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Review

The cross-talk between adipokines and miRNAs in health and obesity-mediated diseases

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ABSTRACT

Background: Multiple studies have revealed a direct correlation between obesity and the development of multiple comorbidities, including metabolic diseases, cardiovascular disorders, chronic inflammatory disease, and cancers. However, the molecular mechanism underlying the link between obesity and the progression of these diseases is not completely understood. Adipokines are factors that are secreted by adipocytes and play a key role in whole body homeostasis. Collaboratively, miRNAs are suggested to have key functions in the development of obesity and obesity-related disorders. Based on recently emerging evidence, obesity leads to the dysregulation of both adipokines and obesity-related miRNAs. In the present study, we described the correlations between obesity and its related diseases that are mediated by the mutual regulatory effects of adipokines and miRNAs.
Methods: We reviewed current knowledge of the modulatory effects of adipokines on miRNAs activity and their relevant functions in pathological conditions and vice versa.
Results: Our research reveals the ability of adipokines and miRNAs to control the expression and activity of the other class of molecules, and their effects on obesity-related diseases.
Conclusions: This study may help researchers develop a roadmap for future investigations and provide opportunities to develop new therapeutic and diagnostic methods for treating obesity-related diseases.

1. Introduction

The global incidence of obesity has been steadily increasing over the past few decades [1]. A global analysis of the prevalence of obesity in 200 countries from 1975 to 2014 revealed an approximately three-fold increase in men and two-fold increase in women. Notably, 2.3% of men and 5% of women included in this analysis had a body mass index (BMI) greater than 35 kg/m^2, indicating severe obesity [2]. Overweight (BMI > 25 kg/m^2 and < 30 kg/m^2) and obesity (BMI > 30 kg/m^2) have been identified as well-established risk factors for some disorders of the cardiovascular system [3], liver [4], skin [5], muscles [6], and reproductive [7], nervous [8], gastrointestinal [9] and respiratory [10] systems.

Adipose tissue (AT) has traditionally been viewed as a major reservoir for energy storage [11]. In the last decade, AT has been described as a pivotal endocrine and metabolic organ involved in immunity and inflammation [12]. Obesity usually leads to major changes in the production and release of adipokines, which are the major bioactive proteins that are predominantly produced by white adipose tissue (WAT) [13]. In addition to the WAT, adipokines are secreted by precursor, endothelial and immune cells, fibroblasts, and other tissues and exert their biological effects by binding to surface receptors [14]. Adipokines are primary mediators with important roles in appetite/satiety and the modulation of energy homeostasis [15]. Adipokines also have some abilities to regulate many processes, including insulin secretion and sensitivity, cellular inflammation, immunity, endothelial function, blood pressure and angiogenesis, cell proliferation, migration and invasion [16].

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Impaired adipokine production is associated with different human diseases, including metabolic diseases [type 2 diabetes mellitus (T2DM), fatty liver disease, and dyslipidemia [17]], cardiovascular diseases [18], musculoskeletal disorders (particularly osteoarthritis) [19], central nervous system diseases [20], and cancers [21]. Although the epidemiological association between adipokine dysregulation and chronic diseases has been established, the exact molecular mechanisms underlying these associations have not yet been completely characterized.

MicroRNAs (miRNAs) are a family of regulatory RNAs that control the expression of target genes at the posttranscriptional level [22,23]. These endogenous and non-coding RNAs commonly induce the degradation of target genes and/or inhibit gene translation by binding to the 3′ untranslated region (3′UTR) of genes [23–25]. Importantly, miRNAs are produced and released by a number of human tissues; thus, their abnormal expression contributes to various diseases [22,23,26–28]. Several investigators have proposed an association between obesity, chronic diseases and miRNA expression [29–31]. Adipokines modulate miRNA expression in human tissues [32]. On the other hand, the endocrine and metabolic functions of AT may be regulated by some miRNAs [33].

Previously, the mutual regulatory effects of miRNAs and adipokines were investigated [34,35]. Accordingly, we reviewed the stimulatory/inhibitory effects of adipokines on miRNAs and vice versa, which resulted in various obesity-associated diseases in humans. Because adipokines and miRNAs exert modulatory effects on the other class of molecules, they represent appropriate molecules for the detection, diagnosis, and treatment of obesity-related diseases.

In this review, we searched for relevant studies bibliographic databases, including Google Scholar, PubMed, and Science Direct. We screened all studies examining the interactions between adipokines and miRNAs and their effects on human health published up to 2019. We also updated studies evaluating the crucial roles of miRNAs in obesity performed from 2018 to 2019. Other similar studies (effects of miRNAs on obesity) published prior to 2018 were excluded.

2. Adipokines modulate miRNA activity

Adipose tissues produce and secrete more than 600 different adipokines that participate in several biological processes in human tissues [16,17]. These adipocyte-related molecules contribute to important physiological processes, including appetite and satiety, insulin sensitivity and secretion, glucose metabolism [15,17,36], inflammatory responses [14,17], immunity [16], cell growth and proliferation [14], blood pressure, lipid metabolism [14,16,36], myocardial contractility, cell adhesion, vascular growth and function, adipogenesis and bone morphogenesis, and lipid accumulation in the liver [14,36]. Adipokines exert their physiological effects by binding to specific adipokine receptors, subsequently activating the related signaling pathways and inducting alterations in the expression of target molecules, such as miRNAs (Fig. 1).

Notably, miRNAs have structural, catalytic and regulatory functions in the human body [25,37]. They are produced by the cooperative activity of RNA polymerase II, Drosha and RNA-induced silencing complex (RISC) in the nucleus and cytoplasm [23,31]. Additionally, miRNAs are released from the intracellular microenvironment and have been detected in biological fluids, such as blood, urine and saliva [38]. The miRNAs bind to the 3′UTR of target genes and silence the expression of these genes through two mechanisms: subsequent degradation of mRNAs via Argonaut/Dicer or inhibition of mRNA translation [30,39,40]. Studies have reported numerous physiological and pathological roles for miRNAs in the regulation of the mRNA expression of target genes. Therefore, their up/downregulation contributes to the pathophysiology of various diseases, including obesity-related diseases [29,30,32].

Recently, miRNAs were reported to contribute to both the initiation and maturation phases of adipogenesis, which is a major step in the development of obesity [41–50]. Therefore, the silencing of Drosha or Dicer markedly inhibits the differentiation of adipocyte precursor cells into mature adipocytes [51–53]. In addition, the blockade of Dicer in mouse preadipocytes suppresses the expression of several adipogenesis-related transcription factors [50,54], such as peroxisome proliferator-activated receptor γ (PPAR γ), members of the CCAAT/enhancer-binding family of proteins (C/EBP), adipocyte determination, differentiation-dependent factor 1 (ADD1), and sterol regulatory element-binding protein 1 (SREBP1), resulting in the inhibition of adipogenesis [55]. The upregulation and/or downregulation of miRNAs modulate the expression of various target genes related to obesity and induce or inhibit obesity-associated processes (Fig. 2). For example, a decrease in the expression of adipogenic markers and adipogenesis has been reported after the silencing of miR-9 and miR-143 [56] or overexpression of miR-155 and miR-221/222 [57], suggesting roles for these miRNAs in adipogenesis. Moreover, miRNAs may exert dual effects on adipogenesis. Although miR-143 activates MAPKK5-MAPK7 signaling cascades related to adipogenesis, it also simultaneously blocks the differentiation of adipocytes during clonal expansion [58].

Roles for miRNAs in obesity-related conditions, such as inflammation [59,60] and insulin resistance (IR) [61,62], have also been reported. Previously, the role of miRNAs in adipogenesis during obesity has been reviewed by other groups [33,40–42,63–65]. Table 1 presents a summary of recent studies published in 2018 [66–94] and 2019 [95–104] in this field. Although the mechanisms underlying the functions of miRNAs in obesity are not completely clear, several studies have proposed that adipokines represent a major modulator of obesity-mediated changes in miRNA expression in human tissues, with effects on health and diseases, which are reviewed in the next sections Fig. 3.

2.1. Leptin regulates miRNAs

Leptin is a 16-kDa non-glycosylated adipokine that is encoded by the ob gene. It modulates food intake, body weight, and fat stores by signaling in the central nervous system [16,105]. It also controls glucose metabolism and insulin activity in peripheral tissues [13,14] by binding to the leptin receptor (ObR) [105–107] and activating several signaling pathways, such as Janus kinase/signal transducers and activators of transcription (JAK/STAT), phosphoinositide-3-kinase /Akt (PI3K/Akt) and mitogen-activated protein kinase (MAPK) [16,106,108–111]. Leptin is generally maintained at concentrations ranging from 2 to 10 ng/ml in non-obese humans, whereas its concentration increases to 100 ng/ml in obese individuals [107,112].

Several in vitro and in vivo studies have identified the modulatory effect of leptin on miRNA expression in various human tissues. For example, in several studies, the regulatory effects of leptin on miR-122 [113,114], miR-27a/b-3p [115], miR-31 and miR-223 [116], miR-132 [117], miR-7 [118], miR-21 [119], miR-93 [120], miR-182 and miR-96 [121], and miR-342-3p [120] expression were reported by the investigators. Leptin exerts inhibitory or stimulatory effects by activating various signaling pathways, including the hedgehog pathway [113,115], PI3K/Akt [114,122], β-Catenin, P38/MAPK [115], MAPK/Erk [117], JAK/STAT3 [121,123] and KLF6 signaling pathways [124]. Subsequently, Leptin-induced activation of these signaling pathways activates their downstream effectors to induce miRNA expression. Animal studies using leptin-deficient ob/ob mice or T2D db/db (OBR knockout) mice revealed alterations in the expression of some miRNAs, such as miR-184 [125], miR-200a [126], miR-103 [127], miR-326 [128] and miR-146a [129], in the absence of leptin or its receptors. In rats fed a HFD, the circulating levels of leptin and some miRNAs, including miR-143 [130], rno-miR-10a at d28 and rno-miR-200a, rno-miR-409-5p, and rno-miR-125a-3p [131], were altered by the consumption of the HFD. In a clinical study, a negative correlation between miR-1301 expression and circulating levels of leptin was reported in the placenta [132]. Meanwhile, in obese patients, the expression of miR-

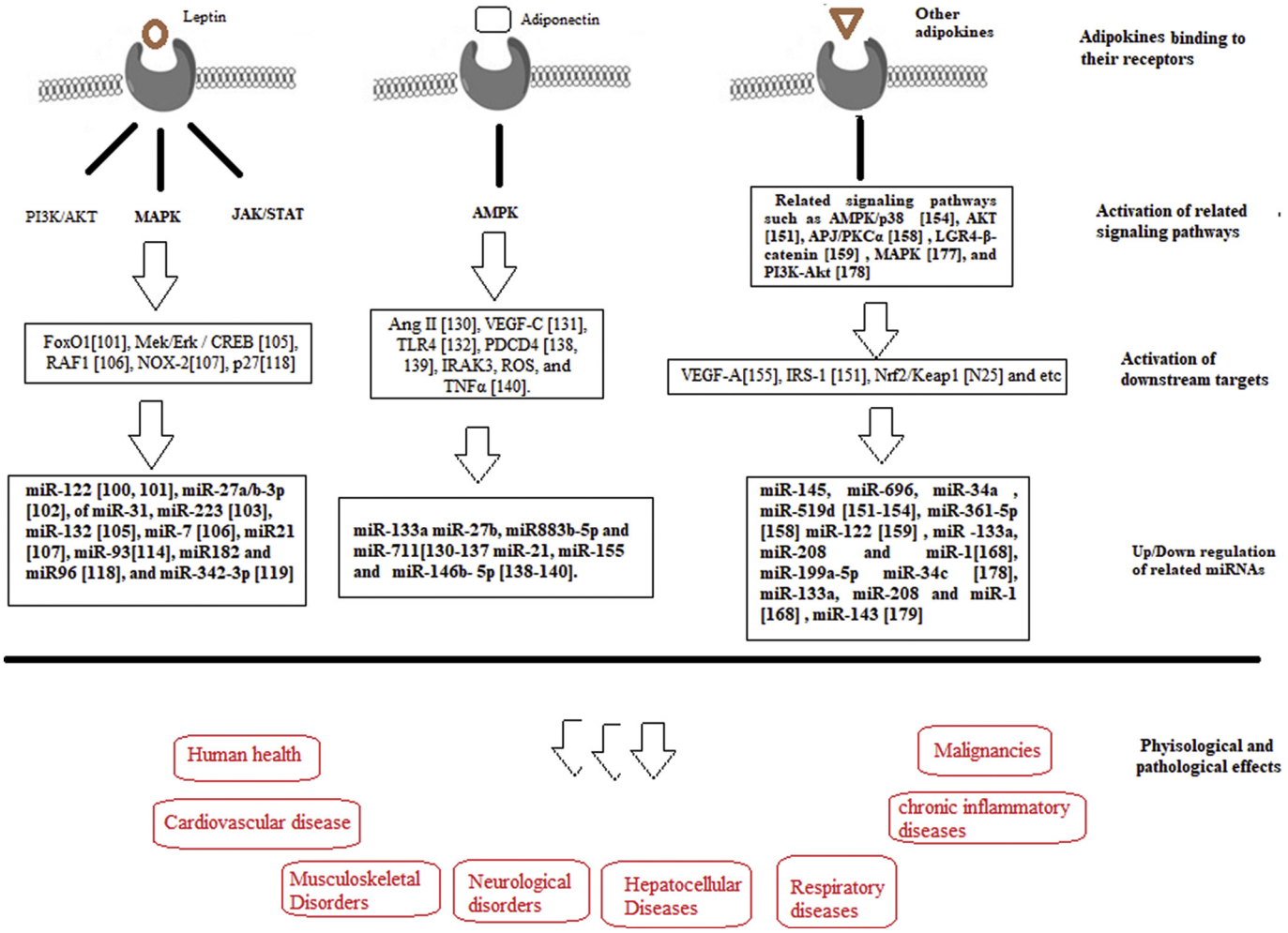

Fig. 1. The adipokines altered the expression pattern of miRNAs by biding to their surface receptors and activation of related signaling pathways and downstream effectors. These adipokines-modulated miRNAs induce various physiological and pathological effects on human tissues.

27b and miR-145 is positively correlated with the expression and activity of leptin receptor [131]. Taken together, the regulatory effects of leptin on the expression of miRNAs are involved in several physiological and pathological conditions, such as malignancies [121,124,133], liver fibrosis [113–115], melatonin synthesis [123], early-onset pre-eclampsia [132], recurrent spontaneous abortion (RSA) [134], renal inflammation [119], memory function [129], insulin and leptin resistance [135], and the functions of skeletal muscles [116] and the hypothalamus [136].

2.2. Adiponectin regulates miRNA expression

Adiponectin, another adipokine with a MW of 30 kDa and composed of 244 amino acids [14], is a member of the complement-1q family of proteins [16,107] that are secreted in a monomeric form by adipocytes and circulate as low-molecular weight (LMW) and high-molecular weight (HMW) oligomers [105,107]. Moreover, the leukocyte elastase enzyme cleaves oligomeric forms of adiponectin to generate the globular form (gAcrp) [107,137]. Adiponectin plays a key role in regulating insulin secretion [13,14,138], exhibits anti-inflammatory and anti-apoptosis activities [14,16] and induces energy expenditure and weight loss [105,138]. It exerts its functions by binding to adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) and subsequently activating downstream signaling pathways, including AMPK, acetyl-CoA carboxylase (ACC), and p38 mitogen-activated protein kinase [14,105,139]. The serum adiponectin level ranges from 7 to 15 mg/ml in non-obese subjects, and its concentration is negatively correlated with overweight and obesity [13,107,140].

Both forms of adiponectin exert a modulatory effect on miRNA expression. For example, the oligomeric form of adiponectin regulates the expression of miR-133a [141], miR-27b [142], miR-883b-5p [143] and miR-711 [144], whereas gAcrp regulates the expression of other miRNAs, such as miR-21, miR-155 [145,146] and miR-146b- 5p [147]. Apparently, the oligomeric and globular forms of adiponectin control miRNA expression through different mechanisms. Therefore, the stimulatory effects of adiponectin on miRNA expression are mediated by AMPK activation and Erk1/2 inhibition [141] and the inhibitory effects are mediated by the CaMKII/AMPK/p38 cascade [142]. Additionally, gAcrp regulates miRNA expression through the MAPK/NFκB pathway [145,146]. The adiponectin-modulated miRNAs target several downstream effectors with important physiological functions, such as angiotensin II (Ang II) [141], VEGF-C [142], the Toll-like receptor-4 [143], programmed cell death 4 (PDCD4) [145], interleukin-1 receptor-associated kinase-3 (IRAK3), reactive oxygen species (ROS), and Tumor necrosis factor-α (TNFα) [147]. Therefore, miRNAs that are regulated by adiponectin are important factors that control cardiac hypertrophy, chondrosarcoma metastasis and lymphangiogenesis, inflammation, T2DM and non-traumatic osteonecrosis [141–150].

2.3. Resistin and miRNAs

Resistin, which is named for its role in mediating resistance to

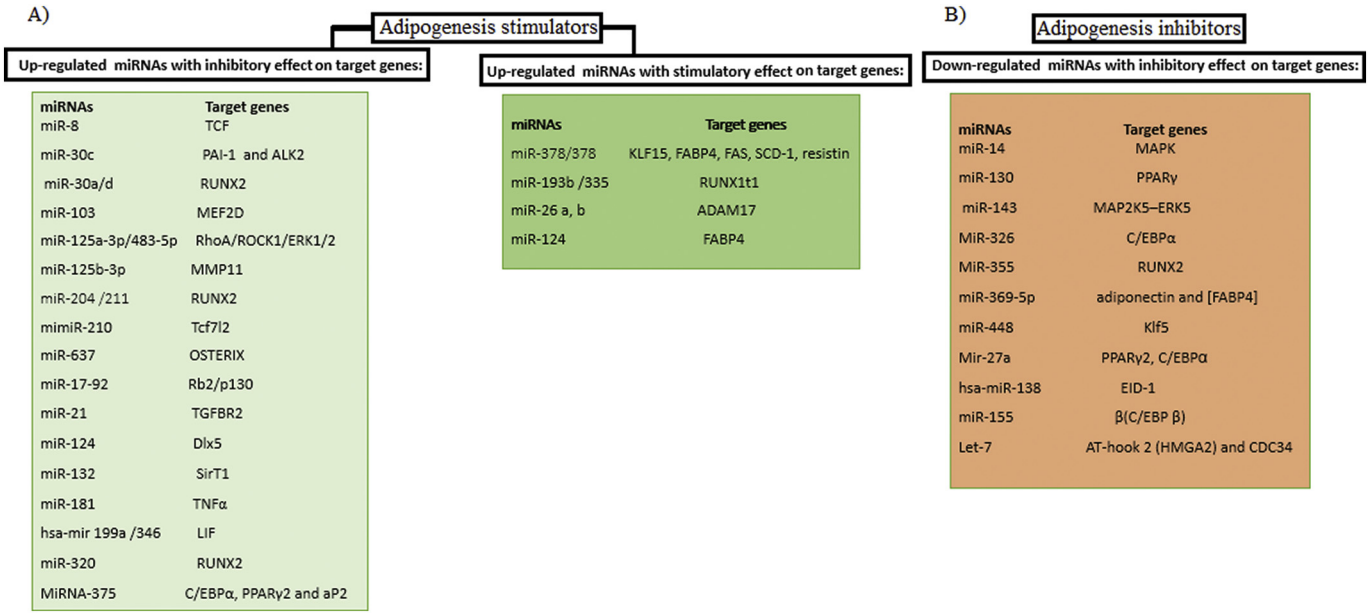

Fig. 2. The most important miRNAs affecting the adipogenesis and their target genes. A) miRNAs with inhibitory/stimulatory effect on target genes resulting to adipogenesis stimulation. B) miRNAs with inhibitory effect on target genes resulting to adipogenesis suppression. TCF (T cell factor); PAI-1 (plasminogen activator inhibitor 1); ALK2 (activin receptor-like kinase 2); RNUX2 (runt-related transcription factor2); MEF2D (Myocyte Enhancer Factor 2D); RhoA (ras homolog gene family), ROCK (Rho-associated protein kinase); ERK1/2 (Extracellular signal-regulated protein kinases 1 and 2); MMP11 (matrix metalloproteinase 11); TCF7L2 (transcription factor 7-like 2); Rb2/p130 (retinoblastoma-like protein 2); TGFBR2 (tumor growth factor beta receptor 2); DLX5 (Distal-Less Homeobox 5); Sirt1 (sirtuin-1); LIF (leukemia inhibitory factor); C/EBP (CCAATenhancer- binding protein); PPARG (Peroxisome Proliferator Activated Receptor Gamma); ap2 (Activating protein 2); FABP4 (fatty acid–binding protein 4); KLF15 (Kruppel-like factor 15); FABP4 (fatty acid binding protein4); FAS (fatty acid synthase); SCD1 (Stearoyl-CoA desaturase); ADAM17 (disintegrin and metalloproteinase domain); EID-1 (e1a-like inhibitor of differentiation 1); CDC34 (cell division cycle 34); Hmga2 (high-mobility group AT-hook 2).

insulin, is a cysteine-rich adipokine with a molecular weight of 10 kDa that is encoded by the RETN gene in some human and rodent tissues, including the WAT [13,151]. The main sources of resistin are peripheral blood mononuclear cells (PBMCs), macrophages, and bone marrow cells, and its expression is induced by TNFα and other inflammatory stimuli [105,152]. The mature resistin protein is secreted as a dimer, and LMW and HMW oligomers have been detected in the circulation [105]. The human resistin receptor and its precise mechanism of action have not yet been completely characterized. However, resistin has been shown to exert its biological functions by binding to TLR4 and adenylyl cyclase-associated protein 1 (CAP1) [105,151,152]. Normally, circulating levels of resistin are maintained at levels ranging from 7 to 22 ng/ml, and these levels are markedly increased in patients with some conditions, such as obesity and diabetes [153,154].

The associations between resistin and the expression of miRNAs regulating obesity-related conditions have been evaluated by some investigators [155–159]. For example, a negative correlation between the expression of miR-206 and resistin during endothelial progenitor cells (EPCs)-mediated angiogenesis was reported by Ming Su et al. [160]. Resistin modulates the expression of miR-145, miR-696, miR-34a and miR-519d [161–164]. Mechanisms underlying the modulatory effects of resistin on miRNA expression remain unclear. However, in a study of human chondrosarcoma cells by Hao Tsai et al., treatment with resistin significantly decreased the expression of miR-519d via the AMPK/p38 signaling pathway [164]. In another study, the binding of miR-206 to its downstream target, VEGF-A, was decreased by resistin [160]. The resistin-mediated changes in miRNA expression control AKT and IRS-1 phosphorylation in HepG2 cells [161], increases the TG content and ectopic deposition of lipids in C2C12 cells [162], inhibits the ATP5S gene expression in HepG2 cells [163] and induces VEGF overexpression in endothelial progenitor cells (EPCs) [160]. Thus, these regulatory effects contribute to some conditions, such as IR, lipid deposition in skeletal muscle, metastasis, autoimmune diseases, and energy hemostasis.

3. The roles of other adipokines in modulating miRNA expression

In addition to leptin, adiponectin and resistin, a wide spectrum of biological molecules are also designated as adipokines. The biochemical characteristics, secretory tissues, functions, and serum levels of well-known adipokines are presented in Table 2 [13,14,16,105].

The regulatory effects of these adipokines on miRNA expression and activation have not been extensively evaluated. However, a limited number of studies have reported the relationships of these adipokines with miRNA expression. The inhibitory effect of apelin on miR-361-5p expression is mediated by the APJ/PKCα pathway in THP-1 macrophages [165] and the inhibitory effect on miR-122 expression is mediated by LGR4-β-catenin signaling [166]. Furthermore, aplein treatment suppresses the expression of some miRNAs involved in obesity-related cardiac contractile dysfunction, such as miR-133a, miR-208 and miR-1 [121]. The interactions between apelin and miRNAs contribute to atherosclerosis, vasoprotection in the aorta, homeostasis of the pulmonary vasculature, management of cardiac hypertrophy and prostate cancer progression [121,165–170].

The positive correlation between visfatin and miR-21 expression in acute coronary syndrome (ACS) [171] and the inhibitory effect of visfatin on miR-199a-5p expression mediated by MAPK signaling in human synovial fibroblasts have also been described [172]. These studies investigated the important roles of miRNAs regulated by visfatin in ACS and osteoarthritis (OA) treatment. Vaspin may be involved in osteogenic differentiation by regulating miR-34c expression through the PI3K/Akt signaling pathway [173]. In other studies, the effects of Activin-A on insulin signaling in cardiomyocytes were mediated by miR-143 upregulation [174], fibroblast growth factor 21 (FGF21) exerted a potent effect on macrophage function by inhibiting miRNA-33 expression [175] and Omentin-1 exerted a significant effect on renal function by regulating the miR-27a-Nrf2/Keap1 axis [176]. Therefore, the potential roles of these adipokines in regulating miRNA expression warrant further in vitro and in vivo investigations.

Table 1
The updated list of studies evaluating the crucial roles of miRNAs in obesity, which are performed in 2019.

miRNA	Samples	Relevant effect
miR-17	Human serum	Development of DM [95]
miR-127	Porcine adipocytes	Attenuates adipogenesis [96]
miR-92a-3p	Adipose-derived mesenchymal stem cells (ADSCs)	Attenuates adipogenesis [97]
miR-214-3p	3T3-L1	Preadipocyte differentiation [98]
miR-425	3t3-L1 pre-adipocytes and mice	Control adipogenesis and adipolysis [99]
miR-145-5p	ADSCs	Suppresses osteogenic differentiation of ADSCs [100]
miR-199a-3p	Bone marrow derived mesenchymal stem cells (BMMSCs)	Adipogenic differentiation of BMMSCs [101]
bta-miR-204	3T3-L1	Adipocyte proliferation, differentiation, and apoptosis [102]
miR-144-3p	Obese mice and 3T3-L1	Adipogenesis [103]
miR-10b-5p	3T3-L1 pre-adipocytes	3T3-L1 cells differentiation [104]
miR-128	Pig preadipocytes	Lipid accumulation [66]
miR-223	Primary intramuscular preadipocytes	Adipocytes differentiation [67]
bta-miR-130a/b	Primary bovine preadipocytes	Preadipocyte differentiation [68]
miR-494-3p	3T3-L1 cells and Male C57BL/6J mice	Mitochondrial biogenesis and thermogenesis [69]
miR-181a	Porcine preadipocyte	Preadipocyte differentiation [70]
miR-30b/193b/ 365	C57BL/6 mice	Development of fetal brown AT [71]
miR-143a-3p	Adipose tissues of obese mice	Proliferation and differentiation of preadipocyte [72]
MiR-499	Primary mouse skeletal muscle satellite cells (SMSCs)	Differentiation in SMSCs [73]
miR-21a-5p	3T3-L1 Cells	Adipogenesis [74]
miR-377-3p	hMSCs	Adipogenic differentiation [75]
miR-200b up	3T3-L1 cells	Preadipocyte proliferation and differentiation [76]
miR-124-3p	Subcutaneous fat of sheep	Adipogenic differentiation [77]
MiR-27b	hASCs	Adipocyte differentiation [78]
miR-204-5p	3T3-L1 cell	Proliferation, apoptosis and differentiation preadipocyte [79]
miR-183	Hircine preadipocytes	Preadipocyte differentiation [80]
gga-miR-140-5p	3T3-L1 cells	Adipocyte differentiation [81]
miR-128-3p	3T3-L1 cells	Adipogenesis and lipolysis [82]
MicroRNA-214-5p	bone marrow stem cells (BMSCs)	Adipogenic differentiation [83]
miR-146b	Porcine primary adipocytes	Consumption of glucose [84]
miR-485	Mouse C2H10T1/2 fibroblast cells	Brown adipogenesis [85]
miR-148a-3p	Rabbit preadipocyte	Preadipocyte differentiation [86]
MicroRNA-125a-5p	Porcine intramuscular preadipocytes	Proliferation, Differentiation and Fatty Acid Composition [87]
miR-125a-5p	High-fat diet (HFD)-fed mice and 3T3-L1 cells	Proliferation and differentiation preadipocyte, [88]
MicroRNA-200a	ST2 bone marrow stromal cells	adipocyte differentiation [89]
miR-155	3T3-L1 preadipocytes	Adipogenesis [90]
miR-124-3p	Stromal vascular fraction (SVF) cells of sheeps	Adipogenic differentiation and lipogenesis [91]
miR-130b	Raw264.7 cells and Atherosclerosis (AS) patients	Adipogenesis and inflammation response [92]
miR-16/15/195	MSCs	Adipogenic and hepatogenic differentiation [93]
miR-19b	SVF cells derived from subcutaneous AT	Browning of ATMale Mice [94]

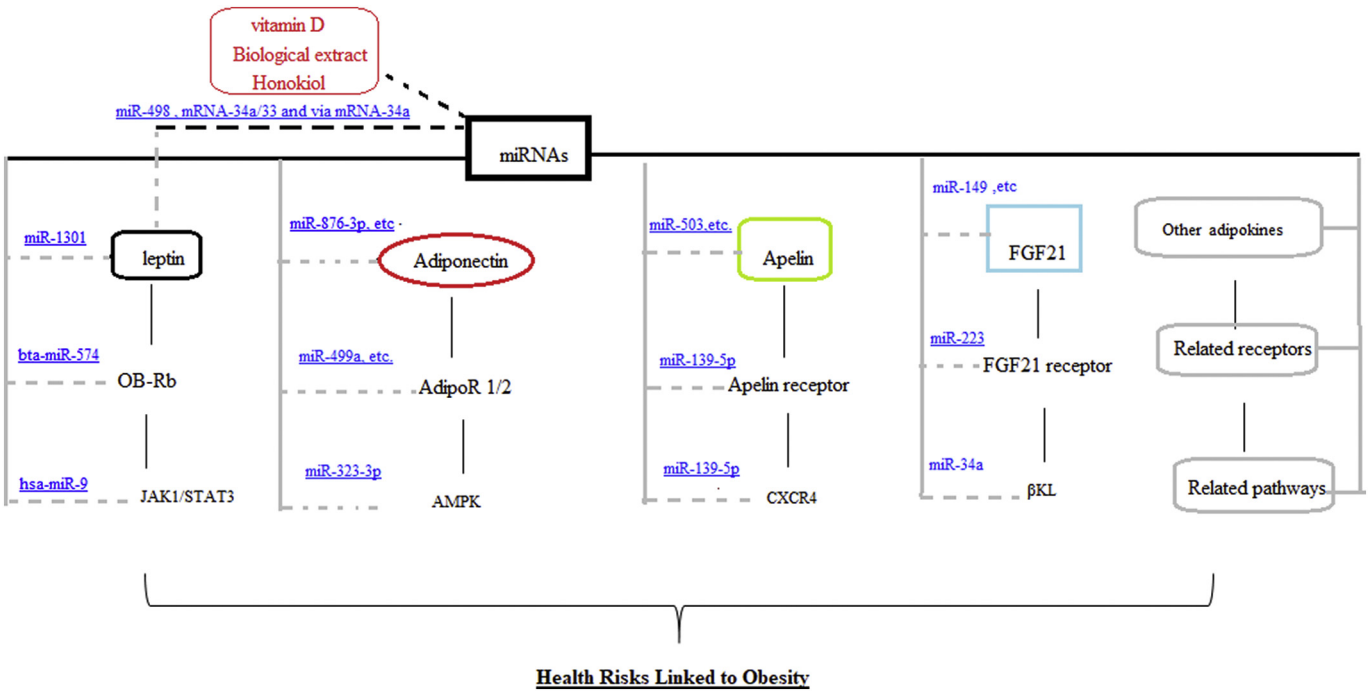

Fig. 3. Some miRNAs may affect obesity-associated conditions by influencing adipokines, their receptor and related signaling pathways. Furthermore, some substances such as vitamin D, biological extracts and Honokiol may affect leptin signaling and functions by miRNAs modulations.

Table 2
Characteristics of some well-known adipokines in human tissues [13,14,16,105].

Adipokines	Properties	Major effects	Status in oboes	Relevant miRNAs miRNAs
Apelin	1.5 kDa, 36 amino acid (AA)	Glucose metabolism	Higher	miR-122 [166], miR-424/503 [168], miR-130/301 [169], miR -133a, miR-208 and miR-1 [121], miR-224 [170]
Visfatin	45-kDa, 491 AA	Insulin secretion	Higher	miR-21 [171],miR–199a [172]
Vaspin	A serine protease inhibitor	Inhibition of serine protease	Elevated	miR-34c [173]
Activin- A	Release from epicedial adipose tissue (EAT)	IR	Elevated	miR-14F3 [248]
Angptl4	encoded by the ANGPTL4 gene	Lipoprotein metabolism	Elevated	miR-132 [180]
FGF21	23 kDa, AA: 209	Glucose hemostasis	Elevated	miR-33 [175], miR-34a, miRNA-100-5p [213–216], Has-miR-577 and Has-miR-583 [217], miR-149 [218], miR-212 [219], MiR-577 [220]
BMP-4 and -7	46 and 49 kDa	Osteoblastic differentiation	Elevated	MiR-876-5p [222], miR-218, miR-191, miR-3070a and miR-33 [260]
DPP-4	88-kDa protein	Glucose hemostasis	Higher	miR-200a [261], miR-29s and miR-let-7s [262], miRNA 29s [263]
Chemerin	163 AA,	Immunity	Increased	miR-155 [264]
SFRP-5	A member of Secreted frizzled-related protein(SFRP)	Insulin sensitivity	Downregulated	MiR-125b [265], MiR-124 [266]
Adipsin	A member of serine protease family	Humoral suppression of infectious agents	Reduced	miR-223 [252]
Lipocalin 2	Member of the lipocalin protein superfamily	Inflammation	Positively associated with adiposity [269]	miR-200 [267], miR-138 [141], miRNAs, 21, 132, an 155 [268], miR-138 [221], miR-130a,
Omentin	313 AA	Insulin signaling	Negatively correlated with obesity [270]	miR-27a [176]
SAA	An acute-phase protein	Systemic inflammation and atherosclerosis	Increased	miR-155 [271]

3.1. Inflammatory adipokines and miRNAs

TNFα, IL1β and IL6 are pro-inflammatory factors that are not only produced by immune cells but are also highly expressed in AT, and thus they may be described as adipokines [14,177]. In human AT, these pro-inflammatory adipokines are secreted by stromal fat cells rather than adipocytes. Circulating levels of these molecules are positively correlated with obesity and are decreased following weight loss [16,177]. They may be involved in modulating the production of other adipokines. For example, both TNFα and IL6 exert a regulatory effect on adiponectin production, and chemerin and leptin production are induced by TNFα [13].

The roles of inflammatory adipokines, such as TNFα, IL6, and IL1β, in obesity-associated conditions have been attributed to alterations in the miRNA profile in several studies [178–185]. In adipose tissues, TNFα and IL6 induce inflammation in response to obesity by up-regulating miR-146b [186]. TNFα and IL6, along with leptin, have been reported to cause obesity-mediated IR via their positive regulatory effects on the expression of miR-378 [187] and miR-221 [188]. Moreover, the interaction between TNFα and promoter elements of the let-7 miRNA, which control the expression of the let-7 mRNA, have been evaluated in the human embryonic kidney (HEK) 293 cell line [189].

In clinical studies, a decrease in miR-21 [190] and miR-221 [191] expression, as well as an increase in miR-146a-5p expression [192] are associated with elevated levels of inflammatory adipokines, such as TLR4, NFκB, IL6, and TNFα in obese patients. In addition, miR-125b and miR143 levels are negatively associated with ovarian levels of the IL1β, IL6, and TNFα mRNAs in obese individuals [193]. Moreover, serum levels of IL6 and IL1β are associated with miR-146a and miR-221 expression in infants born to obese women [194], and the IL6 level is negatively correlated with hsa-miR-197 and hsa-miR-99 expression in patients with NASH, suggesting that miRNAs represent novel diagnostic markers for inflammatory disorders in overweight and obese individuals. In contrast, a study has reported a lack of a significant correlation between inflammatory adipokine and miRNA expression [195]. In two separate experimental studies, polyphenol-rich green tea extract and Apigenin (a flavonoid compound) decreased the levels of inflammatory adipokines and mitigated inflammation and IR by modulating miR-335 [196] and let-7f [197] expression, suggesting that these compounds function as therapeutic mediators that control inflammation induced by miRNA overexpression.

4. miRNAs modulate adipokines expression and activation

Regulatory effects of some miRNAs on adipokines were reported in numerous investigations. The modulatory effects of miRNAs on adipokines are mediated by targeting the expression of adipokines and their receptors, as well as their related signaling pathways and functions. For example, miR-1301 is dysregulated in patients with early-onset preeclampsia and potentially plays a role in the regulation of leptin levels during pregnancy [132]. Several molecules exert anti-leptin effects through the up/downregulation of miRNA expression. For example, vitamin D upregulates miR-498 [198], *Averrhoa carambola* extracts downregulate mRNA-34a/33 [199] and Honokiol activates mRNA-34a [200,201] to abrogate the effects of leptin on human cancerous and non-cancerous cells.

The regulatory effects of miR-876-3p [202], miR-193b [203], miR-378 [204], and miR-21 [205] on adiponectin expression have been evaluated. Notably, miR-876-3p modulates glucose homeostasis and insulin activity by targeting adiponectin [202]. Resistin is also reported to be a target of overexpressed miR-492, and its suppression reverses high glucose-induced IR in HUVECs [206]. Moreover, in a recent study using ApoE-/- mice, an miR-155 deficiency in WAT increased resistin expression, suggesting a new mechanism for the transition of metabolically healthy obesity to classical obesity [207]. In addition, the inhibitory effects of miRNAs on apelin were evaluated in several studies.

Importantly, miR-503 inhibits the hypoxia-induced proliferation, migration and angiogenesis of endothelial progenitor cells by inhibiting apelin expression [208]. In THP-1 macrophages, Cui et al. found that miR-497 suppresses the expression of apelin and induces lipid deposition [209]. In addition, miR-125b [210] and miR-503 [211] promote cardiac fibrosis by blocking apelin, a critical repressor of fibrogenesis. Therefore, the suppression of these miRNAs was suggested as a promising therapeutic strategy for cardiac fibrosis. Moreover, miR-765 impacts arterial stiffening by repressing apelin expression [212]. Furthermore, miRNAs also play key roles in several physiological and pathological conditions by regulating FGF21 expression. For example, miR-100-5p [213], miR-34a [214–216], Has-miR-577, Has-miR-583 [217], miR-149 [218], miR-212 [219] and miR-577 [220] regulate many processes, such as osteoclastogenesis and bone resorption, energy metabolism, non-alcoholic fatty liver disease, pancreatic β-cell function and survival, and beige and brown fat formation, by targeting FGF21. The downregulation of lipocalin-2 and bone morphogenetic protein 4 (BMP-4) by miR-138 [221] and miR-876-5p [222] block hypoxia-induced cardiomyocyte apoptosis and the EMT of lung cancer, respectively.

Reportedly, miR-181a-5p restricts TNFα expression during dendritic cell maturation induced by high mobility group box-1 protein (HMGB1) [223] and adipogenesis [224], suggesting that miR-181a-5p represents a novel target in the treatment of immune dysfunction. In other studies, miR-194-mediated TRAF6 inhibition decreased TNFα release [225], and the hydroxynonenal (4-HNE)-dependent inhibition of miR-29b induced TNFα expression [226], indicating new mechanisms regulating inflammation in human tissues.

Adipokine receptors are another target of the regulatory effects of miRNAs on adipokines. In recent years, several investigations have identified AdipoR1 and 2 as major targets of miRNAs, indicating a crucial role for miRNAs in the posttranscriptional regulation of AdipoR1 and 2 expression that leads to several obesity-associated conditions (reviewed in Table 3) [227–243]. In irradiated mouse skin, specific miRNAs potentially target OBR [244], and these miRNAs are also involved in modulating cutaneous wound healing [245,246]. In addition, bta-miR-574 stimulates mammary gland development and lactation through OBR [247]. The hypothalamic silencing of miR-200a increases the expression of OBR and insulin receptor substrate 2, reduces body weight, and restores hepatic insulin responsiveness. In addition, the overexpression of pre-miR-200a in neuroblastoma cells impairs insulin and leptin signaling. These findings link alterations in leptin and insulin signaling to the upregulation of miR-200a in the hypothalamus and suggest a new target for obesity treatment [126]. Morever, miR-210 induces osteoblastic differentiation by targeting AcvR1b [248].

Signaling pathways and interacting partners of adipokines are also targeted by miRNAs. For example, overexpression of hsa-miR-9 in HSCs blocks the leptin-induced activation of the JAK1/STAT3 signaling pathway and leads to a reduction in α-SMA and collagen I levels [249]. The overexpression of miR-27 suppresses osteoarthritic chondrocytes (OA) by targeting leptin and blocking the NFκB signaling pathway, suggesting a protective role for miR-27 in the pathogenesis of OA [250]. Moreover, miR-139-5p regulates cross-talk between apelin/apelin receptor with CXCR4, which is necessary for vascular maturation [251]. Notably, miR-223 participates in the C/EBPs/miR-223/FGFR2 regulatory feedback loop that is involved in regulating the adipogenic and osteogenic differentiation of mesenchymal stem cells [252]. On the other hand, the opposite effects of leptin and miR-21 mediate liver fibrogenesis [253] and sinusoidal endothelial injury [254] in experimental nonalcoholic steatohepatitis models. The regulatory effects of miRNAs on adipokine expression contribute to obesity-related conditions, and thus additional investigations are required in this field.

Table 3
The list of studies demonstrating adiponectin receptor (AdipoR 1 and 2) as target for miRNA functions.

miRNA	Experiments	Targets	Relevant function	Reference
MiR-499a	Tissue samples and HUVEC cells	E-cadherin, AdipoR 2	Atherosclerosis development	Jiang et al [243]
miR-323-3p	MIN6 cell line	AdipoR1, SIRT-1, AMPK	Cell growth, and insulin secretion	Wang et al [228]
miR-320	Rat model of Duodenal–jejunal bypass (DJB) surgery	AdipoR1 and adiponectin signaling	Gluconeogenesis, lipid metabolism and inflammation	Guo et al [235]
MiR-6835	SU.86.86 and MIN-6 cell lines	AdipoR1	Function of pancreatic islet cells	Wang et al [227]
miR-6835	HUVEC cells	AdipoR1, SIRT-1 and AMPK	Cell proliferation	Liu et al [236]
miR-3908	U87 and U251 cell lines	AdipoR1, AMPK, p-AMPK and SIRT1	Suppression of glioblastoma tumorigenicity	Liu et al [237]
miR-3908	MCF-7	AdipoR1, Flotillin-1	Breast cancer cell migration	Li et al [238]
miR-221	HepG2 and HuH-7 cell lines	AdipoR1	promotion of the EMT	Li et al [239]
miR-150	THP-1 macrophages	AdipoR2, PPARγ, liver x receptor alpha (LXRα), ABCA1, and ABCG1	Lipid accumulation	Li et al [233]
miR-323	In PC specimen, HUVEC cells	VEGF-A, AdipoR1	Prostate cancer vascularization	Gao et al [230]
miR-375	SGBS cells and hMSCs	AdipoR2	Visceral fat mass and the IR.	Kraus et al [240]
miR-218	HepG2 cells	AdipoR2, AMPK and p38	Adiponectin signaling and glucose uptake	Du et al [234]
miR-221	HUVEC cells	AdipoR1	Endothelial nitric oxide production and inflammatory response	Chen et al [242]
miR-150	Myocardial tissues	AdipoR2	Adiponectin resistance	Kreth et al [241]
miR-423-3p upregulation	Hep-2 cell line and in silico assay	AdipoR2 DUSP4, MAP kinase phosphatases (MKP2)	Laryngeal carcinoma progression	Guan et al [229]
miR-221 upregulation	C57BL/6 mice and in HepG2 and C2C12	AdipoR1, polypyrimidine tract–binding protein (PTB)	Muscle differentiation and IR	Lustig et al [231]
miR-221/222 upregulation	MB-231 and MCF10A cell lines tissue samples	AdipoR1, NF-kB and STAT3 pathways	EMT	Hwang et al [232]

5. Clinical/prognostic/diagnostic value of the interactions between adipokines and miRNAs

The clinical relevance of adipokines as biomarkers of fatty mass, the function of WAT, insulin function and inflammatory and metabolic diseases have been reported by different investigators [14,255]. Accumulating evidence has revealed the diagnostic and prognostic potential of circulating miRNAs in major human diseases, including cancer, cardiovascular disease, non-alcoholic fatty liver disease, neurodegenerative disease, infectious diseases, T2DM, obesity, chronic kidney disease, and autoimmune diseases [256,257].

Therefore, association between adipokines and miRNAs may also be helpful in determining the prognosis and diagnosis of obesity-related diseases. The correlations between adipokines and miRNAs have been evaluated in numerous clinical studies, and they have been suggested as novel diagnostic or prognostic markers for related disorders in overweight individuals. Accordingly, a positive correlation between visfatin and miR-21 expression in patients with ACS [176] and between miR-27b/miR-145 and OBR expression in obese patients [119] have been reported. Additionally, Saloua Dimassi et al. reported a positive correlation between the MPs miR-124a and miR-150 and adiponectin, TNFα, or IL6 levels in normal and obese subjects after exercise [258].

The adiponectin level negatively correlates with circulating miRNA levels in patients with childhood obesity [150], patients with hormone-induced non-traumatic osteonecrosis of the femoral head [259], Xinjiang Uygur patients with T2DM [148], and individuals with a polyunsaturated fatty acid-rich diet [149], indicating that adiponectin may exert protective effects on these conditions. In clinical studies, a decrease in miR-21 [190] and miR-221 [191] expression, as well as an increase in miR-146a-5p expression [192] are associated with increased levels of inflammatory adipokines, such as TLR4, NFκB, IL6, and TNFα, in obese patients. In addition, miR125b and miR143 levels are negatively correlated with ovarian levels of the IL1β, IL6, and TNFα mRNAs in obese individuals [193]. Moreover, IL6 and IL1β levels are associated with miR-146a and miR-221 expression in infants born to obese women [194] The IL6 level negatively correlates with hsa-miR-197 and hsa-miR-99 expression in patients with NASH, suggesting that miRNAs represent potentially novel diagnostic markers for inflammatory disorders in overweight and obese individuals. In contrast, another study did not observe significant correlation between inflammatory adipokine and miRNA expression [195].

6. Conclusions

As reviewed here, the obesity-mediated dysregulation of adipokines and miRNAs leads to changes in various biological processes, such as cell proliferation, differentiation, angiogenesis, cell migration, cellular inflammation, molecular biogenesis, and cell signaling. In some conditions, changes in the regulation of miRNA expression induced by adipokine dysregulation results in several types of human obesity-related diseases through the targeting of various molecules. Additionally, the dysregulation of the miRNA profile in obese individuals can target adipokines and their receptors to modulate their activities, potentially leading to the development of obesity-associated disorders. Thus, miRNAs have two major applications in obesity-associated diseases, including their precise and sensitive analysis as valuable biomarkers in early and correct diagnosis of obesity-related diseases and their applications as potential targets in therapeutic strategies. Their abundance, consistency, and stability in the circulation, as well as the good correlations between their levels and certain disorders, along with easy methods for their separation and analysis suggest that they represent reliable diagnostic tools for obesity-related diseases. In some studies, a number of remarkable features have been ascribed to miRNAs, such as effective therapeutic targets in the treatment of various human diseases. However, some challenges remain that restrict the clinical applications of miRNA biomarkers, such as the uncharacterized targets and functions of some miRNAs, their complicated redundancy, off-target effects, and the lack of a suitable standardized method for precisely quantifying miRNAs.

Adipokines have also been proposed as potential targets in therapy for obesity and its related disorders. Thus, the control of adipokines, their receptors and signaling cascades will probably become reliable therapeutic targets for drug industries. Several studies have focused on designing and developing adipokine antagonists and agonists that are able to modulate the functions of their receptors and thereby control adipokine-mediated diseases. Similar to miRNAs, clinical applications of adipokines are also limited because the mechanisms underlying their function and related signaling pathways have not been completely characterized. Researchers have an optimistic outlook that biological and clinical investigations of both adipokines and miRNAs will facilitate their use in the detection and treatment of human metabolic disorders, specifically in obesity-related diseases, in the near future.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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