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Role and Significance of MicroRNAs in the Relationship Between Obesity and Cancer

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MicroRNAs (miRNAs) are small, noncoding RNAs that are essential for regulating gene expression at the posttranscriptional stage. Recent research shows that miRNAs are crucial in the development of two major global health issues: obesity and cancer, two significant health issues worldwide. This study examines the complex mechanisms by which miRNAs govern vital biological processes, including adipogenesis, cancer, and metabolic dysregulation. We highlight the dual function of miRNAs as oncogenes and tumor suppressors in obesity-related malignancies and investigate their potential as prognostic and diagnostic markers. To demonstrate their varied roles, specific examples of vital miRNAs are underscored, such as miR-21, which promotes adipogenesis and is overexpressed in various cancers, and miR-34a, a tumor suppressor involved in cell cycle arrest and apoptosis. In addition, we examined the recent developments in miRNA-based therapies, which include miRNA inhibitors, mimics, and novel delivery vehicles and have the potential for treating obesity-related malignancies. This review aims to clarify, within the framework of miRNA biology, the therapeutic potential of miRNAs in addressing the interrelation between obesity and cancer.

INTRODUCTION

Global health trends reveal an alarming rise in obesity and cancer burdens. Obesity impacts 43.4% of adults worldwide (projected to reach 57.4% by 2025), contributing to 1.6 million deaths annually from noncommunicable diseases like diabetes and cardiovascular conditions. By 2030, obesity rates are anticipated to surge by 115%, with severe obesity [body mass index (BMI) > 35] doubling to 385 million adults. Concurrently, cancer incidence reached 20 million in 2022 (GLOBOCAN data), causing 9.7 million fatalities annually, with lung, breast, and colorectal cancers accounting for most of these deaths.[1] The predominant cancers in men include prostate, lung, stomach, and nonmelanoma skin cancers, whereas in women, breast, lung, colorectal, and cervical cancers are most prevalent.[2] The link between obesity and cancer is well-documented, with epidemiological data indicating that an elevated BMI heightens the risk of several malignancies, including those of the endometrium, rectum, colon, breast, esophagus, pancreas, liver, kidney, and gallbladder.[3]

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Obesity is a multifaceted condition defined by excessive fat buildup owing to an imbalance between energy intake and expenditure. Its etiology includes genetic, environmental, behavioral, and metabolic factors, with chronic positive energy balance being the key driver.[4] Hormonal dysregulation plays a critical role, including leptin resistance, which hinders appetite suppression, energy expenditure, and insulin resistance, leading to hyperinsulinemia and glucose metabolism issues, frequently resulting in type 2 diabetes. In obesity, adipose tissue acts as an endocrine organ, secreting proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6, fostering chronic low-grade inflammation that worsens insulin resistance and metabolic syndrome. Dysregulated lipid metabolism exacerbates complications like non-alcoholic fatty liver disease, while hypoxia in the expanding adipose tissue induces inflammation and fibrosis. These interconnected mechanisms highlight obesity's association with several metabolic and systemic disorders.[4]

Obesity and cancer have a complex and multifaceted relationship that includes mechanisms including chronic hyperinsulinemia, localized inflammation, increased bioavailability of steroid hormones, and abnormal adipokine production by adipocytes. Furthermore, genetic predisposition, obesogenic environment, and epigenetic pathways significantly influence obesity development and its related consequences.[5]

Epigenetics, which denote heritable modifications in gene expression that are independent of DNA sequence alterations, has been identified as a key component regulating gene expression in response to environmental influences.[6] Epigenetic mechanisms, including DNA methylation, histone modifications, and noncoding RNA control, have been linked to the onset of obesity, metabolic disorders, and cancer.[6] MicroRNAs (miRNAs), which are a type of noncoding RNAs, have attracted considerable interest due to their role in gene regulation as well as their potential as therapeutic targets and biomarkers.[7] miRNAs decrease or suppress gene expression by attaching to complimentary sequences in target mRNAs. Since miRNAs play a central role in controlling cellular processes such as proliferation, differentiation, and apoptosis, they have been connected to obesity and cancer development.[8] miRNA biogenesis begins in the nucleus with RNA polymerase II transcribing primary miRNA transcripts (pri-miRNAs), which are subsequently cleaved by the Drosha-DiGeorge Syndrome Critical Region 8 (DGCR8) complex into precursor miRNAs (pre-miRNAs). These are exported to the cytoplasm via Exportin-5, where the Dicer enzyme processes them into mature miRNA duplexes.[9]

The growing global prevalence of obesity and its significant epidemiological link to cancer illustrate the need to explore the molecular pathways that connect these two conditions.[10] miRNAs have emerged as crucial regulators in this setting, with evidence indicating that they modulate the pathways implicated in both obesity and cancer. For example, miR-21, which is overexpressed in both obesity and various cancers, promotes adipogenesis and tumor growth, whereas miR-34a, a tumor suppressor, is implicated in cell cycle arrest and apoptosis. These miRNAs, along with others, provide a promising avenue for exploring the molecular basis of obesity-related cancers and developing targeted therapies.[11] Understanding miRNAs' role in the obesity-cancer nexus is vital for several reasons. First, miRNAs offer a molecular link between the metabolic dysregulation observed in obesity and the oncogenic mechanisms driving cancer. Second, they offer potential as diagnostic and prognostic biomarkers, facilitating earlier detection and more individualized treatment strategies. Finally, therapeutically targeting miRNAs may offer novel approaches to treat obesity-related cancers, addressing both the metabolic and oncogenic aspects of the disease. Clarifying the complex regulatory networks of miRNAs in this context will help us develop effective interventions that mitigate the impact of obesity on cancer risk and progression.

An online search was conducted between January 2025 and February 2025 for research articles and various types of reviews in English published in the last 10 years. The search was performed in the e-medical databases Science Direct and PubMed using the following keywords: "Cancer," "Obesity," "miRNA," "Diagnosis," and "Treatment."

miRNA BIOGENESIS

miRNA biogenesis is a controlled process that begins in the nucleus and ends in the cytoplasm. Initially, miRNA genes are transcribed by RNA polymerase II into pri-miRNAs, which are elongated, hairpin-shaped transcripts.[9] These pri-miRNAs are then converted into pre-miRNAs by the Drosha-DGCR8 complex, also known as the microprocessor complex. Pre-miRNAs are transported to the cytoplasm by Exportin-5, where the RNase III enzyme Dicer cleaves them to produce mature miRNA duplexes.[12] One strand of the duplex, referred to as the guide strand, is incorporated into the RNA-induced silencing complex (RISC), while the other strand, known as the passenger strand, is typically eliminated. The mature miRNA-RISC complex subsequently binds to the complementary regions in the target mRNAs, either destroying them or inhibiting their translation. This complex process ensures precise control over gene expression and underscores the essential function of miRNAs in maintaining cellular homeostasis[13] (Figure 1).

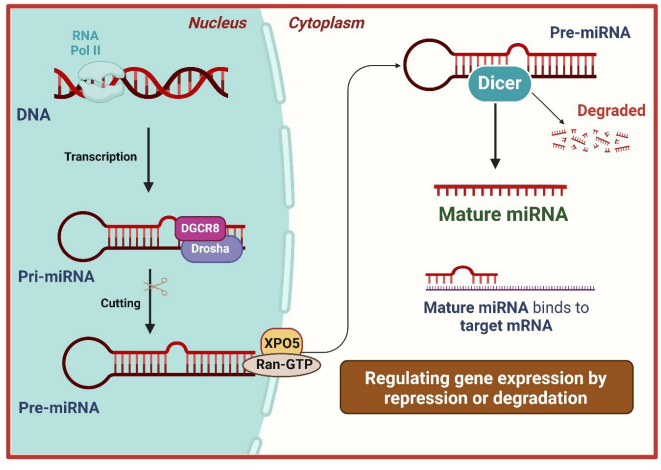

FIG. 1. miRNA biogenesis and function in gene regulation.

ROLE OF miRNAs IN ADIPOGENESIS

Mature adipocyte metabolism and function are influenced by miRNAs in diverse ways, including lipid metabolism, insulin sensitivity, and inflammation within the adipose tissue.[14] Dysregulation of these miRNAs in obesity exacerbates the metabolic dysfunction, insulin resistance, and chronic inflammation, which are key drivers of obesity-related complications, including cancer.[15] Understanding miRNA involvement in adipocyte function provides valuable insights into the molecular mechanisms underlying obesity and related metabolic disorders. Therapeutically targeting these miRNAs may provide novel approaches to treating obesity-related metabolic and inflammatory conditions, thereby enhancing overall health outcomes.

As illustrated in Table 1, miRNAs play a significant role in controlling adipogenesis by either promoting or inhibiting adipocyte differentiation. These miRNAs work on transcription factors and

TABLE 1. Role of miRNAs in the Adipogenesis.

miRNA	Affected gene(s)	Role in adipogenesis	References
miR-143	*ERK5, PPARγ*	Stimulates adipocyte differentiation and triglyceride accumulation	[16]
miR-103	Fatty acid metabolism genes	Enhances adipogenesis and lipid storage	[16]
miR-192	*SCD-1, ALDH3A2*	Regulates lipid homeostasis and adipocyte differentiation	[31]
miR-342-3p	*CtBP2, C/EBPα*	Promotes adipogenesis by activating adipogenic transcription factors	[17]
miR-27, -130	*PPARγ, C/EBPα*	Impedes adipogenesis by targeting PPARγ and C/EBPα	[18]
miR-448	*KLF5*	Inhibits adipogenesis by mitigating KLF5 expression	[32]
miR-138	*PPARγ*	Inhibits adipogenesis by targeting PPARγ	[19]
miR-124a	Adipose triglyceride lipase	Prevents lipolysis and enhances lipid storage	[33]
miR-145	*FOXO1, ABHD5*	Inhibits lipolysis by suppressing FOXO1 and ABHD5	[20]
miR-519d	*PPAR-α*	Inhibits adipogenesis and induces adipocyte hypertrophy	[34]
miR-148a	*Wnt1*	Promotes adipocyte differentiation by inhibiting Wnt1	[35]
miR-342-3p	*CtBP2*	Enhances differentiation by inhibiting CtBP2 and promoting the release of C/EBPα, a key adipogenic transcription factor	[17]
miR-204-5p	*DVL3*	Inhibits Wnt/β-catenin signaling; promotes adipocyte differentiation	[22]
miR-21	*TGF-βR2*	Promotes adipogenesis by inhibiting TGF-βR2 and boosting adiponectin expression	[36]
miR-24	*FABP4*	Inhibits adipocyte differentiation and maturity	[23]
miR-138	*PPARγ*	Impedes adipogenesis by downregulating key adipogenic transcription factors, lowering lipid droplet accumulation	[19]
miR-26b	*PTEN*	Augments insulin sensitivity and glucose uptake by inhibiting PTEN in adipocytes, promoting insulin-stimulated AKT activation	[24]
miR-93	*Tbx3, SIRT7*	Regulates adipogenesis and fat mass by controlling adipogenic transcription factors and increasing lipid accumulation	[15]
miR-301a	*PPARγ*	Suppresses PPARγ expression and inhibits proinflammatory cytokines, thereby mitigating adipogenesis in response to fatty acids	[37]
miR-17-5p	*CREB*	Regulates glucose homeostasis by affecting CREB, a key protein involved in glucose metabolism and adipocyte function	[38]
miR-30d	*MAP4K4*	Protects beta-cells from TNF-α; reduces preadipocyte differentiation in obesity	[27]
miR-143	*PPARγ, aP2, Leptin*	Upregulated in obesity; promotes adipocyte differentiation and fat buildup	[28]
miR-369-5p	*FABP4*	Inhibits adipogenesis	[29]
miR-371	*Sox9*	Promotes adipogenesis	[29]
let-7	*HMGA2*	Upregulated during adipogenesis controls adipose tissue function in obesity	[30]

CREB, cyclic amp response element-binding protein; PTEN, phosphatase and tensin homolog; TNF-α, tumor necrosis factor-alpha.

signaling pathways necessary for adipogenesis or impede the clonal expansion phase, which is critical for the development of adipocytes.[14] During adipogenesis, several miRNAs are upregulated. For example, miR-143 and miR-103 levels increase significantly during adipocyte differentiation and are implicated in lipid metabolism and adipogenesis. Overexpression of miR-143 accelerates adipocyte differentiation by enhancing triglyceride accumulation and upregulating adipogenesis markers. In contrast, miR-103 promotes adipogenesis by targeting genes involved in fatty acid metabolism. However, both miRNAs are downregulated in obese individuals, indicating a possible link between these miRNAs and obesity-associated metabolic dysfunction.[16] Additionally, miRNAs like miR-192 and miR-342-3 play a crucial role in adipogenesis. miR-192 targets lipogenic enzymes like SCD-1 and ALDH3A2, controlling lipid homeostasis and adipocyte differentiation. MiR-342-3p promotes adipogenesis by suppressing CtBP2 and activating adipogenic transcription factors.[17]

miR-27 inhibits adipocyte differentiation. Overexpression of miR-27 impedes PPARγ and C/EBPα expression, which are critical for adipogenesis. miR-27 is also upregulated in obesity and could be regulated by hypoxia. miR-130 targets PPARγ mRNA and reduces adipogenesis, with higher levels found in adipose tissue of individuals with obesity.[18] Other miRNAs like miR-448 and miR-138 mitigate adipogenesis by targeting critical transcription factors such as KLF5 and PPARγ, respectively. miR-448, for example, limits adipocyte differentiation by downregulating KLF5, whereas miR-138 suppresses PPARγ and other adipogenic markers, preventing triglyceride accumulation[19] (Figure 2).

Several studies have also demonstrated that miRNAs affect adipocyte metabolism, lipolysis, and insulin signaling. For instance, miR-124a decreases lipolysis by targeting adipose triglyceride lipase, while miR-145 inhibits lipolysis by downregulating FOXO1 and ABHD5.[20] The miR-148a family is significant because its expression rises during the differentiation of human adipose-derived mesenchymal stem cells and in adipose tissue from individuals with obesity. By blocking Wnt1, an endogenous adipogenesis inhibitor, miR-148a promotes differentiation.[21] By targeting genes like CtBP2, which controls adipogenic transcription factors, other miRNAs, such as miR-342-3p, also increase adipogenesis.[17] Similarly, miR-204-5p stimulates differentiation by impeding Wnt signaling, causing upregulation of key adipogenic markers like FABP4.[22] By controlling the TGF-β signaling pathway, the miR-21 family-and particularly miR-21 itself-influences adipocyte development. miR-21 overexpression has been linked to augmented adiponectin expression and adipocyte differentiation.[23] By downregulating key adipogenic genes, other miRNAs like miR-24 and miR-138 suppress adipogenesis.[19]

Numerous miRNAs, including miR-26b, miR-93, and miR-301a, are crucial for regulating adipogenesis and insulin resistance. For instance, miR-26b increases insulin sensitivity by blocking PTEN, a negative regulator of the PI3K/AKT pathway.[24] Conversely, miR-93

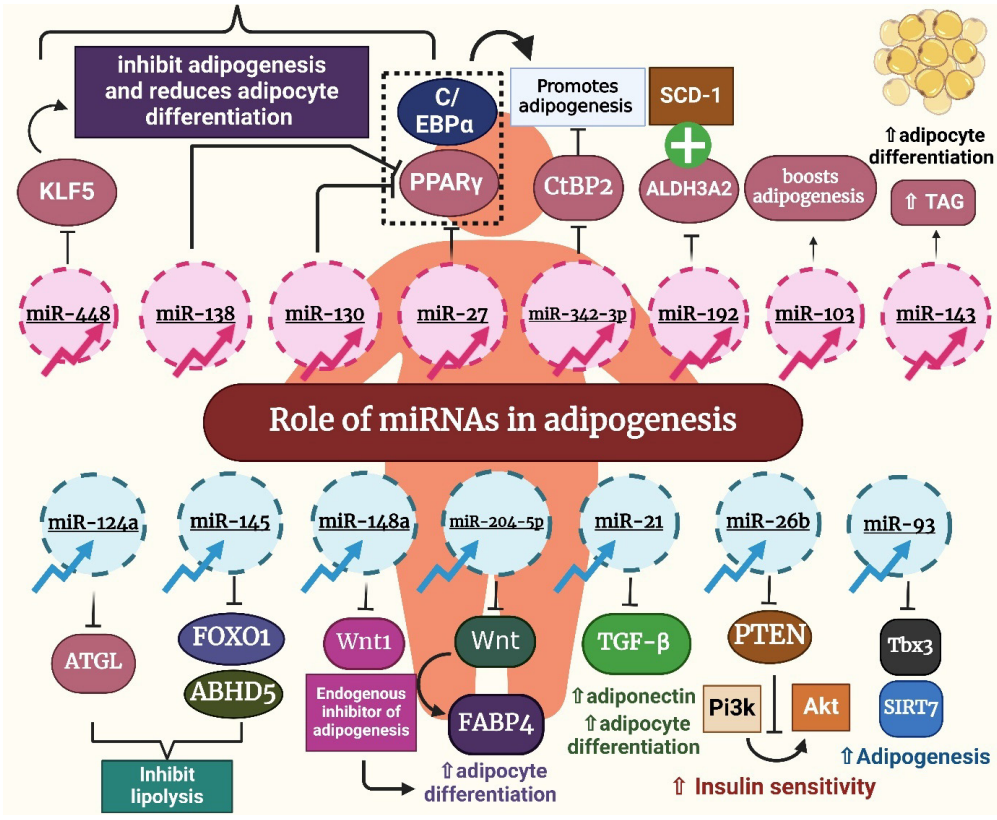

FIG. 2. Role of miRNAs in adipogenesis and the regulatory effects of various miRNAs on adipocyte differentiation, lipolysis, and insulin sensitivity.

controls adipogenesis and fat mass by regulating the expression of key transcription factors like Tbx3 and SIRT7[15] (Figure 2). Insulin resistance, adipose tissue dysfunction, and other obesity-related conditions are exacerbated by the dysregulated expression of certain miRNAs in obesity. miRNAs like miR-17-5p, miR-132, and miR-125a-3p are also implicated in obesity and insulin resistance. In particular, miR-125a-3p is overexpressed in obese individuals and is negatively correlated with insulin receptor expression.[25] Meanwhile, it has been shown that miR-451 influences the AMPK system and contributes to cardiomyopathy brought on by lipotoxicity in obesity.[26]

Adipocytes in individuals with obesity exhibit higher levels of MAP4K4, a PPARγ-inhibitor, which reduces preadipocyte differentiation in the abdominal subcutaneous tissue. miR-30d, a MAP4K4 regulator, can safeguard beta cells from TNF-α-induced suppression by downregulating MAP4K4. However, miR-30d levels decline in obesity, affecting adipocyte differentiation.[27] The miR-30 family is a significant regulator of adipogenesis in human adipose tissue-derived stem cells. miR-30 expression rises during the early stages of adipocyte differentiation and continues to increase until terminal differentiation. Conversely, mice fed with a high-fat diet demonstrated elevated miR-143 levels, correlating with higher body and fat weight. Additionally, miR-143 levels also correlate with adipocyte differentiation markers like PPARγ and aP2 and with plasma leptin levels.[28] miR-369-5p suppresses adipogenesis, whereas miR-371 stimulates it. The former targets FABP4, making them antagonistic regulators of adipocyte differentiation.[29] Furthermore, miR-let7 is upregulated during adipogenesis, affecting adipose tissue quantity and function in obesity.[30]

CORRELATION BETWEEN miRNAs IN OBESITY AND CANCER

Obesity has been linked to a higher risk of developing at least 13 diverse cancer types, including esophageal, gastric, colorectal, liver, prostate, ovarian, kidney, thyroid, meningioma, and multiple myeloma.[39] The relationship between obesity and cancer progression is mediated by multiple underlying pathophysiological mechanisms, including chronic inflammation, insulin resistance, and altered adipokine signaling. miRNAs are essential for regulating these pathways, thereby influencing the development and progression of obesity-related cancers.[40] One important regulator that targets SIRT1 among the miRNAs implicated in adipogenesis and cancer is miR-377. By reducing SIRT1 expression in obese mice, miR-377 contributes to inflammation, insulin resistance, and oxidative stress, which are factors that promote tumor development.[40] Similarly, the miR-34 family, which includes miR-34a, miR-34b, and miR-34c, contributes to cell cycle arrest and apoptosis by regulating p53. These miRNAs prevent breast cancer by downregulating SIRT1 and Bcl-2, augmenting their tumor-suppressive function.[41]

Vascular remodeling is influenced by another prominent miRNA cluster, miR-221 and miR-222, which is associated with the progression of breast cancer. Through the RAS-RAF-MEK pathway, a crucial oncogenic signaling cascade, these miRNAs control the epithelial-to-mesenchymal transition. Furthermore, miR-223 promotes macrophage polarization, helping mitigate inflammation and insulin resistance. The regulation of monocyte metabolism and mitochondrial integrity by miR-125b has been connected to increased apoptosis and inflammation. Meanwhile, the role of miR-100 is significant in regulation of tumor-associated macrophages, where it modulates the mTOR pathway, further influencing cancer progression.[42]

Adiponectin secretion, a crucial variable in metabolic homeostasis, is regulated by several miRNAs. miR-193b, miR-126, and miR-26a boost adiponectin release, helping to protect against insulin resistance and cardiovascular disease. Low adiponectin levels have been linked to a greater risk of postmenopausal breast cancer, highlighting the role of these miRNAs in metabolic and cancer-related pathways.[43] miR-183, another key miRNA, interacts with Wnt/β-catenin signaling, modulating the tumor microenvironment and immune evasion.[44] At the same time, miR-21 promotes adipogenesis and is highly expressed in pancreatic, colon, and breast cancers, where it targets the tumor suppressor PTEN to enhance tumor proliferation and metastasis.[36]

Additional miRNAs also play crucial roles in angiogenesis and metabolic regulation. By targeting factor inhibiting HIF-1α, miR-31 affects endothelial migration, linking hypoxia to tumor growth.[45] miR-126, which is often downregulated in cancer cells, is involved in mitochondrial metabolism and cancer cell energy reprogramming.[46] The miR-130 family has been reported to suppress PPARγ, thus inhibiting adipogenesis. Increased miR-130b expression has been linked to late-stage colorectal cancer and poor prognosis.[47] The miR-193b-365 cluster is essential for brown adipocyte development and has demonstrated anti-tumor effects in breast and gastric malignancies.[48] Similarly, miR-145 acts as a tumor suppressor, inhibiting gastric cancer proliferation and Myc oncogene expression. miR-155, another significant regulator, influences hypoxia responses and inflammation through its impact on C/EBPβ and HIF-1α, affecting lung cancer progression.[49]

ROLE OF miRNAs IN CANCER

Approximately 60% of human genes are miRNA-regulated.[50] One miRNA molecule can bind to several target mRNAs; consequently, one mRNA molecule can be blocked by multiple miRNAs. Interaction with target mRNA molecules is influenced by the bond complementarity and miRNA/mRNA expression levels.[51] Abnormalities in miRNA expression, such as the absence or presence of certain miRNAs or changes in miRNA expression, have been linked to several diseases, including cancer.[52] Cancer cells frequently exhibit miRNA expression anomalies due to gene localization. They are frequently found in genetically unstable regions, fragile sites, or cancer-associated genomic regions, resulting in their loss and reduced miRNA expression.[53]

Historically, miRNA expression in cancer cells was believed to be markedly reduced. Significant overexpression of some miRNAs was only discovered when comparing the miRNA profiles of malignant and normal cells.[54] Based on their role in tumor development, miRNAs are classified as suppressor (inhibiting oncogene expression or apoptosis) or oncogenic (activating oncogenesis or suppressor gene expression).[55] This classification is oversimplified because the overall activity of the regulated genes determines the impact of several miRNAs, such as miR-155 and miR-125b.[55]

Increased expression of genes essential for tumor growth, such as transcription factors or antiapoptotic proteins, results from decreased or absent suppressor miRNAs. In 2017, it was revealed that reduced miR-15 and miR-16 expression in chronic lymphocytic leukemia cells inhibited apoptosis and triggered uncontrolled leukemic cell proliferation by regulating Bcl-2 expression. Reduced miR-146a expression in gastric cancer cells correlates with NFB transcription factor expression and tumor progression.[55] The expression of miR-143, which targets the oncogene Raf1, has been reported to be decreased in an *in vitro* colorectal cancer model.[56]

In cancer cells, DNA methylation controls suppressor miRNA expression.[57] Hypermethylation of miRNA promoters (let-7, miR-34, miR-342, miR-345, miR-9, miR-129, miR-137) downregulates their expression and contributes to the development of colorectal cancer. Reduced miR-143 expression in colorectal cancer cells augments DNMT3A activity and cancer cell proliferation.[58] DNA methylation determines miRNA expression and can impact epigenetic regulators like DNA methyltransferases and histone deacetylase. Certain miRNAs are expressed at higher levels in many colorectal cancer cells, suggesting that they have the capacity to cause cancer.[59] Gene amplification, effective biosynthesis, promoter activity, and increased stability of miRNA molecules can all result in increased miRNA expression.[57] In the past decade, several miRNA molecules have been linked to breast cancer development, progression, and metastasis.[60] The correlation between miRNA expression and breast cancer clinical-pathological characteristics and treatment response has been verified.[60] Research shows that triple-negative breast cancer patients exhibited elevated expression of the oncogenic molecules miR-21, miR-210, and miR-221, which is linked to a shorter disease-free duration and poorer survival.[61]

Downregulation of miR125-b in HER-2-positive tumors or miR-520 in hormone-dependent malignancies can mitigate suppressor potential.[61] Singh and Mo's review article highlights the role of the miRNA families in malignant tumor progression. The study examined the miR-10 family, specifically miR-10a and miR-10b, which contribute to breast cancer growth and metastasis.[61] MiR-10b overexpression is associated with a higher TNM cancer risk, including larger primary tumors, lymph node metastases, elevated cellular proliferation, and HER-2 receptor amplification.[61] Steroid receptors and E-cadherin concentrations negatively correlate with metastasis, suggesting a role in regulating the epithelial-mesenchymal transition mechanism (EMT). The oncogenic miR-21 family has been linked to cancer progression, particularly ductal breast cancer, and reduced overall survival.[61]

The researchers identified the miR-200 family, miR-205, and miR-145 as suppressor miRNAs with decreased expression in malignant breast tissue relative to healthy tissue. miRNAs 200 and 205 may suppress metastasis via the EMT pathway, whereas miR-145 impacts cell apoptosis.[61] In a 2019 study by Loh et al.[60] the miR-200 family exhibits significant carcinogenic potential. High miR-200 levels have been linked to breast cancer's propensity for distant metastasis and treatment refractoriness. Overexpression of miRNA suppresses several genes with an inhibitory effect. The "oncomiR-1" cluster of six miRNAs (miR-17-92; miR-17, miR-18, miR-19a, miR-20, miR-19b and miR-92) downregulates Rbl2 suppressor gene expression.[54] Cell proliferation is augmented by oncogenic miRNAs, including miR-24, miR-31, and miR-21, which silence cyclin-dependent kinases inhibitors.[54,61]

CLINICAL IMPORTANCE OF miRNAs (DIAGNOSIS AND PROGNOSIS)

Because they can bind to protein complexes and/or pack into extracellular vesicles, miRNAs are highly stable in the extracellular environment. This makes them not only extremely stable extracellular molecules but also potential biomarkers for diagnosis, prognosis, and therapy.[62,63] Certain investigations have directly evaluated the miRNA level variations in the peripheral serum between metabolically healthy obese and metabolically abnormally obese individuals. Among these, as indicated in Table 2, miR-21[64], miR-331-3p[65], miR-452-3p[65], miR-485-5p[65], miR-153-3p[65], miR-182-5p[65], and miR-433-3p[65] have direct targets of action and might be employed as promising diagnostic biomarkers. miR-24-3p[66], miR-155[67], miR-21-5p[68], miR-22-3p[68], miR-150-5p[68], miR-155-5p[68], miR-27-3a[68], miR-181a-5p[69], and miR-374a-5p[70] are potential prognostic biomarkers (Figure 3).

The hepatic metabolic pathway plays a crucial role in the development of obesity-related insulin resistance. Previous research has revealed that hepatic glucose, lipid, and energy metabolism influence the development of obesity-related insulin resistance, and miRNAs play a critical role in all three hepatic metabolic pathway.[71,72] The mechanisms underlying miR-802[73], miR-30b[71], and miR-424-5p[72] have been extensively studied and can be employed as preliminary candidates for early diagnostic biomarkers of obesity-related insulin resistance.

It is now generally accepted that obese individuals are more likely to develop certain cancers, including those of the liver, pancreas, and endometrium.[74] Thus, altered circulating miRNA levels in individuals with obesity may be considered a poor prognostic factor for the development of these tumors. Based on this theory, certain dysregulated miRNAs in patients with obesity are believed to be involved in endometrial (miR-103)[75] and pancreatic malignancies (miR-142-3p, miR-103, miR-21).[76,77]

Numerous studies have demonstrated the diagnostic value of individual miRNAs (miR-19b-3p, miR-20b-5p, miR-24-3p, miR-92a-2-5p, miR-106a-3p, miR-106a-5p, miR-152, and miR-211) or their combinations. These molecules (for example, miR-1246 + miR-206 + miR-24 + miR-373) enable the identification of breast cancer with high specificity (96%) and sensitivity (98%) even in the early phases of cancer development.[78] Furthermore, miRNA expression alterations are connected to the breast cancer subtype (miR-16-5p, miR-21-5p, miR-342, and miR-199a-5p), clinical stage, and severity (miR-21, miR-210, and miR-221), or progression (miR-525-5p and miR-106a-5p).[8] Serum miR-21 has previously been identified as a potentially independent marker of poor prognosis in obesity-related breast cancer patients.[8] Another miRNA that contributes significantly to the development of chemoresistance in breast cancer is miR-9-5p. It is an important factor in determining breast cancer prognosis, and high expression levels suggest a poor prognosis.[79]

TABLE 2. Clinical Importance of miRNAs as Diagnostic/Prognostic Biomarkers for Obesity-Related Diseases.

miRNA	Diagnostic/prognostic	Obesity-related disorder	Reference
miR-21	Diagnostic	Metabolically abnormal obesity	64
miR-331-3p			65
miR-452-3p			
miR-485-5p			
miR-153-3p			
miR-182-5p			
miR-433-3p			
miR-24-3p	Prognostic	Metabolically abnormal obesity	66
miR-155			67
miR-21-5p			68
miR-22-3p			
miR-150-5p			
miR-155-5p			
miR-27-3a			
miR-181a-5p			69
miR-374a-5p			70
miR-802	Diagnostic	Insulin resistance	73
miR-30b			71
miR-424-5p			72
miR-103	Prognostic	Endometrial carcinoma	75
miR-142-3p	Prognostic	Pancreatic cancer	76,77
miR-103			
miR-21			
miR-19b-3p	Diagnostic	Breast cancer	78
miR-20b-5p			
miR-24-3p			
miR-92a-2-5p			
miR-106a-3p			
miR-106a-5p			
miR-152			
miR-211			
miR-1246 + miR-206 + miR-24 + miR-373 combination	Diagnostic	Breast cancer	78
miR-16-5p	Diagnostic (subtype classification)	Breast cancer	8
miR-21-5p			
miR-342			
miR-199a-5p			
miR-21	Prognostic	Breast cancer	8
miR-210			
miR-221			
miR-525-5p			
miR-106a-5p			
miR-21	Prognostic	Breast cancer	8
miR-9-5p			79
miR-21	Diagnostic	Breast cancer	81
miR-1246			
miR-105			82
miR-222			
miR-17-5p	Diagnostic	Breast cancer recurrence	83
miR-93-5p			
miR-130a-3p			
miR-340-5p			

Compared to free miRNAs in whole blood or serum, miRNAs packaged within EVs are more stable and trustworthy because the phospholipid bilayer enveloping EVs protects them from degradation by nucleases in physiological fluids. Over the last decade, EV-miRNAs have received a lot of interest because of their diagnostic, prognostic, and therapeutic applications.[80] A pioneering study published in 2016 discovered that miR-21 and miR-1246 are selectively abundant in human breast cancer exosomes, and their analysis may be relevant for breast cancer diagnosis.[81] According to a different study, metastatic breast cancer patients exhibited significantly higher levels of EV-miR-21 and EV-miR-105 expression compared to non-metastatic or healthy controls and EV-miR-222 may be able to distinguish between the basal-like and luminal B subtypes from the luminal A subtypes.[82] Sueta et al.[83] found that four of the 11 EV-miRNAs (miR-17-5p, miR-93-5p, miR-130a-3p, and miR-340-5p) were substantially associated with recurrence based on a logistic regression analysis, and that these EV-miRNAs were differentially expressed between patients who experienced recurrence and those who did not.

THERAPEUTIC INTERVENTION

miRNA expression is altered in the tissues and serum of cancer patients.[8] This can alter gene function by regulating its expression.[84] In addition to serving as diagnostic or prognostic cancer indicators, these miRNAs can also be targeted in cancer therapy, particularly in aggressive forms of obesity-associated cancer.[8] Developing miRNA-based therapeutics targeting both obesity and cancer entails focusing on specific miRNAs that are significant in both conditions.

Therapeutic strategies involving miRNAs typically focus on miRNA mimics and miRNA inhibitors (antagomirs), as shown in Table 3.[85] While miRNA mimics aim to restore the function of tumor-suppressing miRNAs, antagomirs suppress oncogenic miRNAs. However, achieving efficient and targeted delivery of these miRNA therapeutics to specific tissues is still being explored. Nanoparticle-based delivery systems are presently being investigated as an economically viable strategy to enhance miRNA stability and targeting, without inciting an immune response.[86]

MRX34 is an miRNA mimic that is employed as a liposomal nanoparticle formulation to replace the tumor suppressor miR-

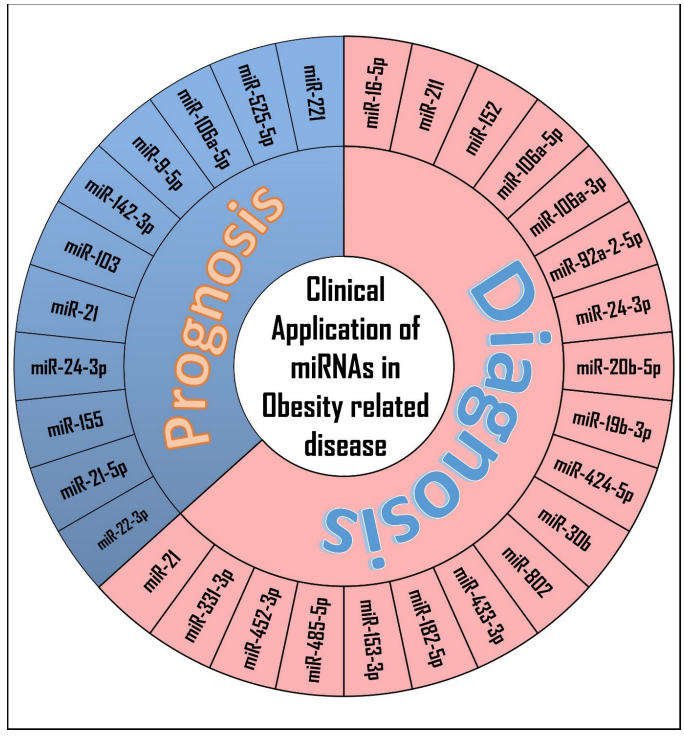

FIG. 3. Clinical applications of miRNAs in obesity-related diseases.

TABLE 3. miRNA-Based Therapeutics in Obesity-Related Cancer.

miRNA involved	Therapeutic intervention	Mechanism	References
miR-34a	MRX34 is an miRNA mimic formulated as a liposomal nanoparticle	It exhibits acceptable efficiency in refractory obesity-associated solid tumors. However, fatal immunological adverse events were reported, causing clinical trial termination.	86,87
miR-206	PEG-conjugated AuNPs	Arrests cells in the G0-G1 phase, activating apoptosis and suppressing the obesity-associated oncogenic pathways NOTCH 3.	88
miR-142-3p	miR-142-3p mimic using nanoparticles	Lowers the expression HMGA1, an oncogene, by targeting the AKT/ERK/STAT3 pathway.	89
miR-21	miR-21 antagomir	Reduces tumor growth and regulates inflammatory responses.	86,90
miR-467	miR-467 antagomir	Decreases tumor mass and impedes the angiogenesis process and tumor progression by regulating the target inflammation and glucose metabolism signaling pathways.	91,92
miR-155	AntagomiR MRG-106	Decreases PGE2 in the Cox2/ PTGES1/PGE2 pathway.	99
miR-221 and 222	miR-221 and 222 antagomirs	Restores ERα and PTEN expression, arrests cells in the G1 phase, inhibits cell growth and migration, and restores the sensitivity of the resistant breast cancer cell line MCF-7 TamR to tamoxifen.	98

34a, whose activity is downregulated in melanoma, hepatocellular carcinoma, renal carcinoma, and non-small cell lung cancer.[86] It exhibited acceptable efficiency in refractory obesity-associated solid tumors in a phase I clinical trial.[87] However, fatal immunological adverse events have been reported in a few patients, leading to the cessation of the clinical trial.[43] miR-206 has been effectively delivered to breast cancer cells via PEG-conjugated gold nanoparticles, arresting the cells in the G0-G1 phase, inducing apoptosis, and downregulating the obesity-associated oncogenic pathway NOTCH 3.[88] miR-142-3p mimic was administered previously to breast cancer lesions using nanoparticles to reduce the expression of HMGA1, an oncogene, by targeting the AKT/ERK/STAT3 pathway[89] (Figure 4).

Numerous malignancies linked to obesity, including ovarian, breast, and colon cancers, have overexpressed miR-21, which is also associated with obesity-induced inflammation.[86] Targeting miR-21 with antagomirs has shown the potential to impede tumor growth and modulate inflammatory responses.[86,90] miR-467 is overexpressed in breast cancer cells and is linked to hyperglycemia-induced pathways.[8] It downregulates thrombospondin-1 expression and promotes inflammation at the tumor site by recruiting macrophages. This boosts cancer growth, stimulated by the hyperglycemic effect on the angiogenesis processes.[91] In murine models of hyperglycemia, miR-467 antagomir was utilized to reduce tumor mass and inhibit angiogenesis and tumor progression by modulating the target signaling pathways of inflammation and glucose metabolism.[91,92]

miR-155 is another oncomiR that plays a vital role in breast cancer development and disrupts metabolism. It regulates glucose and prostaglandin metabolism.[93] Negative outcomes in breast cancer, including high histological grade, decreased expression of hormone receptors, and proliferation Ki67 index, have been associated with higher expression of miR-155-5p.[94] The antagomiR MRG-106 was investigated to inhibit miR-155 in a phase 1 breast cancer clinical trial by lowering PGE2 in the Cox2/PTGES1/PGE2 pathway[95] (Figure 5). Increased miRNA expression impacted not only patients' survival but also their sensitivity to cancer therapy.[96] Drug resistance is a significant problem that limits the effectiveness of cancer treatment. Patients with tamoxifen-resistant breast cancer who have metastases and recurrences had higher levels of miR-221 than those who do not.[97] Inhibiting miR-221 and miR-222 restored ERα and PTEN expression, arrested cells in the G1 phase, inhibited cell growth and migration, and restored the sensitivity of the resistant breast cancer cell line MCF-7 TamR to tamoxifen.[98]

Depicts the therapeutic potential of miRNA-based therapies in cancer by utilizing miRNA antagonists to target specific cancer-related pathways.

CONCLUSION AND FUTURE DIRECTIONS

Obesity and cancer are linked by a complex interplay of environmental, genetic, and epigenetic variables. miRNA dysregulation is critical to both disease development and progression. This review underscores the significance of miRNAs in adipogenesis, carcinogenesis, and obesity-cancer relationships. The precise balance between activated and downregulated miRNAs may be the driving force behind obesity-related cancer. Because their dysregulation can induce metabolic abnormalities, inflammation, and cancer, these molecules are potential biomarkers and therapeutic targets. Despite advances in understanding miRNAs in obesity and cancer, many questions still remain. The mechanisms by which these noncoding RNA impact gene expression and adipose tissue-tumor cell interactions are unclear. Additional research is required to understand these pathways and evaluate the diagnostic, prognostic, and therapeutic potential of miRNAs. Obesity and cancer are linked by miRNA dysregulation. Understanding the complex regulatory networks of these miRNAs may help researchers understand obesity-related

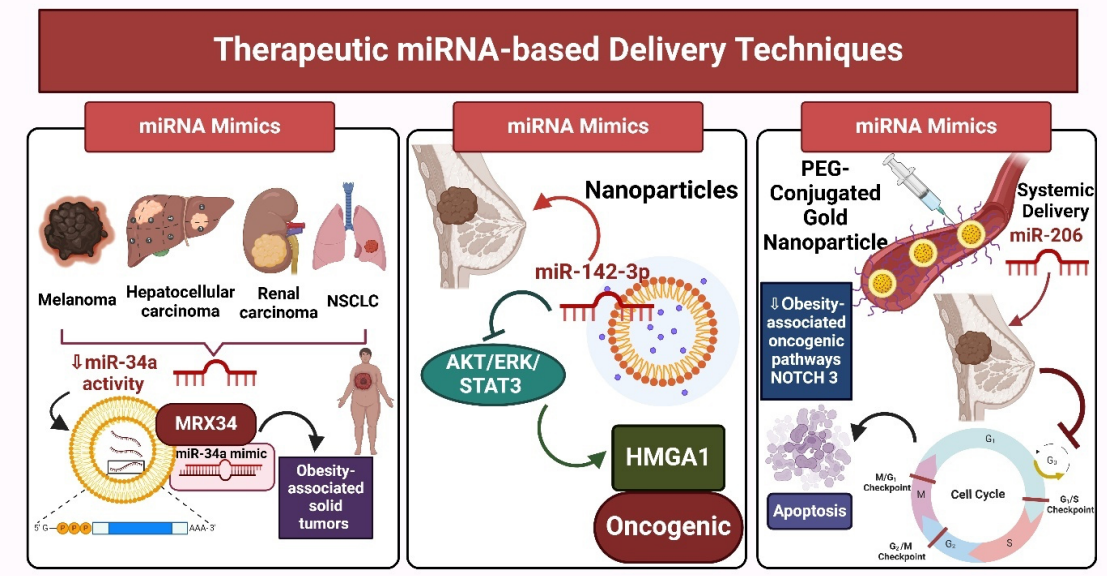

FIG. 4. Therapeutic strategies for delivering miRNA mimics for treating cancer and obesity-associated solid tumors.

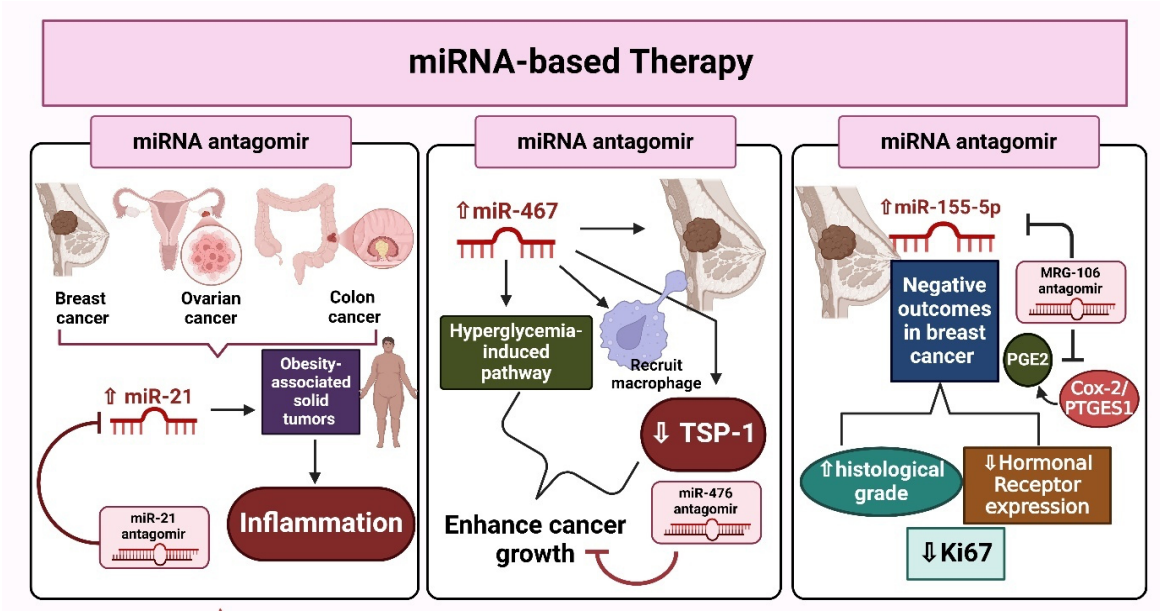

FIG. 5. miRNA-based therapies in cancer.

cancers and develop novel diagnostic and therapeutic strategies. Understanding the molecular mechanisms of fat and cancer is critical, given their increasing global prevalence. Future research should focus on miRNA translation to enhance patient outcomes by early detection, customized treatment, and targeted therapeutics.

Future research should focus on identifying the precise mechanisms by which miRNAs influence gene expression in adipogenesis and carcinogenesis, particularly in the setting of the obesity-cancer axis. Advanced methodologies, including single-cell RNA sequencing, CRISPR/Cas9 screening, and 3D organoid models, can offer deeper insights into miRNA function and its role in the tumor microenvironment. Moreover, multiomics techniques and longitudinal research are required to determine the precise miRNAs influencing the shift from obesity to cancer and to understand how they promote metastasis.

The development of robust miRNA-based biomarkers for early detection and prognosis is another critical area. Liquid biopsies, machine learning algorithms, and large-scale clinical trials can all aid in validating miRNA signatures for clinical use. In terms of therapeutics, challenges such as delivery efficiency and off-target effects must be addressed. Nanoparticle-based delivery systems, gene editing technologies, and personalized medicine approaches hold promise for improving the efficacy and specificity of miRNA-based treatments. Furthermore, the epigenetic regulation of miRNAs, including DNA methylation and histone modifications, warrants additional research because these mechanisms play a vital role in miRNA dysregulation in obesity and cancer.

Another poorly understood area is the interaction between cancers and adipose tissue that is mediated by miRNAs. Exosome isolation and co-culture systems can help uncover how miRNAs secreted by adipocytes influence tumor growth and vice versa. Additionally, the impact of lifestyle interventions, such as diet and exercise, on miRNA expression and function should be explored to understand how these alterations influence the risk of obesity-related cancer. Finally, the role of miRNAs in regulating immune responses in obesity-related cancers is an emerging area of interest, with the potential for combining miRNA-based therapies with immunotherapies to boost anti-tumor immunity.

LIMITATIONS OF CURRENT miRNA THERAPIES

Clinical translation of miRNA-based therapeutics presents with difficulties, such as patient heterogeneity driven by variations in the tumor microenvironment, genetics, and epigenetics that make standardized therapy challenging. Off-target effects arise from the regulation of multiple mRNAs by miRNAs and their interactions with other noncoding RNAs, risking unintended disruptions to normal cellular processes.[100] Delivery systems struggle with biological barriers and specificity, although nanoparticles and exosomes show promise. Immunogenicity from viral vectors remains a concern, while nonviral alternatives encounter stability and efficiency hurdles. Long-term safety and efficacy data are lacking, with risks of chronic toxicity, resistance, and unforeseen complications. Addressing these issues requires indivdualized approaches, advanced delivery technologies, rigorous testing, and scalable production methods to ensure targeted, secure, and effective therapies.[100]

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