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Review

Exosome-Derived microRNAs: Bridging the Gap Between Obesity and Type 2 Diabetes in Diagnosis and Treatment

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Abstract: Obesity and type 2 diabetes represent global public health challenges that are continuously growing at an alarming rate. The etiology of obesity is complex and multifactorial, with a substantial interplay between behavioral, biological, and environmental factors. Dysregulation of immunometabolism through chronic low-intensity inflammation in obesity has long been recognized as the main driver of insulin resistance and the development of type 2 diabetes. However, the intricate mechanisms underlying these alterations have yet to be fully elucidated. Exosomes are extracellular vesicles that carry biomolecules including various types of RNA molecules. Of particular importance are microRNAs (miRNAs), known as modulators of gene expression whose altered expression is observed in various pathophysiological conditions. Recent research suggests that exosome-derived miRNAs, such as miR-155, miR-27a, and miR-29, play an essential role in the regulation of inflammatory processes, while miR-122 and miR-192 are associated with metabolic dysfunction. These and many other miRNAs influence signaling pathways that are critical for maintaining insulin sensitivity, thereby contributing to the development of insulin resistance in individuals with obesity. Hence, there is a growing interest in the potential of exosomes and miRNAs as biomarkers for the early detection of insulin resistance and other obesity-related complications, as well as promising therapeutic targets or next-generation drug delivery carriers. This review provides a comprehensive overview of the interplay between exosome-derived miRNA, obesity, and type 2 diabetes and summarizes the latest findings in exosome biology.

Keywords: obesity; type 2 diabetes; exosomes; microRNA; biomarkers; therapy; insulin resistance

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1. Introduction—Obesity and Type 2 Diabetes

1.1. Obesity as the Beginning of Diabetes

Obesity and type 2 diabetes (T2D) represent global public health challenges that are continuously growing at an alarming rate. According to recent data, it is estimated that more than 650 million people worldwide are obese, while the most devastating data are on the number of children and adolescents with obesity [1]. The World Health Organization rates obesity as a prominent health problem that is easily recognized but often overlooked, undiagnosed, and untreated. Obesity substantially increases the risk of metabolic diseases, and there is no doubt that obesity is a major driver for the development of T2D. However, despite the shared genetic and environmental features, the mechanisms linking these two conditions remain unclear. In line, reports show that 86% of adults with T2D are overweight or obese; 52% are classified as obese, and 8.1% have morbid obesity.

Over the last hundred years or more, information as well as knowledge addressing obesity has been harvested from a wealth of research, although a single primary cause has yet to be identified. Instead, several factors—including behavioral, biological, and environmental influences—are widely recognized as contributors. Foremost, among these are dietary habits, particularly the increasing consumption of high-calorie, processed foods rich in sugar and fat, along with a sedentary lifestyle and insufficient exercise. In addition, psychological factors such as emotional stress, depression, and other mental health issues can also lead to overeating or unhealthy eating patterns. While lifestyle changes are essential, they alone have not been sufficient to halt the growing obesity epidemic. This underscores the importance of biological factors, including genetic susceptibility and, metabolic and immune factors, in the development of obesity. While monogenic causes of obesity are rare and cannot explain the scale of the obesity pandemic, numerous mutations in genes encoding molecules such as leptin, adiponectin, and glucose transporters 2 and 4 as well as the large number of genes identified by genome-wide association studies can influence caloric intake and, metabolism, including food processing, fat storage, and body-fat distribution. However, the strength of genetic influence on weight disorders varies significantly among individuals. Research indicates that genes account for about 25% of the predisposition to being overweight in some people, while the genetic influence in others is 70% to 80% [2].

Nowadays, it is known that persistent fat-positive balance leads to weight gain, white adipose tissue (WAT) enlargement, and low-grade inflammation which may underlie the development of tissue dysfunction, insulin resistance, and metabolic comorbidities such as cardiovascular disease, diabetes, and cancer [3]. As discussed later, enlarged adipose tissue, particularly visceral tissue, is a main source of chronic inflammation while being the most important cog in the complex developmental mechanism. Therefore, it is important to determine the size and distribution of adipose tissue, and body mass index has been used as a non-invasive measure of adiposity for more than a century [4]. Although widely used, it has significant limitations as it does not distinguish between fat and muscle mass and may not accurately reflect the distribution of body fat or the risk of developing obesity-associated comorbidities [4].

Low-grade inflammation is characterized by elevated levels of circulating pro-inflammatory cytokines, which have deleterious effects on the central nervous system and disrupt the function of organs involved in maintaining immune responses and metabolic processes [5]. Furthermore, the metabolic disturbance that occurs in obesity leads to an up- or down-regulation of metabolic pathways that influence the differentiation, phenotype, and functions of immune cells as well as the further production of cytokines and chemokines. In line with this, studies have shown that obesity increases intracellular lipid metabolism and glucose uptake in macrophages, which can trigger their M1 polarization [6]. In addition, inflammation can interfere with insulin signaling, glucose metabolism, and lipid homeostasis, contributing to insulin resistance. Each of the above factors can interact with the others, making obesity a complex disease with multiple interrelated elements. To integrate all these findings, the concept of dysregulated immunometabolism in obesity has

been postulated. A step forward in understanding the dysregulation of immunometabolism underlying obesity is the increasing evidence that the above-mentioned interactions are also driven and regulated by the microbiome–gut–brain axis. Despite lifestyle changes and the best available medical and surgical treatments for obesity and T2D, gaps in pathophysiology and clinical management remain. Since their discovery in 1993, evidence and understanding of the physiological significance of microRNAs (miRNAs) have steadily grown. Distinct miRNA profiles have been identified in patients with metabolic disorders, such as obesity and T2D [7], compared to healthy individuals, positioning them as potential new biomarkers. Additionally, the recognition that miRNAs are transported within extracellular vesicles [8] has opened a new perspective, suggesting that they act as an endocrine factor involved in maintaining communication between organs. This insight could also open new avenues for understanding the mechanisms behind obesity-related complications in various organs and pave the way for the development of improved treatments.

1.2. Adipose Tissue—A Critical Player in the Disturbance of Immunometabolism

Adipose tissue is an important player in controlling metabolism, and it is divided into two main classes: WAT, where lipids, in the form of triglycerides, are mainly stored in a single droplet within the adipocytes, and brown adipose tissue, predominantly located in the neck, supraclavicular, perirenal/adrenal, and vertebral fat depots. Compared to WAT, brown adipose tissue stores lipids in multiple lipid droplets, maintains body temperature, and is less involved in immunometabolic control. WAT is found at various locations in the human body. Based on its anatomical location, functional characteristics, and impact on obesity development, it is classified into two main types: subcutaneous and visceral adipose tissue. Besides storage function and contrary to earlier perceptions, nowadays it is well established that adipose tissue is an active endocrine organ that releases numerous pro-inflammatory and anti-inflammatory molecules, known as adipocytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL) 6, resistin, leptin, and adiponectin, which have several local, peripheral, and central effects [9]. Thus, adipose tissue regulates the metabolism of various tissues both directly and indirectly through the production of bioactive molecules, having a tremendous impact on metabolic homeostasis.

Total body fat is mainly stored in subcutaneous adipose tissue since it is the preferred site for storage of excess fat, while visceral adipose tissue stores 5–20% of the total body fat. Although adipose tissue is highly adaptable and can increase its mass by more than twofold, the storage capacity of adipose tissue varies among individuals. Storing lipids in WAT protects the rest of the body from the expansion of visceral adipose tissue, ectopic lipid accumulation, and lipotoxicity. In obesity, prolonged lipid overload leads to changes in adipose tissue features, including size, function, inflammatory state, and adipokine secretion of adipocytes resulting in metabolic disturbance and rise in insulin resistance [10].

Fundamentally, the excessive fat accumulation and expansion of WAT are also related to inflammatory cell activation. It has been shown that metabolic stress in hypertrophic and/or hyperplasia adipocytes induces the surface expression of ligands for stress receptor Ncr1 [11]. After ligand binding, the signal initiates the recruitment of NK cells but also the polarization of tissue-resident macrophage from phenotype M2 to M1 (Figure 1) [12]. This results in a shift from anti-inflammatory cytokine production [13] to pro-inflammatory cytokine production mediated by TNF-α, IL6, and IL1β [12,14–17]. This production is mediated by the activation of toll-like receptors 2 and 4 stimulated by the elevation of saturated fatty acids [18]. This is regulated through the activation of nuclear factor kappa B/c-Jun N-terminal kinases (NF-κB/JNK) pathways [19]. Consequently, the macrophage shift induces activation and influx of other adipose-resident immune cells, such as Th1 and Th 17 CD4+ T cells, cytotoxic CD8+ T cells, B cells, and NK cells, which in turn produce cytokines that further amplify the inflammation [20]. Concomitantly, the cytokines and cells contribute to a chronic low-grade pro-inflammatory state, thereby contributing to systemic inflammation, impaired insulin signaling, and insufficient insulin production by

β-cells in the pancreas, which are critical factors and main drivers in the development of metabolic diseases, particularly in the development of T2D.

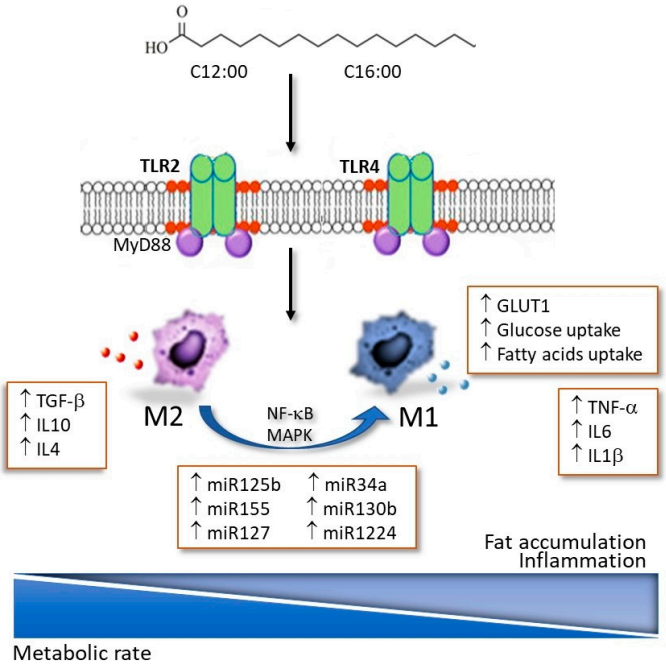

Figure 1. The interplay between fat accumulation and adipose tissue-derived exosomal miRNAs in macro-phage activation and polarization. The polarization of macrophages from the M2 to the M1 phenotype leads to a shift from the production of anti-inflammatory cytokines to pro-inflammatory cytokines, including TNF-α, IL6, and IL1β. This pro-inflammatory cytokine production is driven by the activation of TLR 2 and 4, which are stimulated by elevated levels of saturated fatty acids. TLR, toll-like receptor; GLUT1, glucose transporter type 1; TNF, tumor necrosis factor; TGF, transforming growth factor; IL, interleukin; miR, microRNA; ↑, up-regulation.

The expansion of adipose tissue creates a low-oxygen microenvironment, leading to angiogenesis, reduced vascular density, decreased production of vascular growth factor A, and activation of hypoxia-inducible factor 1A. These changes promote the activation of pro-fibrotic pathways and the NF-κB signaling pathway, which together accelerate pro-inflammatory conditions, drive alterations in the extracellular matrix, and impair fatty acid uptake by adipocytes [10]. Although the primary function of adipose tissue is the storage of lipids, it contains a variety of non-immune and immune cells, including macrophages, T, and B cells.

Due to insulin resistance in obesity, the dysregulation of lipolysis in adipose tissue leads to an impaired, yet constant release of fatty acids into the circulation. The resulting elevated concentration of fatty acids contributes to their accumulation, initially in the liver and subsequently in other organs including skeletal muscles. It has been established that individuals with a given level of BMI, with low muscle mass and higher total body fat percentage and waist circumference, are more likely to have T2D, and face an increased risk of death, highlighting the importance of skeletal muscles. Increased muscle mass improves insulin sensitivity and metabolic health, which can help mitigate some of the negative effects of obesity. Recent research has revealed that adipose tissue, along with other metabolic tissues, communicates with different tissues through small membrane-bound particles called extracellular vesicles. In obesity, these vesicles play a key role in facilitating crosstalk between macrophages, adipose tissue, and other organs. Additionally, they have been found to contain the lipid droplet-associated protein perilipin1, as well as phospholipids, neutral lipids, free cholesterol, and miRNAs [21].

1.3. Type 2 Diabetes

T2D is a long-term metabolic disorder caused by impaired insulin secretion and/or action due to partially understood pathophysiological mechanisms. These mechanisms are complex and involve interactions between chronic inflammation, abnormal lipid accumulation, endoplasmic reticulum stress, and oxidative stress. It is one of the most widespread chronic diseases in the adult population, and, therefore, it is recognized as a serious public health problem with a significant impact on human lives and healthcare costs. In many parts of the world, urbanization and economic development have led to its increased prevalence [22]. Clinical studies to date have reported a large number of young adults diagnosed with T2D, most of whom are obese [23]. One of the key pathophysiological mechanisms behind the onset and progression of T2D is insulin resistance. It is generally recognized that in the early stages of insulin resistance, β-cells overwork to increase insulin secretion in order to keep blood glucose levels stable. The ability of β-cells to compensate is largely determined by genetic factors. However, with disease progression, β-cells lose their ability to produce insulin to counteract the rise in blood glucose levels, ultimately leading to prediabetes or the development of T2D.

As mentioned above, prolonged overnutrition and an excess of metabolites lead to lipid accumulation, metabolic stress, and cellular infiltration in adipose tissue, which in turn triggers the release of pro-inflammatory factors like IL1β and TNF-α [24]. These factors disrupt insulin receptor activation and its downstream IRS1/PI3K/Akt2 signaling pathway through various mechanisms. Pioneering research by Hotamisligil et al. demonstrated elevated levels of TNF-α in the adipose tissue of obese individuals. On the other hand, it has been shown that TNF-α neutralization improves insulin sensitivity in obese rodents [25,26]. Mentioned metabolic disorders can disrupt the transcription of key genes involved in the insulin signaling pathway, leading to its down-regulation, which is the first step toward impaired glucose uptake and hyperglycemia. Additionally, they can activate alternative signaling pathways. Pro-inflammatory cytokines, such as TNF-α and IL1β, inhibit the transcription of insulin signaling molecules by activating stress-related pathways like NF-κB, JAK/STAT, and JNK. These pathways further interfere with the normal expression of genes related to insulin signaling [27]. Finally, an excessive influx of fatty acids into adipose tissue leads to incomplete oxidation of fatty acids, production of reactive oxygen species, and, as expected, accumulation of toxic metabolites, such as ceramides and diacylglycerols, that can directly interfere with the insulin signaling pathway by inhibiting Akt, activation of NF-κB, and JNK-mediated signaling [28].

Low-grade inflammation, combined with the excessive production of metabolites, triggers the phosphorylation of the IκB kinase (IKK) complex and the degradation of IκB, leading to the translocation of NF-κB into the nucleus. NF-κB can negatively affect insulin signaling and glucose homeostasis through various direct and indirect mechanisms. One well-known pathway involves the activation of inducible nitric oxide synthase (iNOS) and the subsequent production of nitric oxide. Furthermore, a component of the activated IKK complex can directly phosphorylate insulin receptor substrate (IRS) 1 on serine residues, thereby inhibiting its activation. In addition to its role in the insulin signaling pathway, according to available data, NF-κB plays a significant role in the development of diabetes complications. Its activation leads to the aggravation of kidney fibrosis [29] and promotes apoptosis of human endothelial cells by enhancing caspase-3 activity, which also delays wound healing in diabetic foot ulcerations [30]. As previously mentioned, inflammatory factors such as IL6 and interferon (INF)-γ can inhibit the IRS1 signaling cascade by activating JAK2/STAT3, which in turn up-regulates the expression of suppressor of cytokine signaling 3. JAK/STAT3 is also found to promote the NF-κB cascade [31]. Like NF-κB, increased phosphorylation of STAT3, as a result of increased IL6 synthesis, impairs immune cell activation, recruitment, and survival, leading to delayed wound healing.

As JNK activity is increased in obesity as well as diabetes and responds to various cellular stress signals activated by pro-inflammatory cytokines, free fatty acids, and hyperglycemia, it is considered one of the key mediators in the transition between obesity

and T2D [32]. JNK plays a broad role across various tissues and serves as a key effector in the intricate MAPK signaling pathway, and it is the last kinase to be activated within the MAPK/JNK pathway.

It has been established that JNK1 knockout mice are protected from high-fat diet induced inflammation, obesity, and insulin resistance, likely due to JNK's effect on hypothalamic inflammation, which influences the central regulation of energy balance by insulin and leptin. Initially, these effects were linked to a reduction in serine-307 phosphorylation of IRS1, which impairs proper activation of the insulin signaling pathway However, later studies showed that a serine-to-alanine mutation at residue 307 (S307A) on IRS1, which prevents JNK1-mediated phosphorylation, does not protect mice from HFD-induced insulin resistance. This led to the suggestion that JNK1, as a Ser/Thr kinase, likely phosphorylates multiple sites on IRS1/2 [32,33]. Interestingly, several miRNAs have been shown to regulate the NF-κB and JNK signaling pathway, either by targeting key components of the pathway or by modulating upstream or downstream signaling elements. Therefore, we will further discuss its crosstalk.

2. Exosomes and miRNAs

2.1. Biogenesis and Composition of Exosomes

Exosomes are small, 30 to 150 nm bilayered extracellular vesicles secreted from all cell types [34]. Although they were primarily considered cellular waste, exosomes were found to be a novel mechanism of intercellular communication [35]. Released from the parental cells into the extracellular space, exosomes exert local effects, or they enter circulation causing distal systemic effects. However, a significant number of studies have shown that exosomes act not only as messengers of information between cells but also as a relevant biomarker of a certain physiological status and pathophysiological changes [34,35]. As they are naturally produced in the human body, they are able to evade recognition by the immune system and subsequent removal. Furthermore, exosomes are recognized as vehicles for the efficient delivery of drugs to the target cells, a characteristic for which it was shown to increase bioavailability and reduce side effects [35]. Therefore, according to all the above advantages, it is clear why interest in a more detailed study of the biology and mechanisms of exosomes is constantly growing.

Exosomes are generated in a complex process by an endosomal route [35,36]. This process is under the regulation of several proteins of endosomal sorting complexes required for transport (ESCRT) protein family, which act together with certain accessory proteins, such as Alix, TSG101, HSC70, and HSP90β. Along with membrane-bound tetraspanins CD63, CD81, and CD9, these proteins are considered markers of exosomes as they are present as the main constituents of the exosomes regardless of the type of cells from which the exosomes originate [35]. In addition to proteins, exosomes contain other bioactive molecules, such as lipids (sphingolipids, cholesterol, phosphatidylserine, saturated fatty acids, and ceramides), DNA (genomic DNA, mitochondrial DNA), and various types of RNA [37–40], among which miRNA has been receiving the most attention lately [41]. An illustration of the structure and components of exosomes, including proteins, lipids, and nucleic acids, is shown in Figure 2.

2.2. Exosomal miRNAs and Their Role in Physiological and Pathophysiological Conditions

miRNAs are noncoding RNA molecules of ~22 nucleotides synthesized in a tightly regulated multiple-step process that includes DGCR8/DROSHA, Dicer, Exportin-5, and RISC molecular complexes [42,43]. Although several miRNAs are expressed in a tissue or developmental stage-specific manner, thus contributing to tissue-specific mRNA and protein expression profiles, most of them are widely expressed [18,44]. The main function of these small RNAs is to modulate gene expression through translation inhibition, thereby affecting the stability of the mRNA. Accordingly, one single miRNA can target multiple mRNAs, but one mRNA can also be targeted by several miRNAs [45]. As such, miRNAs regulate a wide range of cellular physiological processes (proliferation, differentiation,

development, homeostasis, and apoptosis); however, changes in their expression have been reported in many pathophysiological conditions (inflammation, neurodegeneration, tumorigenesis) making them potential novel biomarkers, not only of physiological status but also of various pathophysiological changes and diseases [41,46]. Therefore, the study of exosome-derived miRNAs gives a better insight into the etiology of diseases, but also opens up the possibility of using them as a new therapeutic strategy by modulating their expression.

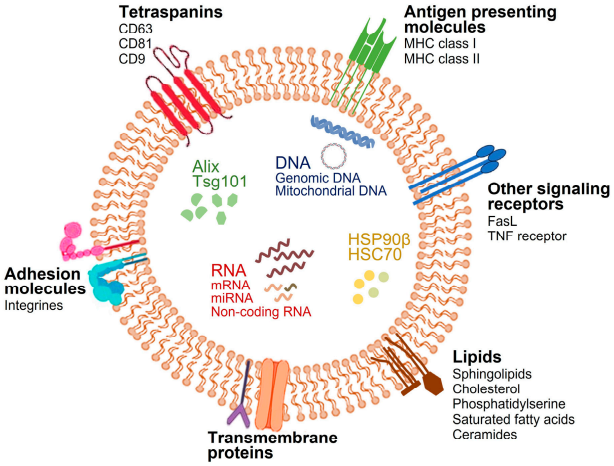

Figure 2. The structure and content of an exosome. Alix, ALG-2-interacting protein X; Tsg101, tumor susceptibility gene 101; HSP, heat shock protein; HSC, heat shock cognate; FasL, fas ligand; TNF, tumor necrosis factor; mRNA, messenger RNA; miR, microRNA.

2.3. Exosomal miRNA as Biomarkers in Obesity and Type 2 Diabetes

There is a growing interest in the research on the biomarker potential of exosomal miRNAs, which could indicate changes at the organ level and thus help in the early diagnosis as well as monitoring of diseases. Significantly, miRNA sequencing studies showed that exosomes collected from blood and conditioned media of specific cell types contain hundreds of different miRNAs [47,48], and changes in the profile of those miRNAs are a reliable indicator of the physiological responses to the development of metabolic diseases, including obesity and T2D [41,49]. So far, a difference in the expression profile of exosomal miRNAs of adipose tissue or plasma between lean and obese subjects has already been demonstrated, indicating their involvement in the induction and promotion of obesity [49–51]. In addition, miRNA from exosomes derived from the adipose tissue of obese individuals, either adipocyte or adipose tissue macrophages, have been specifically shown to be involved in promoting glucose intolerance and insulin resistance, stimulating lipogenesis and adipocyte hypertrophy, as well as enhancing inflammation [49,50]. All of the above indicates the use of miRNAs as biomarkers of obesity, although detailed molecular mechanisms of their involvement need further investigation.

A significant role of exosomal miRNA has been already shown in the development and progression of T2D and its complications. Based on numerous research, exosomal miRNAs have a strong relationship with β-cell damage and dysfunction, as well as the development of insulin resistance [52]. Furthermore, they are also involved in the development of T2D-related complications, such as diabetic nephropathy, diabetic foot ulcer, diabetic peripheral neuropathy, and diabetic cardiomyopathy [52]. Therefore, exosomal miRNAs can be used as very relevant biomarkers for the early detection of insulin resistance and diabetes, as well as related chronic complications [53].

2.4. Therapeutic Challenges of Exosomal miRNAs in Obesity and Type 2 Diabetes

Due to the deep correlation between epidemiology and pathogenesis, therapeutic management of both, obesity and T2D, includes lifestyle changes and adjustments, phar-

macotherapy, and newer treatment methods such as bariatric surgery [54]. Moreover, it was shown that available pharmacotherapeutic treatments recommended for either obesity or T2D have a mutual effect on each other, meaning that anti-obesity drugs can be anti-diabetic to some extent and vice versa [54]. However, although effective in reducing body weight and regulating blood glucose levels, these therapeutics have a significant number of disadvantages, such as side effects due to the necessary long-term use, dose adjustments, or even high costs [54]. Therefore, there is a growing need for the development of a new therapy that, in addition to effectiveness, would prevent or at least reduce the development of side effects, as well as the cost of treatment. Profiling analysis showed a strong correlation between the dysregulation in the expression of miRNAs and the development of metabolic diseases, including obesity and T2D [43]. This expression disturbance refers not only to the endogenous miRNAs that are tissue- or cell-specific and involved in adipogenesis, insulin resistance, lipid and glucose metabolism, or induction of inflammation, but also to the exogenous miRNAs that circulate through the biological fluids packed in exosomes and act as systemic signaling molecules in distant tissues [55–58]. Although of great potential, the use of miRNAs in general in the treatment of metabolic disorders has not been sufficiently investigated [59]. On the other hand, they have been investigated in terms of therapy for various other diseases, including autoimmune diseases, metabolic syndrome, neurocognitive disorders, and cancer, and some miRNA-based therapeutics are already in clinical trials for certain diseases [60]. When it comes to metabolic disorders, only two miRNAs, miR-103 and miR-107, have entered clinical trials in the treatment of T2D, NAFLD, and NASH, although the therapeutic potential of a much larger number has been demonstrated by research in animal models [60]. These studies showed the anti-obesity action of miRNA, as well as the role of exosomal miRNA in the prevention of glucose intolerance and insulin resistance [60]. Overall, exosomal miRNAs hold great potential as therapeutic agents for treating metabolic disorders, and further research should delve into their mechanisms of action. There are several advantages to utilizing exosomal miRNAs in therapy, particularly circulating miRNAs, as they can be easily isolated and detected through non-invasive methods.

2.5. Circulating miRNAs as Biomarkers and Therapeutic Targets of Insulin Resistance—Challenges and Limitations

Insulin resistance is the underlying factor in the etiology of T2D, and the presence of excessive adipose tissue mass may contribute to mechanisms that trigger its development. On the other hand, obesity and insulin resistance must also be viewed as a two-way street: the possibility that insulin resistance promotes the development of obesity should also be considered. As obesity represents a significant health risk with severe consequences, and its association with insulin resistance has been confirmed, the need for its rapid, effective, and simple diagnosis has become a global priority since current tools are not sufficient for prompt diagnoses. Based on the described dysregulation in the expression of circulating miRNAs in insulin resistance and liquid biopsy as a new minimally invasive technique, these molecules have been proposed as potential biomarkers [41] although certain limitations in their use still need to be explored. The first issue that could pose a technical problem is their stability. miRNAs are generally stable in serum or plasma samples as they are encapsulated in exosomes or bound to proteins and lipoproteins, which protects them from degradation [61]. Surprisingly, miRNAs have been shown to remain stable over long periods, even under storage conditions well above −80 °C, and are not affected by the patient's food intake status [62]. Despite their shown stability, variability in miRNA levels could be a consequence of different factors, such as sample collection, processing, and storage conditions, so each test should be optimized separately as the observed variability can affect the reproducibility and reliability of miRNA-based diagnostics. The next issue is standardization or the lack of standardized protocols in miRNA manipulation. Sample preparation procedures, methods for their analysis, and approaches to standardize results differ greatly [63], and this lack of global standardization can lead to inconsistent results

across different studies and clinical settings with very little comparability. Moreover, the detection and quantification of miRNAs requires the use of sensitive and specific techniques (real-time PCR and next-generation sequencing) that can be affected by technical variations and require rigorous validation, making them a serious analytical challenge.

There are several advantages of using exosomal miRNAs as therapeutic agents, but this also poses some challenges in terms of their targeting. The delivery of miRNA-based therapeutics to specific tissues or cells remains a major challenge because an effective delivery system must protect the highly sensitive content from degradation, ensure uptake into cells, and release the miRNAs in a controlled manner [64]. To overcome these issues and optimize the process, different delivery vehicles, such as viral vectors, nanoparticles, and exosomes, are currently being investigated. Each of these carriers has its advantages and limitations, including potential immunogenicity, toxicity, and scalability [65]. Since miRNAs can target multiple mRNAs, their application can lead to several off-target effects, causing unintended and potentially dangerous biological consequences, including toxicity, a major concern in the use of miRNA therapeutics [64]. Therefore, the specificity of miRNA-based therapies needs to be thoroughly reviewed as a crucial step in minimizing the possibility of such effects. Strategies aiming to improve specificity and reduce toxicity in miRNA-based treatments are, therefore, being actively researched [66]. Furthermore, to achieve the desired therapeutic effect by administration of miRNA inhibitors or mimics that typically show moderate efficacy, the required dose is very high, consequently increasing the risk of unwanted side effects. Finally, the functional complexity of miRNAs, molecules that participate in multiple signaling pathways and interact with various targets, introduces an additional challenge in developing effective and safe miRNA-based therapies [64].

2.6. Future Perspectives for miRNA-Based Therapies and Biomarker Development

Recently, numerous clinical trials have been designed to investigate the use of miRNA mimics as a replacement for tumor-suppressive miRNAs as well as miRNA inhibitors to inhibit oncogenic miRNAs in cancer therapy but also lipid metabolism, inflammation, and fibrosis in liver diseases [67]. For example, the role of a liposomal mimic of miR-34a, MRX34, was evaluated in patients with refractory solid tumors. Treatment with dexamethasone premedication and MX34 demonstrated a manageable toxicity profile and some clinical activity in the majority of patients [68]. A study analyzing miR-122 revealed significantly differential expression of that particular miRNA between cancer and healthy patients, and the overall survival rate predictions in hepatocellular carcinoma as well as other types of cancer varied significantly. The authors concluded that miR-122 may serve as an indispensable biomarker for the diagnosis, prognostic evaluation, and targeted therapy in pan-cancer [69]. Certain miRNAs (i.e., microR (miR)-22, miR-122, and miR-132) can exacerbate or attenuate fibrotic and carcinogenic processes in hepatic cells linked to metabolic dysfunction-associated steatotic liver disease, its progression to metabolic dysfunction-associated steatohepatitis and hepatocellular carcinoma. The authors conclude that modulating these miRNAs, either by synthetic mimics or inhibitors, represents a promising therapeutic strategy that could be maintained since preclinical models demonstrate that miRNA-based therapies can attenuate liver inflammation, reduce fibrosis, and inhibit tumorigenesis [70].

The incorporation of miRNA-based therapy and the development of novel non-invasive molecular biomarkers through the use of liquid biopsy techniques in blood and other body fluids is an emerging approach in T2D management. Some of the recognized circulating miRNAs could serve as a non-invasive diagnostic tool for predicting the development of T2D, especially in the elderly population. New miRNA molecular marker candidates are also being investigated as effectors in monitoring metabolic responses of prescribed anti-diabetic drugs to help predict and track the development of chronic complications in T2D [71]. Studies are exploring their stability in plasma and serum, as well as their correlation with disease states to deepen the understanding of possible etiological pathways to disease onset [72]. The search for new blood-based or urinary biomarkers

for T2D is being conducted using advanced "omics" technologies, encompassing specific gene variations and metabolites associated with glucose intolerance and other related traits. Although reports associate numerous biomarkers with the risk of developing T2D, the utility of most of them for clinical prediction is still largely unknown. A separate ongoing research line focuses on the validation of these biomarkers in clinical settings to improve the accuracy of T2D diagnosis and treatment [71].

When it comes to the use of miRNA-based therapies or biomarkers, issues of stability, standardized protocols for collection and processing, effective delivery, and minimization of off-target effects are crucial. By overcoming these challenges and leveraging ongoing research, miRNA-based therapies and biomarkers hold great promise for improving the diagnosis and treatment of T2D and other diseases. Continued advancements in this field are expected to lead to more effective and personalized medical interventions.

3. Obesity-Derived Exosomal miRNAs: Bridging the Gap Between Insulin Resistance and Type 2 Diabetes

3.1. miRNAs as New Messengers in Intercellular Communication

As previously described, miRNAs act as mediators of gene expression, and any dysregulation in their expression is associated with the development of many diseases including diabetes, cardiovascular disease, kidney disease, and cancer [73]. Except for local action in the cell, miRNAs can be released in the extracellular space and, more importantly, in extracellular fluids either packaged in extracellular vesicles, mainly exosomes, associated with high-density lipoprotein or RNA-binding protein nucleophosmin or they are in a complex with proteins, especially Argonaute 2 [74–76]. As such, miRNAs are protected from degradation by ribonucleases present in body fluids. Moreover, the level of extracellular or circulating miRNA expression in the body fluids is constant, and any alteration can indicate the development of a certain disease [76]. Therefore, circulating miRNAs are shown to be useful as potential biomarkers of disease [77–79]. More importantly, it was shown that circulating miRNAs act as messengers in intercellular communication under physiological but also pathophysiological conditions, thus contributing to the development and progression of a wide variety of human diseases, such as cardiovascular, autoimmune, neurodegenerative, liver, and inflammatory diseases, as well as cancer [77,80–85]. These are mostly miRNAs that are packaged in exosomes, by which miRNAs are transferred between cells either locally or to distant sites.

3.2. The Role of Circulating miRNA in Obesity, Insulin Resistance and Type 2 Diabetes

Obesity is characterized by a chronic low-grade inflammation developing in adipose tissue, which is considered to have a pivotal role in the development of insulin resistance, thus increasing the risk and contributing to the development of T2D [86]. Although many studies have focused on explaining the relationship between obesity and T2D, the whole mechanism is still not fully understood. So far, a significant correlation between changes in the expression of circulating miRNAs and the development of obesity and insulin resistance, as well as related metabolic disorders has been shown [87]. However, despite numerous research, either the origin or relationship with adipose tissue, as well as the detailed mechanism of action of many circulating miRNAs in the induction of insulin resistance and T2D, have not yet been fully or at all investigated (Figure 3). An increased expression of miR144 in whole blood of patients with T2D was shown to be associated with the development of T2D through a negative modulation of the expression of IRS1, a key molecule in insulin signaling [88,89]. Furthermore, an increased level of miR-144 in obesity was in association with reduced expression of immune-responsive gene 1 (*Irg1*), which was restored after miR-144 silencing in vitro and in vivo, demonstrating that miR-144 can impair intracellular liver metabolism and nuclear factor E2-related factor 2 (NRF2) activity [90]. miR-122 was shown to be robustly elevated in the blood of obese patients with a tendency to increase with the degree of obesity [91], while it was shown to be reduced in response to diet-induced weight loss [92]. Besides the involvement in obesity, an increase

in the level of circulating miR-122 was shown to be related to the development of insulin resistance, metabolic syndrome, and T2D [93]. Following this, an increase in the circulating miR-122 correlated with the obtained homeostatic model assessment for insulin resistance (HOMA-IR) data, indicating its involvement in insulin resistance. Furthermore, a positive correlation with the increase in lipid subspecies containing saturated and monounsaturated fatty acids demonstrated an association with the development of metabolic syndrome and T2D, and a significant reduction in miR-122 was shown in vitro and in vivo after statin treatment, which confirmed the involvement of miR-122 in lipid metabolism. In a study by Parrizas et al. [94], miR-192 and miR-193b are described as biomarkers for prediabetes due to their significantly increased expression in the serum of prediabetic subjects but not in T2D patients, and the same effect was shown in an animal model of glucose tolerance caused by high-fat diet. Although the mechanism of action of miR-192 in obesity and insulin resistance has not been investigated, miR-193b-3p has been shown to affect glucose metabolism by directly targeting YWHAZ/14-3-3ζ and up-regulating the transcription factor Forkhead box O (FOXO) 1 downstream of the PI3K-Akt pathway in T2D [95]. Contrary to the described down-regulation of miR-192 in diabetes compared to the condition that precedes it, the study by Jaeger et al. has shown an elevation of miR-192 together with miR-194 in the serum of patients with the presence of both T2D and T1D, as well as a correlation of increased expression of both miRNAs with blood parameters of insulin resistance [96]. Additionally, miR-194 has previously been shown to be differentially regulated through different stages of insulin resistance until the onset of T2D as an adaptive response to facilitate tissue glucose uptake and metabolism and is involved in multiple aspects of glucose metabolism in skeletal muscle, potentially through mechanisms that include Akt, glycogen synthase kinase-3, and oxidative phosphorylation [97].

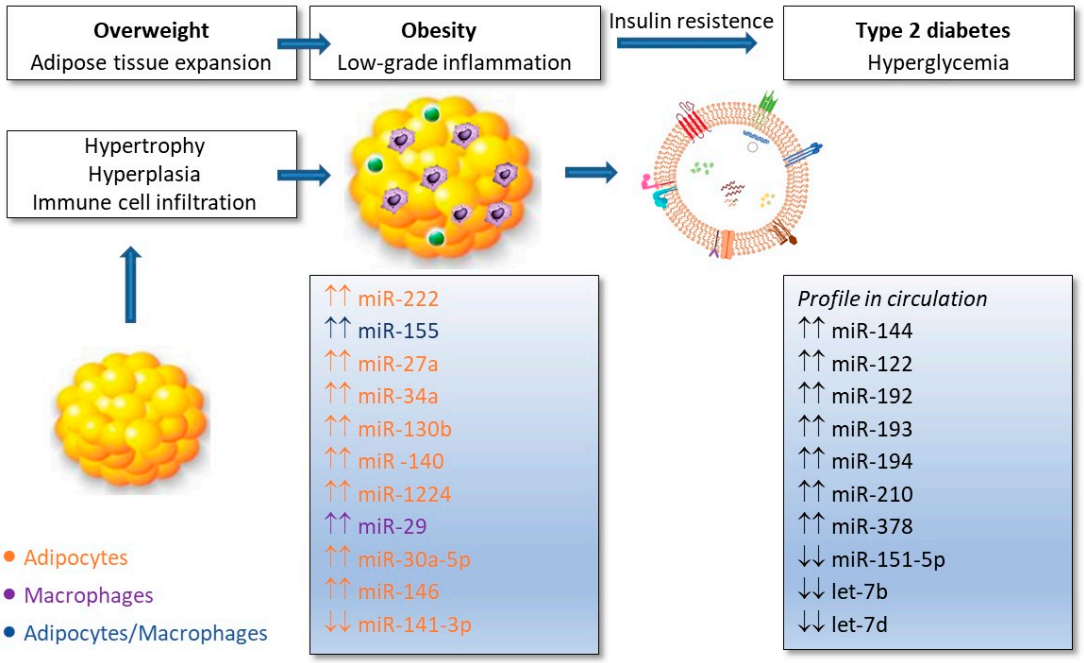

Figure 3. The involvement of adipose tissue-derived exosomal miRNAs in the development of obesity-induced insulin resistance and the subsequent progression of T2D. The figure illustrates miRNAs originating from exosomes of altered adipose tissue that contribute to enhanced inflammation in obesity and the induction of insulin resistance through studied mechanisms. Additionally, another list of miRNAs highlights those with altered expression in the plasma of obese and/or T2D patients, with or without an explained mechanism and origin. miR, microRNA; ↑↑, up-regulation; ↓↓, down-regulation.

A detailed study by Jones et al. showed a correlation between circulating plasma miRNA levels and obesity with a phenotype of insulin sensitivity, insulin resistance, or T2D in human individuals, as well as the origin of those miRNAs in a mouse model of obesity [98]. However, apart from the circulating miRNAs that have already been shown to be related to obesity and associated metabolic disorders, like miR-144, authors also demonstrated the involvement of other miRNAs, such as miR-23b, miR-26a, miR-28-5p, miR-30-3p, miR-374b, miR-365, and miR-32, in the development of these diseases without defined plasma levels or role in obesity. This indicates the need for a more detailed investigation of the involvement as well as a molecular mechanism of dysregulated exosomal miRNA in causing insulin resistance and associated T2D. Moreover, this opens the possibility of the usage of circulating miRNAs as relevant biomarkers of obesity and insulin resistance phenotypes in obesity and T2D. However, since obesity is known to be a trigger for the development of insulin resistance and consequently T2D, it is of great importance to determine the origin of circulating miRNAs and, more importantly, their relationship with abnormal adipose tissue, as well as a mechanism of their action in the target tissue. Therefore, this review aims to present and emphasize the significance of circulatory exosomal-derived miRNAs originating from obesity-changed adipose tissue in the development of insulin resistance, a key mechanism that leads to the development of T2D.

3.3. The Involvement of Adipose Tissue-Derived Exosomal miRNAs in Adipose Tissue Inflammation During Obesity

Exosomal miRNAs are significantly involved in the initiation and prolongation of inflammation associated with the expansion of adipose tissue in obesity, which is mediated by the activation of immune cells, mainly macrophages (Table 1). Infiltration of macrophages into adipose tissue is a crucial factor that induces dysfunction of adipose tissue, thus contributing to the induction of inflammation and related metabolic disorders [99].

The most investigated exosomal miRNA involved in the induction of adipose tissue inflammation is miR-155, whose increased expression is shown in circulation and adipose tissue in obesity, more so in adipose tissue macrophages than in adipocytes [100]. Adipocyte-derived exosomal miR-155 can be transferred to adipose tissue macrophages, where it triggers inflammation by promoting the inflammatory STAT1 signaling pathway and suppressing the anti-inflammatory STAT6 pathway through the activation of the pro-inflammatory M1 macrophages [51,58]. Moreover, the expression of miR-155 in a significantly increased number of adipose tissue macrophages may be the first sign of the upcoming development of systematic inflammation, as it was shown that the increase in the expression of this miRNA is present despite the increase in adipocyte markers of inflammation such as IL6, C-reactive protein, and TNF-α [100]. Besides M1 macrophage activation, miRNAs affect the polarization of anti-inflammatory M2 macrophages. An increased level of adipocyte-derived exosomal miRNAs, such as miR-34a, miR-130b, or miR-1224, inhibit anti-inflammatory M2 macrophages activation by suppressing Krüppel-like factor 4 (KLF4), peroxisome proliferator-activated receptor (PPAR-γ), or Wnt/β-catenin signaling pathways, respectively, thus contributing to the exacerbation of obesity-induced adipose tissue inflammation [101–103]. However, Pan et al. showed that adipose tissue-specific deletion of miR-34a reduced local and systemic inflammation through enhanced polarization of macrophages from M1 to M2 phenotype [102]. Besides adipose tissue inflammation, increased expression of the same miR-34a also induces metabolic inflammation and insulin resistance, effects that are shown to be reversed by specific ablation of miR-34a [102]. The polarization of macrophages from M1 to M2 phenotype is also regulated by modulation of PPAR-γ activation, which is ultimately mediated by a change in miR-130b expression [103]. Accordingly, it can be concluded that exosomal miRNAs originating from adipocytes significantly contribute to the development of inflammation in obesity, primarily by polarizing macrophages and modulating the activation of related signaling pathways.

3.4. The Involvement of Adipose Tissue-Derived Exosomal miRNAs in the Induction of Insulin Resistance and Type 2 Diabetes

Obesity is the most significant risk factor in the development of insulin resistance, which is a major pathological mechanism that leads to the development of T2D. Based on the published data, it can be assumed that exosomes and their cargo act as communication media in obesity-induced insulin resistance [104]. There is a growing number of evidence of the involvement of miRNAs in the induction and promotion of insulin resistance associated with obesity (Table 1). Previously mentioned adipose tissue macrophage-derived exosomal miR-155 suppresses PPAR-γ and reduces the expression of PPAR-γ target gene glucose transporter type 4 (GLUT4), thus contributing to the development of insulin resistance by inhibiting insulin signaling and glucose tolerance in adipocytes and skeletal muscle [100,105,106]. Overexpression of miR-155 derived from adipose tissue macrophages plays an important role in reducing insulin sensitivity through PPAR-γ down-regulation and suppression of Akt phosphorylation in hepatocytes [105]. However, an investigation of the impact of the complete deletion of miR-155 showed protection from high-fat-diet-induced insulin resistance and glucose tolerance in mice, not just in adipocytes, but also in other insulin-sensitive tissues. A similar effect was shown for adipose tissue-derived exosomal miR-27a. Elevated expression of miR-27a transferred by exosomes from adipocytes to skeletal muscle cells also suppresses PPAR-γ, which ultimately leads to insulin resistance and impairment of insulin-dependent glucose uptake in skeletal muscle [106,107]. In addition, overexpressed miR-29 in adipose tissue macrophage-derived exosomes can be transferred into adipocytes, myocytes, and hepatocytes, which promotes insulin resistance by targeting PPAR-δ [108]. Furthermore, adipose tissue-derived exosomal miR-222 induces insulin resistance in skeletal muscle, but also in hepatocytes, by inhibiting IRS1 [109]. Up-regulation of this miRNA was shown to reduce the expression of GLUT4 and, therefore, glucose uptake in adipocytes [110].

In addition to modulating metabolism in adipocytes and skeletal muscle, exosomal miRNAs derived from adipose tissue also modulate liver metabolism. In contrast to the previously mentioned reduction in insulin sensitivity by overexpression of adipose tissue macrophage-derived exosomal miR-155, it has been shown that a decreased expression of miR-141-3p in adipocyte-derived exosomes transferred to hepatocytes contributes to the development of insulin resistance and reduced glucose uptake by hepatocytes [111], as seen in the case of miR-141-3p. The molecular mechanism involves the inhibition of Akt phosphorylation through the activation of phosphatase and tensin homolog deleted on chromosome ten (PTEN), mediated by a decrease in the expression of miR-141-3p in adipocyte-derived exosomes during obesity.

3.5. The Effect of Adipose Tissue-Derived Exosomal miRNAs on the Homeostasis of Pancreatic β-Cells

Adipose tissue-derived exosomal miRNAs affect pancreatic β-cells, although direct crosstalk between adipocytes and pancreatic β-cells mediated by exosomes and their cargo remains unclear. In general, adipose tissue-derived extracellular vesicles have a positive or negative effect on the survival, proliferation, and function of pancreatic β-cells and human pancreatic islets, depending on the state of obesity [112]. The change in the miRNA profile in adipocytes related to obesity induces local, but also systemic inflammation and the development of insulin resistance, and this effect can impact β-cells homeostasis [112]. For example, in vitro analysis demonstrated that the up-regulation of miR-155 in adipocyte-derived vesicles treated with inflammatory cytokines has a significant role in glucose and lipid metabolism, as well as β-cell function. In addition, an increased level of miR-30a-5p in cytokine-treated adipocyte-derived vesicles was shown to be related to β-cell dysfunction, while miR-146 was shown to be related to the induction of apoptosis of β-cells.

Table 1. Role of key miRNAs associated with obesity, insulin resistance, and T2D.

miRNA	Target Molecules	Signaling Pathways	Role in Obesity, Insulin Resistance and T2D	Reference
miR-27a	PPAR-γ	PPAR	Increased insulin resistance and impairment of insulin-dependent glucose uptake in skeletal muscle	[106] [107]
miR-29a	PPAR-δ	PPAR	Promotes insulin resistance in adipocytes, myocytes, and hepatocytes	[108]
miR-222	IRS1, GLUT4	Insulin signaling	Induces insulin resistance in skeletal muscle and hepatocytes. Reduces glucose uptake in adipocytes	[109] [110]
miR-144	IRS1	Insulin signaling	Impairs insulin signaling A potential therapeutic target in T2D	[88] [89]
miR-378a	C/EBPα, PGC-1β	PGC-1, adipogenesis	Enhances lipid storage and reduces thermogenesis	[113]
miR-103/107	Caveolin-1	Insulin signaling	Impair insulin sensitivity and glucose homeostasis. Promote adipocyte expansion	[114]
miR-34a	KLF4	-	Inhibits M2 macrophage activation	[102]
miR-130b	PPAR-γ	PPAR	Inhibits M2 macrophage activation	[103]
miR-1224	MSI2	Wnt/β-catenin	Inhibits M2 macrophage activation	[101]
miR-155	STAT1, STAT6, PPAR-γ/GLUT4	JAK/STAT, PPAR	Regulates inflammation in obesity. Modulates insulin signaling and glucose tolerance	[51] [58] [105] [100]

Abbreviations: T2D, type 2 diabetes; PPAR, peroxisome proliferator-activated receptor; IRS1, insulin receptor substrate 1; GLUT4, glucose transporter type 4; C/EBP, CCAAT-enhancer-binding proteins; PGC, peroxisome proliferator-activated receptor-gamma coactivator; KLF, Krüppel-like factor; MSI2, Musashi RNA binding protein; STAT, signal transducer and activator of transcription; JAK, Janus kinase; miR, microRNA.

4. Conclusions and Future Directions

In conclusion, there is an undeniable link between obesity and T2D, with insulin resistance serving as the bridge between the two conditions, alongside altered expression of various miRNAs. miRNAs play a crucial role, as they are transported by exosomes—small extracellular vesicles—not only to nearby tissues but also systemically to distant ones, where they exert their effects. Since exosome-derived miRNAs are found in nearly all body fluids, including plasma and serum, they have potential as easily accessible biomarkers for different stages of the disease and could serve as therapeutic targets by modulating their expression to influence disease progression. However, several challenges such as stability, reproducibility, efficient delivery carriers, and minimization of off-target effects and toxicity need to be addressed to uncover their full potential in clinical use. Continuous research and technological advancements are, therefore, essential to overcome these issues and utilize the diagnostic and therapeutic properties of miRNAs.

Given the significant advancements in research on exosome-derived miRNAs in obesity and T2D, adipocyte-derived exosomal miRNAs associated with insulin resistance may be reliable biomarkers of insulin resistance and the development of T2D. Additionally,

they hold promise for therapeutic applications. Some studies have already shown that administering miRNA mimics or anti-miRNAs has potential in the treatment of T2D [115]. However, further research is necessary due to the large number of dysregulated miRNAs involved in insulin resistance, as well as uncertainties around the concentration and delivery of such therapies to the target tissues through circulation. Finally, one thing is certain: the awarding of the Nobel Prize in 2024 for the discovery of miRNA will reignite interest and bring miRNA research into focus. How we manage and apply the knowledge that has accumulated over the years remains to be seen.

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