BMC Genomics* **2022**, *23*, 660. [CrossRef]

61. Lindgren, E.M.; Nielsen, R.; Petrovic, N.; Jacobsson, A.; Mandrup, S.; Cannon, B.; Nedergaard, J. Noradrenaline Represses PPAR (Peroxisome-Proliferator-Activated Receptor) Gamma2 Gene Expression in Brown Adipocytes: Intracellular Signalling and Effects on PPARgamma2 and PPARgamma1 Protein Levels. *Biochem. J.* **2004**, *382*, 597–606. [CrossRef]
62. Fang, X.; Stroud, M.J.; Ouyang, K.; Fang, L.; Zhang, J.; Dalton, N.D.; Gu, Y.; Wu, T.; Peterson, K.L.; Huang, H.D.; et al. Adipocyte-Specific Loss of PPAR γ Attenuates Cardiac Hypertrophy. *JCI Insight* **2016**, *1*, e89908. [CrossRef] [PubMed]
63. Wallach, J.D.; Wang, K.; Zhang, A.D.; Cheng, D.; Grossetta Nardini, H.K.; Lin, H.; Bracken, M.B.; Desai, M.; Krumholz, H.M.; Ross, J.S. Updating Insights into Rosiglitazone and Cardiovascular Risk through Shared Data: Individual Patient and Summary Level Meta-Analyses. *BMJ* **2020**, *368*, l7078. [CrossRef] [PubMed]
64. Song, B.W.; Lee, C.Y.; Kim, R.; Kim, W.J.; Lee, H.W.; Lee, M.Y.; Kim, J.; Jeong, J.Y.; Chang, W. Multiplexed Targeting of MiRNA-210 in Stem Cell-Derived Extracellular Vesicles Promotes Selective Regeneration in Ischemic Hearts. *Exp. Mol. Med.* **2021**, *53*, 695–708. [CrossRef] [PubMed]
65. Eguchi, S.; Takefuji, M.; Sakaguchi, T.; Ishihama, S.; Mori, Y.; Tsuda, T.; Takikawa, T.; Yoshida, T.; Ohashi, K.; Shimizu, Y.; et al. Cardiomyocytes Capture Stem Cell-Derived, Anti-Apoptotic MicroRNA-214 via Clathrin-Mediated Endocytosis in Acute Myocardial Infarction. *J. Biol. Chem.* **2019**, *294*, 11665–11674. [CrossRef] [PubMed]
66. Luo, Q.; Guo, D.; Liu, G.; Chen, G.; Hang, M.; Jin, M. Exosomes from MiR-126-Overexpressing Adscs Are Therapeutic in Relieving Acute Myocardial Ischaemic Injury. *Cell Physiol. Biochem.* **2017**, *44*, 2105–2116. [CrossRef]
67. Pan, J.; Alimujiang, M.; Chen, Q.; Shi, H.; Luo, X. Exosomes Derived from MiR-146a-Modified Adipose-Derived Stem Cells Attenuate Acute Myocardial Infarction-Induced Myocardial Damage via Downregulation of Early Growth Response Factor 1. *J. Cell Biochem.* **2019**, *120*, 4433–4443. [CrossRef]
68. Xing, X.; Li, Z.; Yang, X.; Li, M.; Liu, C.; Pang, Y.; Zhang, L.; Li, X.; Liu, G.; Xiao, Y. Adipose-Derived Mesenchymal Stem Cells-Derived Exosome-Mediated MicroRNA-342-5p Protects Endothelial Cells against Atherosclerosis. *Aging* **2020**, *12*, 3880–3898. [CrossRef]
69. Liu, Y.; Sun, Y.; Lin, X.; Zhang, D.; Hu, C.; Liu, J.; Zhu, Y.; Gao, A.; Han, H.; Chai, M.; et al. Perivascular Adipose-Derived Exosomes Reduce Macrophage Foam Cell Formation through MiR-382-5p and the BMP4-PPARγ-ABCA1/ABCG1 Pathways. *Vascul. Pharmacol.* **2022**, *143*, 106968. [CrossRef] [PubMed]
70. Liu, Y.; Sun, Y.; Lin, X.; Zhang, D.; Hu, C.; Liu, J.; Zhu, Y.; Gao, A.; Han, H.; Chai, M.; et al. Perivascular Adipose-Derived Exosomes Reduce Foam Cell Formation by Regulating Expression of Cholesterol Transporters. *Front. Cardiovasc. Med.* **2021**, *8*, 697510. [CrossRef] [PubMed]
71. Xie, Z.; Wang, X.; Liu, X.; Du, H.; Sun, C.; Shao, X.; Tian, J.; Gu, X.; Wang, H.; Tian, J.; et al. Adipose-Derived Exosomes Exert Proatherogenic Effects by Regulating Macrophage Foam Cell Formation and Polarization. *J. Am. Heart Assoc.* **2018**, *7*, e007442. [CrossRef]
72. Akawi, N.; Checa, A.; Antonopoulos, A.S.; Akoumianakis, I.; Daskalaki, E.; Kotanidis, C.P.; Kondo, H.; Lee, K.; Yesilyurt, D.; Badi, I.; et al. Fat-Secreted Ceramides Regulate Vascular Redox State and Influence Outcomes in Patients With Cardiovascular Disease. *J. Am. Coll. Cardiol.* **2021**, *77*, 2494–2513. [CrossRef] [PubMed]
73. Li, X.; Ballantyne, L.L.; Yu, Y.; Funk, C.D. Perivascular Adipose Tissue-Derived Extracellular Vesicle MiR-221-3p Mediates Vascular Remodeling. *FASEB J.* **2019**, *33*, 12704–12722. [CrossRef]
74. Jafari, N.; Kolla, M.; Meshulam, T.; Shafran, J.S.; Qiu, Y.; Casey, A.N.; Pompa, I.R.; Ennis, C.S.; Mazzeo, C.S.; Rabhi, N.; et al. Adipocyte-Derived Exosomes May Promote Breast Cancer Progression in Type 2 Diabetes. *Sci. Signal* **2021**, *14*, eabj2807. [CrossRef] [PubMed]
75. Tromp, J.; Claggett, B.L.; Liu, J.; Jackson, A.M.; Jhund, P.S.; Køber, L.; Widimský, J.; Boytsov, S.A.; Chopra, V.K.; Anand, I.S.; et al. Global Differences in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial. *Circ. Heart Fail.* **2021**, *14*, 468–477. [CrossRef] [PubMed]
76. Wu, N.N.; Bi, Y.; Ajoolabady, A.; You, F.; Sowers, J.; Wang, Q.; Ceylan, A.F.; Zhang, Y.; Ren, J. Parkin Insufficiency Accentuates High-Fat Diet-Induced Cardiac Remodeling and Contractile Dysfunction Through VDAC1-Mediated Mitochondrial Ca^{2+} Overload. *JACC Basic. Transl. Sci.* **2022**, *7*, 779–796. [CrossRef] [PubMed]
77. Zhao, X.; Si, L.; Bian, J.; Pan, C.; Guo, W.; Qin, P.; Zhu, W.; Xia, Y.; Zhang, Q.; Wei, K. Adipose Tissue Macrophage-Derived Exosomes Induce Ferroptosis via Glutathione Synthesis Inhibition by Targeting SLC7A11 in Obesity-Induced Cardiac Injury. *Free Radic. Biol. Med.* **2022**, *182*, 232–245. [CrossRef] [PubMed]
78. Nie, H.; Pan, Y.; Zhou, Y. Exosomal MicroRNA-194 Causes Cardiac Injury and Mitochondrial Dysfunction in Obese Mice. *Biochem. Biophys. Res. Commun.* **2018**, *503*, 3174–3179. [CrossRef]
79. Li, F.; Zhang, K.; Xu, T.; Du, W.; Yu, B.; Liu, Y.; Nie, H. Exosomal MicroRNA-29a Mediates Cardiac Dysfunction and Mitochondrial Inactivity in Obesity-Related Cardiomyopathy. *Endocrine* **2019**, *63*, 480–488. [CrossRef] [PubMed]
80. 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. *Obesity* **2020**, *28*, 1932–1940. [CrossRef]

81. Crewe, C.; Joffin, N.; Rutkowski, J.M.; Kim, M.; Zhang, F.; Towler, D.A.; Gordillo, R.; Scherer, P.E. An Endothelial-to-Adipocyte Extracellular Vesicle Axis Governed by Metabolic State. *Cell* **2018**, *175*, 695–708.e13. [CrossRef] [PubMed]
82. Clement, E.; Lazar, I.; Attané, C.; Carrié, L.; Dauvillier, S.; Ducoux-Petit, M.; Esteve, D.; Menneteau, T.; Moutahir, M.; Le Gonidec, S.; et al. Adipocyte Extracellular Vesicles Carry Enzymes and Fatty Acids That Stimulate Mitochondrial Metabolism and Remodeling in Tumor Cells. *EMBO J.* **2020**, *39*, e102525. [CrossRef]
83. Sansone, P.; Savini, C.; Kurelac, I.; Chang, Q.; Amato, L.B.; Strillacci, A.; Stepanova, A.; Iommarini, L.; Mastroleo, C.; Daly, L.; et al. Packaging and Transfer of Mitochondrial DNA via Exosomes Regulate Escape from Dormancy in Hormonal Therapy-Resistant Breast Cancer. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E9066–E9075. [CrossRef] [PubMed]
84. Van Marken Lichtenbelt, W.D.; Vanhommerig, J.W.; Smulders, N.M.; Drossaerts, J.M.A.F.L.; Kemerink, G.J.; Bouvy, N.D.; Schrauwen, P.; Teule, G.J.J. Cold-Activated Brown Adipose Tissue in Healthy Men. *N. Engl. J. Med.* **2009**, *360*, 1500–1508. [CrossRef]
85. Zhou, X.; Li, Z.; Qi, M.; Zhao, P.; Duan, Y.; Yang, G.; Yuan, L. Brown Adipose Tissue-Derived Exosomes Mitigate the Metabolic Syndrome in High Fat Diet Mice. *Theranostics* **2020**, *10*, 8197–8210. [CrossRef]
86. Dracheva, K.V.; Pobozheva, I.A.; Anisimova, K.A.; Balandov, S.G.; Hamid, Z.M.; Panteleeva, A.A.; Vasilevsky, D.I.; Pchelina, S.N.; Miroshnikova, V.V. Omentin-1 and Adiponectin Secretion via Adipose Tissue Extracellular Vesicles. *Atherosclerosis* **2021**, *331*, e146. [CrossRef]
87. Feijóo-Bandín, S.; Aragón-Herrera, A.; Moraña-Fernández, S.; Anido-Varela, L.; Tarazón, E.; Roselló-Lletí, E.; Portolés, M.; Moscoso, I.; Gualillo, O.; González-Juanatey, J.R.; et al. Adipokines and Inflammation: Focus on Cardiovascular Diseases. *Int. J. Mol. Sci.* **2020**, *21*, 7711. [CrossRef]
88. Li, J.; Gong, L.; Liu, S.; Zhang, Y.; Zhang, C.; Tian, M.; Lu, H.; Bu, P.; Yang, J.; Ouyang, C.; et al. Adipose HuR Protects against Diet-Induced Obesity and Insulin Resistance. *Nat. Commun.* **2019**, *10*, 2375. [CrossRef] [PubMed]
89. Guarnieri, A.R.; Anthony, S.R.; Gozdiff, A.; Green, L.C.; Fleifil, S.M.; Slone, S.; Nieman, M.L.; Alam, P.; Benoit, J.B.; Owens, A.P.; et al. Adipocyte-Specific Deletion of HuR Induces Spontaneous Cardiac Hypertrophy and Fibrosis. *Am. J. Physiol. Heart Circ. Physiol.* **2021**, *321*, 228–241. [CrossRef]
90. Su, M.; Li, W.; Yuan, Y.; Liu, S.; Liang, C.; Liu, H.; Zhang, R.; Liu, Y.; Sun, L.; Wei, Y.; et al. Epididymal White Adipose Tissue Promotes Angiotensin II-Induced Cardiac Fibrosis in an Exosome-Dependent Manner. *Transl. Res.* **2022**, *248*, 51–67. [CrossRef]
91. Liu, T.; Sun, Y.C.; Cheng, P.; Shao, H.G. Adipose Tissue Macrophage-Derived Exosomal MiR-29a Regulates Obesity-Associated Insulin Resistance. *Biochem. Biophys. Res. Commun.* **2019**, *515*, 352–358. [CrossRef] [PubMed]
92. Kulaj, K.; Harger, A.; Bauer, M.; Caliskan, Ö.S.; Gupta, T.K.; Chiang, D.M.; Milbank, E.; Reber, J.; Karlas, A.; Kotzbeck, P.; et al. Adipocyte-Derived Extracellular Vesicles Increase Insulin Secretion through Transport of Insulinotropic Protein Cargo. *Nat. Commun.* **2023**, *14*, 709. [CrossRef] [PubMed]
93. Li, Y.Z.; Tian, Y.; Yang, C.; Liu, Y.F.; Qu, S.L.; Huang, L.; Zhang, C. Adipose Tissue Macrophages-Derived Exosomal MiR-500a-5p under High Glucose Promotes Adipocytes Inflammation by Suppressing Nrf2 Expression. *Int. J. Biochem. Cell Biol.* **2025**, *178*, 106713. [CrossRef] [PubMed]
94. Patra, D.; Ramprasad, P.; Sharma, S.; Dey, U.; Kumar, V.; Singh, S.; Dasgupta, S.; Kumar, A.; Tikoo, K.; Pal, D. Adipose Tissue Macrophage-Derived MicroRNA-210-3p Disrupts Systemic Insulin Sensitivity by Silencing GLUT4 in Obesity. *J. Biol. Chem.* **2024**, *300*, 107328. [CrossRef] [PubMed]
95. Zhang, Y.; Mei, H.; Chang, X.; Chen, F.; Zhu, Y.; Han, X. Adipocyte-Derived Microvesicles from Obese Mice Induce M1 Macrophage Phenotype through Secreted MiR-155. *J. Mol. Cell Biol.* **2016**, *8*, 505–517. [CrossRef] [PubMed]
96. Sou, Y.L.; Chilian, W.M.; Ratnam, W.; Zain, S.M.; Syed Abdul Kadir, S.Z.; Pan, Y.; Pung, Y.F. Exosomal miRNAs and isomiRs: Potential biomarkers for type 2 diabetes mellitus. *Precis. Clin. Med.* **2024**, *7*, pbae021. [CrossRef] [PubMed]
97. Li, M.; Hou, Y.; Chen, Y.; Sun, C.; Liang, M.; Chu, X.; Wen, X.; Yuan, F.; Peng, C.; Wang, C.; et al. Palmitic Acid Promotes MiRNA Release from Adipocyte Exosomes by Activating NF-KB/ER Stress. *Nutr. Diabetes* **2024**, *14*, 75. [CrossRef]
98. Zhao, H.; Shang, Q.; Pan, Z.; Bai, Y.; Li, Z.; Zhang, H.; Zhang, Q.; Guo, C.; Zhang, L.; Wang, Q. Exosomes From Adipose-Derived Stem Cells Attenuate Adipose Inflammation and Obesity Through Polarizing M2 Macrophages and Beiging in White Adipose Tissue. *Diabetes* **2018**, *67*, 235–247. [CrossRef] [PubMed]
99. Ali, S.; Vidal-Gómez, X.; Piquet, M.; Vergori, L.; Simard, G.; Dubois, S.; Ducluzeau, P.H.; Pomiès, P.; Kamli-Salino, S.; Delibégovic, M.; et al. Circulating Extracellular Vesicle-Carried PTP1B and PP2A Phosphatases as Regulators of Insulin Resistance. *Diabetologia* **2024**, *68*, 231–242. [CrossRef]
100. Yu, Y.; Du, H.; Wei, S.; Feng, L.; Li, J.; Yao, F.; Zhang, M.; Hatch, G.M.; Chen, L. Adipocyte-Derived Exosomal MiR-27a Induces Insulin Resistance in Skeletal Muscle Through Repression of PPARγ. *Theranostics* **2018**, *8*, 2171–2188. [CrossRef]
101. Huang, X.Y.; Chen, J.X.; Ren, Y.; Fan, L.C.; Xiang, W.; He, X.J. Exosomal MiR-122 Promotes Adipogenesis and Aggravates Obesity through the VDR/SREBF1 Axis. *Obesity* **2022**, *30*, 666–679. [CrossRef]
102. Ojima, K.; Muroya, S.; Wada, H.; Ogawa, K.; Oe, M.; Takimoto, K.; Nishimura, T. Immature Adipocyte-Derived Exosomes Inhibit Expression of Muscle Differentiation Markers. *FEBS Open Bio* **2021**, *11*, 768–781. [CrossRef]

103. Han, Y.; Ye, S.; Liu, B. Roles of Extracellular Vesicles Derived from Healthy and Obese Adipose Tissue in Inter-Organ Crosstalk and Potential Clinical Implication. *Front. Endocrinol.* **2024**, *15*, 1409000. [CrossRef] [PubMed]
104. Zhou, C.; Huang, Y.Q.; Da, M.X.; Jin, W.L.; Zhou, F.H. Adipocyte-derived extracellular vesicles: Bridging the communications between obesity and tumor microenvironment. *Discov. Oncol.* **2023**, *14*, 92. [CrossRef]
105. Nunez Lopez, Y.O.; Casu, A.; Kovacova, Z.; Petrilli, A.M.; Sideleva, O.; Tharp, W.G.; Pratley, R.E. Coordinated regulation of gene expression and microRNA changes in adipose tissue and circulating extracellular vesicles in response to pioglitazone treatment in humans with type 2 diabetes. *Front Endocrinol* **2022**, *13*, 955593. [CrossRef] [PubMed]
106. Gesmundo, I.; Pardini, B.; Gargantini, E.; Gamba, G.; Birolo, G.; Fanciulli, A.; Banfi, D.; Congiusta, N.; Favaro, E.; Deregibus, M.C.; et al. Adipocyte-Derived Extracellular Vesicles Regulate Survival and Function of Pancreatic β Cells. *JCI Insight* **2021**, *6*, 141962. [CrossRef] [PubMed]
107. Wang, D.; Zhang, X.; Li, Y.; Jia, L.; Zhai, L.; Wei, W.; Zhang, L.; Jiang, H.; Bai, Y. Exercise-Induced Browning of White Adipose Tissue and Improving Skeletal Muscle Insulin Sensitivity in Obese/Non-Obese Growing Mice: Do Not Neglect Exosomal MiR-27a. *Front. Nutr.* **2022**, *9*, 940673. [CrossRef]
108. Sadeghzadeh, S.; Ashkezari, M.D.; Seifati, S.M.; Mehrjardi, M.Y.V.; Tezerjani, M.D.; Sadeghzadeh, S.; Ladan, S.A.B. Circulating MiR-15a and MiR-222 as Potential Biomarkers of Type 2 Diabetes. *Diabetes Metab. Syndr. Obes.* **2020**, *13*, 3461–3469. [CrossRef] [PubMed]
109. Li, D.; Song, H.; Shuo, L.; Wang, L.; Xie, P.; Li, W.; Liu, J.; Tong, Y.; Zhang, C.Y.; Jiang, X.; et al. Gonadal White Adipose Tissue-Derived Exosomal MiR-222 Promotes Obesity-Associated Insulin Resistance. *Aging* **2020**, *12*, 22719–22737. [CrossRef]
110. Gong, Q.; Hu, Z.; Zhang, F.; Cui, A.; Chen, X.; Jiang, H.; Gao, J.; Chen, X.; Han, Y.; Liang, Q.; et al. Fibroblast growth factor 21 improves hepatic insulin sensitivity by inhibiting mammalian target of rapamycin complex 1 in mice. *Hepatology* **2016**, *64*, 425–438. [CrossRef]
111. Dang, S.Y.; Leng, Y.; Wang, Z.X.; Xiao, X.; Zhang, X.; Wen, T.; Gong, H.Z.; Hong, A.; Ma, Y. Exosomal Transfer of Obesity Adipose Tissue for Decreased MiR-141-3p Mediate Insulin Resistance of Hepatocytes. *Int. J. Biol. Sci.* **2019**, *15*, 351–368. [CrossRef] [PubMed]
112. Zhang, Y.; Qian, B.; Yang, Y.; Niu, F.; Lin, C.; Yuan, H.; Wang, J.; Wu, T.; Shao, Y.; Shao, S.; et al. Visceral Adipocyte-Derived Extracellular Vesicle MiR-27a-5p Elicits Glucose Intolerance by Inhibiting Pancreatic β-Cell Insulin Secretion. *Diabetes* **2024**, *73*, 1832–1847. [CrossRef]
113. Lino, M.; Garcia-Martin, R.; Muñoz, V.R.; Ruiz, G.P.; Nawaz, A.; Brandão, B.B.; Dreyfus, J.; Pan, H.; Kahn, C.R. Multi-Step Regulation of MicroRNA Expression and Secretion into Small Extracellular Vesicles by Insulin. *Cell Rep.* **2024**, *43*, 114491. [CrossRef]
114. Lin, H.; Chen, X.; Pan, J.; Ke, J.; Zhang, A.; Liu, Y.; Wang, C.; Chang, A.C.Y.; Gu, J. Secretion of MiRNA-326-3p by Senescent Adipose Exacerbates Myocardial Metabolism in Diabetic Mice. *J. Transl. Med.* **2022**, *20*, 278. [CrossRef] [PubMed]
115. Wang, Y.; Chen, L.M.; Liu, M.L. Microvesicles and Diabetic Complications--Novel Mediators, Potential Biomarkers and Therapeutic Targets. *Acta Pharmacol. Sin.* **2014**, *35*, 433–443. [CrossRef] [PubMed]
116. Chen, Y.; Li, G.; Liu, M.L. Microvesicles as Emerging Biomarkers and Therapeutic Targets in Cardiometabolic Diseases. *Genom. Proteom. Bioinform.* **2018**, *16*, 50–62. [CrossRef]
117. Liu, M.L.; Williams, K.J. Microvesicles: Potential Markers and Mediators of Endothelial Dysfunction. *Curr. Opin. Endocrinol. Diabetes Obes.* **2012**, *19*, 121–127. [CrossRef]
118. Zhang, W.; Chen, S.; Liu, M.L. Pathogenic Roles of Microvesicles in Diabetic Retinopathy. *Acta Pharmacol. Sin.* **2018**, *39*, 1–11. [CrossRef]
119. Le Jeune, S.; Sadoudi, S.; Charue, D.; Abid, S.; Guigner, J.M.; Helley, D.; Bihan, H.; Baudry, C.; Lelong, H.; Mirault, T.; et al. Low Grade Intravascular Hemolysis Associates with Peripheral Nerve Injury in Type 2 Diabetes. *PLoS ONE* **2022**, *17*, e0275337. [CrossRef]
120. Gan, L.; Xie, D.; Liu, J.; Bond Lau, W.; Christopher, T.A.; Lopez, B.; Zhang, L.; Gao, E.; Koch, W.; Ma, X.L.; 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*, 968–983. [CrossRef]
121. Shan, Y.X.; Yang, T.L.; Mestril, R.; Wang, P.H. Hsp10 and Hsp60 Suppress Ubiquitination of Insulin-like Growth Factor-1 Receptor and Augment Insulin-like Growth Factor-1 Receptor Signaling in Cardiac Muscle: Implications on Decreased Myocardial Protection in Diabetic Cardiomyopathy. *J. Biol. Chem.* **2003**, *278*, 45492–45498. [CrossRef]
122. Gao, J.; Li, X.; Wang, Y.; Cao, Y.; Yao, D.; Sun, L.; Qin, L.; Qiu, H.; Zhan, X. Adipocyte-Derived Extracellular Vesicles Modulate Appetite and Weight through MTOR Signalling in the Hypothalamus. *Acta Physiol.* **2020**, *228*, e13339. [CrossRef]
123. Yoshida, M.; Satoh, A.; Lin, J.B.; Mills, K.F.; Sasaki, Y.; Rensing, N.; Wong, M.; Apte, R.S.; Imai, S. ichiro Extracellular Vesicle-Contained ENAMPT Delays Aging and Extends Lifespan in Mice. *Cell Metab.* **2019**, *30*, 329–342.e5. [CrossRef] [PubMed]
124. Tokizane, K.; Brace, C.S.; Imai, S. ichiro DMHPpp1r17 Neurons Regulate Aging and Lifespan in Mice through Hypothalamic-Adipose Inter-Tissue Communication. *Cell Metab.* **2024**, *36*, 377–392.e11. [CrossRef] [PubMed]

125. Biessels, G.J.; Despa, F. Cognitive Decline and Dementia in Diabetes Mellitus: Mechanisms and Clinical Implications. *Nat. Rev. Endocrinol.* **2018**, *14*, 591–604. [CrossRef] [PubMed]
126. Wang, J.; Li, L.; Zhang, Z.; Zhang, X.; Zhu, Y.; Zhang, C.; Bi, Y. Extracellular Vesicles Mediate the Communication of Adipose Tissue with Brain and Promote Cognitive Impairment Associated with Insulin Resistance. *Cell Metab.* **2022**, *34*, 1264–1279.e8. [CrossRef] [PubMed]
127. Khan, M.J.; Singh, P.; Dohare, R.; Jha, R.; Rahmani, A.H.; Almatroodi, S.A.; Ali, S.; Syed, M.A. Inhibition of miRNA-34a Promotes M2 Macrophage Polarization and Improves LPS-Induced Lung Injury by Targeting Klf4. *Genes* **2020**, *11*, 966. [CrossRef]
128. Pan, Y.; Hui, X.; Hoo, R.L.C.; Ye, D.; Chan, C.Y.C.; Feng, T.; Wang, Y.; Lam, K.S.L.; Xu, A. Adipocyte-Secreted Exosomal MicroRNA-34a Inhibits M2 Macrophage Polarization to Promote Obesity-Induced Adipose Inflammation. *J. Clin. Investig.* **2019**, *129*, 834–849. [CrossRef] [PubMed]
129. Zhang, D.; Yao, X.; Teng, Y.; Zhao, T.; Lin, L.; Li, Y.; Shang, H.; Jin, Y.; Jin, Q. Adipocytes-Derived Exosomal MicroRNA-1224 Inhibits M2 Macrophage Polarization in Obesity-Induced Adipose Tissue Inflammation via MSI2-Mediated Wnt/β-Catenin Axis. *Mol. Nutr. Food Res.* **2022**, *66*, e2100889. [CrossRef]
130. Kumar, V.; Kiran, S.; Kumar, S.; Singh, U.P. Extracellular Vesicles in Obesity and Its Associated Inflammation. *Int. Rev. Immunol.* **2022**, *41*, 30–44. [CrossRef] [PubMed]
131. Bai, Y.; Sun, Q. Macrophage Recruitment in Obese Adipose Tissue. *Obes. Rev.* **2015**, *16*, 127–136. [CrossRef]
132. Zhou, Z.; Tao, Y.; Zhao, H.; Wang, Q. Adipose Extracellular Vesicles: Messengers From and to Macrophages in Regulating Immunometabolic Homeostasis or Disorders. *Front. Immunol.* **2021**, *12*, 666344. [CrossRef]
133. Ortega, F.J.; Moreno, M.; Mercader, J.M.; Moreno-Navarrete, J.M.; Fuentes-Batllevell, N.; Sabater, M.; Ricart, W.; Fernández-Real, J.M. Inflammation Triggers Specific MicroRNA Profiles in Human Adipocytes and Macrophages and in Their Supernatants. *Clin. Epigenetics* **2015**, *7*, 49. [CrossRef] [PubMed]
134. Dekkers, M.C.; Lambooij, J.M.; Pu, X.; Fagundes, R.R.; Enciso-Martinez, A.; Kats, K.; Giepmans, B.N.G.; Guigas, B.; Zaldumbide, A. Extracellular Vesicles Derived from Stressed Beta Cells Mediate Monocyte Activation and Contribute to Islet Inflammation. *Front. Immunol.* **2024**, *15*, 1393248. [CrossRef] [PubMed]
135. Gofton, C.; Upendran, Y.; Zheng, M.H.; George, J. MAFLD: How Is It Different from NAFLD? *Clin. Mol. Hepatol.* **2023**, *29*, S17–S31. [CrossRef] [PubMed]
136. Lopez-Yus, M.; Hörndler, C.; Borlan, S.; Bernal-Monterde, V.; Arbones-Mainar, J.M. Unraveling Adipose Tissue Dysfunction: Molecular Mechanisms, Novel Biomarkers, and Therapeutic Targets for Liver Fat Deposition. *Cells* **2024**, *13*, 380. [CrossRef]
137. Basil, B.; Myke-Mbata, B.K.; Eze, O.E.; Akubue, A.U. From Adiposity to Steatosis: Metabolic Dysfunction-Associated Steatotic Liver Disease, a Hepatic Expression of Metabolic Syndrome—Current Insights and Future Directions. *Clin. Diabetes Endocrinol.* **2024**, *10*, 39. [CrossRef] [PubMed]
138. Mladenović, D.; Vesković, M.; Šutulović, N.; Hrnčić, D.; Stanojlović, O.; Radić, L.; Macut, J.B.; Macut, D. Adipose-Derived Extracellular Vesicles—A Novel Cross-Talk Mechanism in Insulin Resistance, Non-Alcoholic Fatty Liver Disease, and Polycystic Ovary Syndrome. *Endocrine* **2024**, *85*, 18–34. [CrossRef] [PubMed]
139. Zhao, Y.; Zhao, M.F.; Jiang, S.; Wu, J.; Liu, J.; Yuan, X.W.; Shen, D.; Zhang, J.Z.; Zhou, N.; He, J.; et al. Liver Governs Adipose Remodelling via Extracellular Vesicles in Response to Lipid Overload. *Nat. Commun.* **2020**, *11*, 719. [CrossRef]
140. Payet, T.; Gabinaud, E.; Landrier, J.F.; Mounien, L. Role of Micro-RNAs Associated with Adipose-Derived Extracellular Vesicles in Metabolic Disorders. *Obes. Rev.* **2024**, *25*, e13755. [CrossRef]
141. Kranendonk, M.E.G.; Visseren, F.L.J.; Van Herwaarden, J.A.; Nolte-'t Hoen, E.N.M.; De Jager, W.; Wauben, M.H.M.; Kalkhoven, E. Effect of Extracellular Vesicles of Human Adipose Tissue on Insulin Signaling in Liver and Muscle Cells. *Obesity* **2014**, *22*, 2216–2223. [CrossRef]
142. Rong, B.; Feng, R.; Liu, C.; Wu, Q.; Sun, C. Reduced Delivery of Epididymal Adipocyte-Derived Exosomal Resistin Is Essential for Melatonin Ameliorating Hepatic Steatosis in Mice. *J. Pineal Res.* **2019**, *66*, e12561. [CrossRef] [PubMed]
143. Gu, H.; Yang, K.; Shen, Z.; Jia, K.; Liu, P.; Pan, M.; Sun, C. ER Stress-Induced Adipocytes Secrete-Aldo-Keto Reductase 1B7-Containing Exosomes That Cause Nonalcoholic Steatohepatitis in Mice. *Free Radic. Biol. Med.* **2021**, *163*, 220–233. [CrossRef]
144. Song, H.; Canup, B.S.B.; Ngo, V.L.; Denning, T.L.; Garg, P.; Laroui, H. Internalization of Garlic-Derived Nanovesicles on Liver Cells Is Triggered by Interaction with CD98. *ACS Omega* **2020**, *5*, 23118–23128. [CrossRef] [PubMed]
145. Li, C.J.; Fang, Q.H.; Liu, M.L.; Lin, J.N. Current Understanding of the Role of Adipose-Derived Extracellular Vesicles in Metabolic Homeostasis and Diseases: Communication from the Distance between Cells/Tissues. *Theranostics* **2020**, *10*, 7422–7435. [CrossRef] [PubMed]
146. Cione, E.; Cannataro, R.; Gallelli, L.; De Sarro, G.; Caroleo, M.C. Exosome MicroRNAs in Metabolic Syndrome as Tools for the Early Monitoring of Diabetes and Possible Therapeutic Options. *Pharmaceuticals* **2021**, *14*, 1257. [CrossRef]
147. Koeck, E.S.; Iordanskaia, T.; Sevilla, S.; Ferrante, S.C.; Hubal, M.J.; Freishtat, R.J.; Nadler, E.P. Adipocyte Exosomes Induce Transforming Growth Factor Beta Pathway Dysregulation in Hepatocytes: A Novel Paradigm for Obesity-Related Liver Disease. *J. Surg. Res.* **2014**, *192*, 268–275. [CrossRef] [PubMed]

148. Malhi, H.; Kaufman, R.J. Endoplasmic Reticulum Stress in Liver Disease. *J. Hepatol.* **2011**, *54*, 795–809. [CrossRef]
149. Lu, M.M.; Ren, Y.; Zhou, Y.W.; Xu, L.L.; Zhang, M.M.; Ding, L.P.; Cheng, W.X.; Jin, X. Antagonizing Adipose Tissue-Derived Exosome MiR-103-Hepatocyte Phosphatase and Tensin Homolog Pathway Alleviates Autophagy in Non-Alcoholic Steatohepatitis: A Trans-Cellular Crosstalk. *World J. Gastroenterol.* **2023**, *29*, 4528–4541. [CrossRef] [PubMed]
150. Dewidar, B.; Meyer, C.; Dooley, S.; Meindl-Beinker, N. TGF-β in Hepatic Stellate Cell Activation and Liver Fibrogenesis-Updated 2019. *Cells* **2019**, *8*, 1419. [CrossRef] [PubMed]
151. Chavey, C.; Mari, B.; Monthouel, M.N.; Bonnafous, S.; Anglard, P.; Van Obberghen, E.; Tartare-Deckert, S. Matrix Metalloproteinases Are Differentially Expressed in Adipose Tissue during Obesity and Modulate Adipocyte Differentiation. *J. Biol. Chem.* **2003**, *278*, 11888–11896. [CrossRef] [PubMed]
152. Shimoda, M.; Khokha, R. Metalloproteinases in Extracellular Vesicles. *Biochim. Biophys. Acta (BBA) Mol. Cell Res.* **2017**, *1864*, 1989–2000. [CrossRef] [PubMed]
153. Lijnen, H.R.; Maquoi, E.; Demeulemeester, D.; Van Hoef, B.; Collen, D. Modulation of Fibrinolytic and Gelatinolytic Activity during Adipose Tissue Development in a Mouse Model of Nutritionally Induced Obesity. *Thromb. Haemost.* **2002**, *88*, 345–353. [CrossRef] [PubMed]
154. Li, C.J.; Liu, Y.; Chen, Y.; Yu, D.; Williams, K.J.; Liu, M.L. Novel Proteolytic Microvesicles Released from Human Macrophages after Exposure to Tobacco Smoke. *Am. J. Pathol.* **2013**, *182*, 1552–1562. [CrossRef]
155. Marino, L.; Ni, B.; Farrar, J.S.; Lownik, J.C.; Pearce, J.V.; Martin, R.K.; Celi, F.S. Adipose Tissue-Selective Ablation of ADAM10 Results in Divergent Metabolic Phenotypes Following Long-Term Dietary Manipulation. *Adipocyte* **2024**, *13*, 2339418. [CrossRef]
156. Matthews, J.; Villescas, S.; Herat, L.; Schlaich, M.; Matthews, V. Implications of ADAM17 Activation for Hyperglycaemia, Obesity and Type 2 Diabetes. *Biosci. Rep.* **2021**, *41*, BSR20210029. [CrossRef] [PubMed]
157. Folkesson, M.; Li, C.; Frebelius, S.; Swedenborg, J.; Wågsäter, D.; Williams, K.J.; Eriksson, P.; Roy, J.; Liu, M.L. Proteolytically Active ADAM10 and ADAM17 Carried on Membrane Microvesicles in Human Abdominal Aortic Aneurysms. *Thromb. Haemost.* **2015**, *114*, 1165–1174. [CrossRef]
158. DiStefano, J.K.; Piras, I.S.; Wu, X.; Sharma, R.; Garcia-Mansfield, K.; Willey, M.; Lovell, B.; Pirrotte, P.; Olson, M.L.; Shaibi, G.Q. Changes in Proteomic Cargo of Circulating Extracellular Vesicles in Response to Lifestyle Intervention in Adolescents with Hepatic Steatosis. *Clin. Nutr. ESPEN* **2024**, *60*, 333–342. [CrossRef] [PubMed]

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