REVIEW ARTICLE

Molecular Biology

The novel importance of miR-143 in obesity regulation

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Obesity and substantially increased risk of metabolic diseases have become a global epidemic. microRNAs have attracted a great deal of attention as a potential therapeutic target for obesity. MiR-143 has been known to specifically promote adipocyte differentiation by downregulating extracellular signal-regulated kinase 5. Our latest study found that miR-143 knockout is against diet-induced obesity by promoting brown adipose tissue thermogenesis and inhibiting white adipose tissue adipogenesis. Moreover, LPS- or IL-6-induced inhibition of miR-143 expression in brown adipocytes promotes thermogenesis by targeting adenylate cyclase 9. In this review, we will summarize the expression and functions of miR-143 in different tissues, the influence of obesity on miR-143 in various tissues, the important role of adipose-derived miR-143 in the development of obesity, the role of miR-143 in immune cells and thermoregulation and discuss the potential significance and application prospects of miR-143 in obesity management.

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INTRODUCTION

Tight and flexible control of energy homeostasis is fundamental for organism health and its dysregulation contributes to obesity, a worldwide epidemic in our current society [1]. Obesity is an energy imbalance between calories consumed and calories expended, and long-term excessive energy intake leads to metabolic disorders (especially glucose and lipid metabolism). In severe situations, obesity leads to a substantially increased risk of metabolic diseases (for example type 2 diabetes mellitus [2] and hyperlipidemia [3]), cardiovascular diseases [4], and some types of cancer (for example breast [5] and lung [6]). Since the amount or activity of brown/beige fat inversely correlates with body mass index in adult humans, brown/beige fat is believed to help reduce adiposity [7–9]. The epidemic of obesity and diabetes has greatly increased the interest in this metabolically active type of fat. In the past two decades, microRNAs (miRNAs) have attracted extensive attention due to being highly conserved across species and also being involved in many metabolic regulation activities by silencing target genes. Currently, miRNAs, particularly in brown/beige fat due to their regulatory functions in the initiation and progression of obesity, have gained extensive attention in exploring effective biomarkers for early and fast diagnosis and novel treatment targets for obesity [10, 11]. As a member of the miR-143/145 cluster, the gene of miR-143 is highly conserved across mammalian species. miR-143 displays a specific function in regulating metabolic activity, such as adipocyte differentiation [12–17], insulin resistance [18], glycolysis [19–34], smooth muscle cell proliferation [35], and intestinal epithelial regeneration [36]. The purpose of this review is to describe our current understanding of how miR-143 acts in the adipose tissue, liver, and body circulation to affect obesity. Firstly, we will summarize recent advances in understanding the expression pattern of miR-143 in various organs. Secondly, we will discuss expression changes of miR-143 that occur in the adipose tissue, liver, and blood circulation in the setting of obesity and highlight how these changes contribute to metabolic dysfunction. Thirdly, we will discuss the relationship between miR-143 and immune disorders and thermoregulation. Finally, we will evaluate the possibility of miR-143 as a biomarker of obesity and the potential therapeutic implications of targeting the miR-143 to treat obesity and associated diseases.

THE EXPRESSION PATTERN OF MIR-143 IN VARIOUS ORGANS

In humans, miR-143 is located at sites 149428918–149429023 (in intron) on chromosome 5, and miR-143 traverses a canonical biogenesis pathway involving compartmentalized processing by two RNase III enzymes [37]. In the nucleus, primary miR-143 transcripts bearing inverted repeats are cleaved by Drosha to release pre-miR-143 hairpins. In the cytoplasm, they are cleaved by Dicer to yield miR-143-3p/miR-143-5p duplexes, which are then loaded onto Argonaute effector proteins [38]. Following the removal of miR-143-5p species, the single-stranded miR-143-3p-argonaute complex, in association with GW182/TNRC6 cofactors, seeks regulatory targets. We sorted out the sequences of miR-143

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Table 1. Sequence of miR-143 in various species.

Abbreviation	Species	Accession	Sequence of miR-143 (5′–3′)
hsa-miR-143	*Homo sapiens*	MIMAT0000435	UGAGAUGAAGCACUGUAGCUC
ptr-miR-143	*Pan troglodytes*	MIMAT0002257	UGAGAUGAAGCACUGUAGCUCA
ggo-miR-143	*Gorilla gorilla*	MIMAT0002258	UGAGAUGAAGCACUGUAGCUCA
ppa-miR-143	*Pan paniscu*	MIMAT0002261	UGAGAUGAAGCACUGUAGCUCA
ppy-miR-143	*Pongo pygmaeus*	MIMAT0002259	UGAGAUGAAGCACUGUAGCUCA
mml-miR-143	*Macaca mulatta*	MIMAT0006201	UGAGAUGAAGCACUGUAGCUC
lla-miR-143	*Lagothrix lagotricha*	MIMAT0002260	UGAGAUGAAGCACUGUAGCUCA
mmu-miR-143	*Mus musculus*	MIMAT0000247	UGAGAUGAAGCACUGUAGCUC
rno-miR-143	*Rattus norvegicus*	MIMAT0000849	UGAGAUGAAGCACUGUAGCUCA
cgr-miR-143	*Cricetulus griseus*	MIMAT0023772	UGAGAUGAAGCACUGUAGCUC
mdo-miR-143	*Monodelphis domestica*	MIMAT0004113	UGAGAUGAAGCACUGUAGCUCG
ssc-miR-143	*Sus scrofa*	MIMAT0013879	UGAGAUGAAGCACUGUAGCUC
oar-miR-143	*Ovis aries*	MIMAT0030032	UGAGAUGAAGCACUGUAGCUC
cfa-miR-143	*Canis familiaris*	MIMAT0006682	UGAGAUGAAGCACUGUAGCUC
bta-miR-143	*Bos taurus*	MIMAT0009233	UGAGAUGAAGCACUGUAGCUCG
eca-miR-143	*Equus caballus*	MIMAT0013063	UGAGAUGAAGCACUGUAGCUC
oan-miR-143	*Ornithorhync-hus anatinus*	MIMAT0007144	UGAGAUGAAGCACUGUAGCUC
gga-miR-143	*Gallus gallus*	MIMAT0048646	UGAGAUGAAGCACUGUAGCUCG
xla-miR-143	*Xenopus laevis*	MIMAT0046457	UGAGAUGAAGCACUGUAGCUC
xtr-miR-143	*Xenopus tropicalis*	MIMAT0003686	UGAGAUGAAGCACUGUAGCUCG
aca-miR-143	*Anolis carolinensis*	MIMAT0021770	UGAGAUGAAGCACUGUAGCUC
pma-miR-143	*Petromyzon marinus*	MIMAT0019473	UGAGAUGAAGCACUGUAACUCC
ola-miR-143	*Oryzias latipes*	MIMAT0022668	UGAGAUGAAGCACUGUAGCU
dre-miR-143	*Danio rerio*	MIMAT0001840	UGAGAUGAAGCACUGUAGCUC
ccr-miR-143	*Cyprinus carpio*	MIMAT0026224	UGAGAUGAAGCACUGUAGCU

Data from miRbase.

in different species from miRBase and found that the first 20 bases of miR-143 are conserved not only in mammals but also in non-mammals (for example *Gallus gallus*, *Danio rerio*, and *Xenopus laevis*) (Table 1).

As early as 2002, it was first reported that miR-143 was expressed in the mouse spleen, heart, cortex, and midbrain [39]. Following reports found that miR-143 is wildly expressed in different tissues [18, 36, 40–42], including the liver [18, 40], small intestine [42], and colon [36] where miR-143 expression has not been detected before [39]. In humans, miR-143 shows a similar expression pattern to that in murine [12]. But in pigs, miR-143 exhibits different expression patterns [43]. Expression patterns in different species and organs are summarized in Table 2. The expression of miR-143 still needs to be refined since inconsistent results are given in different reports. Although miR-143 has been proven to be wildly expressed and regulate a large number of metabolic activities, conditional overexpression or tissue-specific knockout of miR-143 or miR-143/145 did not overt developmental defects of tissue and organ under normal diet (ND) or normal conditions [18, 36, 40, 44].

MIR-143 REGULATES THE ADIPOGENESIS

In obesity, the adipose tissue undergoes dynamic remodeling including an increase in size (hypertrophy) and the number of adipocytes (hyperplasia) [45, 46]. miR-143 may play an important regulatory role in this process. The miR-143 in mature adipocytes is significantly higher than that in stromal vascular fraction (SVF) preadipocytes [14], and the expression of miR-143 is increased during the differentiation of human white preadipocytes [12], 3T3-L1 cells [13–16], and adipose tissue-derived stromal cells (ADSCs) [17]. In addition to regulating adipocyte differentiation, miR-143 has also been reported to regulate milk fat synthesis in bovine mammary epithelial cells [47].

It is widely acknowledged that the MAPK signaling pathway plays a pivotal role in many essential cellular processes, including cell proliferation and differentiation [48]. Mitogen-activated protein 2 kinase kinase 5 (MAP2K5 or MEK5) and extracellular signal-regulated kinase 5 (ERK5) are important target genes for miR-143 to regulate adipocyte differentiation [12, 17]. The adipogenic differentiation process involves several successive steps, and the MEK5-ERK5 cascade regulated by miR-143 plays an important role in each step. During the clonal expansion stage, the overexpression of miR-143 inhibits the adipogenic differentiation by targeting MAPK signaling pathway [17]. In the growth arrest stage or terminal differentiation stage, the overexpression of miR-143 inactivates MEK5-ERK5 and promotes cell differentiation via the phosphorylation of peroxisome proliferator-activated receptor-gamma (PPARγ) [49, 50]. PPARγ, a member of the nuclear receptor superfamily, is a master regulator in lipid metabolism by controlling networks of gene expression for lipid accumulation [51], lipolysis [52, 53], and browning of white adipocyte [54]. It is phosphorylated within the AF1 region by MAPKs, inhibiting ligand binding and altering cofactor recruitment which represses its transcriptional activity [51, 55]. A recent study pointed out that by binding to nerve growth factor-induced B alpha (Nur77), PPARγ promotes the ubiquitination and degradation of Nur77 mediated by the ubiquitin ligase trim13, which in turn leads to the loss of Nur77's transcriptional inhibition of CD36 and FABP4, thereby promoting fatty acid uptake and cell proliferation [56]. In addition,

Table 2. Expression profiles of miR-143 in various organs.

Documents	Method	Genera	The expression of miR-143	No expression
[39]	qRT-PCR	Mouse	Spleen > Heart > Cortex > Midbrain	Liver, small intestine, colon
[41]	Northern blot	Mouse	Aorta > Fat > Lung > Skin > Skeletal muscle > L. ventricle > Atrium > R. ventricle > Spleen > Kidney > Liver > Brain	
[18]	Northern blot	Mouse	BAT > WAT > Skeletal muscle > Liver	
[36]	qRT-PCR	Human and mouse	Intestinal mesenchyme	Intestinal epithelium
[40]	miRNA microarray	Mouse	Bladder > Aorta > Lung > Heart > Liver > Brain > Skeletal muscle	
[42]	Small RNA RNA-seq	Mouse	Fibroblast ≈ Smooth muscle cell > Endothelial ≈ Epithelial	Red blood cell, lymphocyte
[12]	Northern blot	Human	Thymus ≈ Heart > Kidney > Lung > Spleen > Brain > Liver	
[43]	qRT-PCR	Porcine	Large intestine > Pancreas > Spleen > Lung > Small intestine > Heart > Ovary > Hypothalamus ≈ Stomach > Liver > Kidney > Cerebrum > Cerebellum	

our newly published research showed that miR-143 knockout (KO) inhibited the differentiation of primary white adipocytes, but did not affect the differentiation of primary brown adipocytes [57].

Although the target genes of miR-143 and the transcription factors regulated by these target genes have such a great influence, a large number of reports have focused on the regulation of miR-143 on adipogenesis of white adipocytes and rarely on other aspects of lipid metabolism. The studies of the functions of miR-143 in lipid metabolism, especially lipolysis and fatty acid transport, need to be supplemented and improved, and the different roles of miR-143 in the differentiation of brown and white adipocytes need further study.

MIR-143 REGULATES THE GLYCOLYSIS AND GLUCONEOGENESIS

Glucose and fatty acids are predominant sources of energy for the human and animal body. In addition to adipogenesis, numerous studies have shown that miR-143 targets hexokinase 2 (HK2) to inhibit glycolysis [19–34]. MiR-143 is regarded as a novel type 2 diabetes regulator [18, 26, 58] that regulates insulin resistance through the oxysterol-binding protein-related protein 8 (ORP8)-AKT signaling pathway, and overexpression of miR-143 in the liver impairs glucose metabolism under physiological conditions [18]. Interestingly, ORP8 also inhibits sustained phosphorylation of glycogen synthase kinase 3α/β (GSK3α/β) via insulin-stimulated AKT activation [18]. Recently, our research showed that miR-143KO significantly inhibited gluconeogenesis in the liver of mice induced by high-fat diet (HFD) [59]. It was found that miR-143 targets mitogen-activated protein kinase 11 (MAPK11) [59], thereby inhibits gluconeogenesis by repressing the activity of phosphoenolpyruvate carboxykinase 1 (PCK1) and glucose-6-phosphatase catalytic (G6PC) [60]. Changes in glucose metabolism of mice with obesity after miR-143KO require a deeper assessment, including glycolysis, glycogen synthesis and glycogenolysis. Specific liver miR-143KO mice are also an important model for assessing the contribution of miR-143-regulated hepatic glycolysis and gluconeogenesis to obesity.

MIR-143 IS INVOLVED IN THE PROGRESSION OF OBESITY

Obesity leads to dysregulation of miR-143 expression

Since the first demonstration of the link between obesity and energy metabolism of a miRNA in drosophila melanogaster [61], numerous studies have been performed in this field, including miR-143 (Fig. 1). Intriguingly, the effect of obesity on the

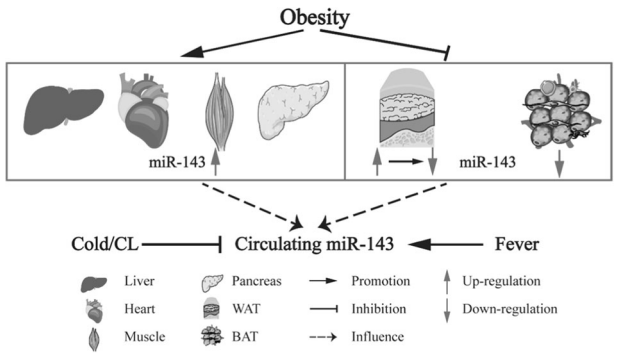

Fig. 1 Obesity can upregulate the expression of miR-143 in the liver, heart, muscle, and pancreas, first up- and then down-regulate the expression of miR-143 in the WAT and downregulate the expression of miR-143 in BAT. Although studies of circulating miR-143 expression in obesity have been inconsistent, cold exposure and CL316,243 treatment decreased circulating miR-143 expression, whereas fever had the opposite effect.

Table 3. Differentially expressed circulating miR-143 in obesity and metabolic disease.

Study and year	Sample size	Age	Detection methods/endogenous controls	Differentially expressed miRNAs
[74]	100 patients with obesity, 100 patients with overweight, 50 control participants with non-obesity	12–18 years	Real-time qPCR analysis, RNU43	miR-143, miR-142-3p, miR-140-5p, miR-222, miR-130↑ miR-532-5p, miR-423-5p, miR-520c-3p, miR-146a, and miR-15a↓
[62]	50 metabolic syndrome patients and 50 controls	40–65 years	miRNA microarrays/real-time qPCR analysis, U6	miR-143-3p, miR-20a-3p, miR-365a-3p, miR-29a-3p, let-7i-5p, and miR-99a-5p↑ miR-375, miR-154-5p, miR-346 and miR-382-5p↓
[75]	16 normal diet rat, 16 pre-diabetes rat, 16 T2D rat	6 weeks	Real-time qPCR analysis, unisp6 RNA spike	miR-143 and miR-375↑ (T2D vs. ND)
[77]	23 patients with morbid obesity, 30 patients with obesity, 30 control participants with non-obesity	32–61 years	Real-time qPCR analysis, U6	miR-143 and miR-223↓
[76]	45 patients with obesity, 41 control participants with non-obesity	12–17 years	Real-time qPCR analysis, NA	miR-27, miR-378 and miR-370↑ miR-143, miR-335 and miR-758↓

expression of miR-143 in WAT remains controversial. A study suggests that miR-143 increased adipogenesis in adipocytes by affecting several key lipid metabolism genes, but the expression of miR-143 in isolated mature adipocytes from *ob/ob* mice is downregulated compared with adipocytes from wild-type (WT) mice [14]. Furthermore, the expression level of miR-143 in WAT is significantly reduced in both the diet-induced mice [18, 62] and the *db/db* mice [18]. Similarly, miR-143 is lower in the subcutaneous white adipose tissue (scWAT) of subjects with obesity and insulin-resistant than in scWAT of subjects with obesity and insulin-sensitive, and both subjects with obesity and resistant and obesity and sensitive were lower than lean subjects [63]. However, other studies have reported that the miR-143 is highly expressed in WAT of HFD-induced mice compared with the mice fed ND [64] and it was positively related to the body weight of mice or adipocyte volume in swine [64–67]. Meanwhile, our latest research found that the expression of miR-143 first rose and then decreased in WAT of HFD-induced mice [57]. This reverse pattern may be similar to the role of miR-143 in adipocyte differentiation [17]. In the early stage of HFD-induced, miR-143 increased in WAT, which promoted adipocytes expansion and stored energy. In the middle and late stages of HFD-induced, excessive obesity may inhibit the expression of miR-143 in WAT through feedback regulation, and reduced adipogenesis. This view is supported by the increased expression of adipogenic genes during adipogenesis whose expression is decreased in obesity and diabetes mellitus [68]. More importantly, we also found that miR-143 in brown adipose tissue (BAT) was significantly reduced in the process of HFD-induced obesity in mice, and the reduced miR-143 could resist obesity by promoting thermogenesis [57].

The upregulation of miR-143 in the liver of patients with obesity is contrary to the expression of miR-143 in BAT [18, 62]. The liver is the central metabolic organ that regulates glucose and lipid metabolism [69]. The upregulated miR-143 specifically inhibits the insulin AKT pathway by targeting the ORP8, thereby inhibiting AKT phosphorylation, and contributing to the development of obesity-induced insulin resistance [18]. In addition to the liver, miR-143 is also upregulated in the heart, muscle and pancreas of mice with obesity [18, 62]. The upregulation of miR-143 in the heart may be related to impaired exercise ability, as studies have reported that exercise training decreased the expression of miR-143 in the heart and serum [70, 71]. Previous studies have reported that miR-143KO promotes both proliferation and chemotaxis and inhibits differentiation of vascular smooth muscle cells (VSMCs), and the downregulation of miR-143 expression is associated with increased hemodynamic stress in the aorta of mice [35, 41, 44]. So, the upregulated of miR-143 in the heart and muscle induced by obesity may be to inhibit the coarctation and altered vessel histology, such as that occurring with atherosclerosis. Moreover, the upregulated expression of miR-143 in the pancreas does not alter the glucose-stimulated insulin secretion and morphology of pancreatic β-cell [18], and the function of miR-143 in the pancreas needs further study. To sum up, miR-143 is tissue-specifically expressed with multiple functions.

Circulating miR-143 changes in obesity and its related disorders

Evidence is accumulating that circulating miRNAs act as a new class of endocrine factors [72, 73]. Circulating miRNAs, which are released by many types of tissues including the adipose tissues, are valuable biomarkers yielding important insights into the pathogenesis of obesity. It is found that the level of circulating miR-143 is closely related to the occurrence of obesity. However, there are still great doubts about the expression pattern of circulating miR-143 in obesity and its related disorders (Table 3). On the one hand, circulating miR-143 has been shown to significantly increase morbidly adolescents with obesity and was positively correlated with body mass index (BMI), waist-to-hip ratio

(WHR), diabetic control, and lipid profile parameters [74]. It was also significantly elevated in metabolic syndrome patients (MetS, defined according to standards generated by the joint committee for developing Chinese guidelines on the prevention and treatment of dyslipidemia in adults) compared with controls both in serum and urine samples [62], and was accompanied by an increasing trend in the homeostasis model assessment of insulin resistance (HOMA-IR), high-density lipoprotein-cholesterol (HDL-c) ratio and percentage of body fat [62]. miR-143 was also elevated in PBMCs of HFD/streptozotocin-treated type 2 diabetes mellitus rats [75]. On the other hand, in other studies, circulating miR-143 in children with obesity was significantly lower compared to those of controls, and miR-143 was correlated negatively with leptin, HOMA-IR, triglycerides (TG), BMI, and waist circumference (WC) [76]. In another report, circulating miR-143 levels were significantly lower in subjects with morbidly obesity and obesity than the normal or overweight subjects, but it did not yield any correlation between miR-143 levels and BMI and WHR [77]. Therefore, those conflicting data hints that the effect of obesity and its complications on circulating miR-143 needs to be verified by more studies.

More importantly, antagomiR-143 treated (downregulation of circulating miR-143) mice with obesity showed significant amelioration in insulin tolerance test, glucose tolerance test and the size of adipocytes in scWAT and epididymal white adipose tissue (eWAT), compared with control, but the body weight and the weight of WAT did not change [62], which may be due to the limited inhibitory effect of antagomiR-143 in the tissue. Extracellular vesicles (EVs), a type of nano-scale vesicles secreted by cells, mediate intercellular communications by transferring biological molecules, such as mRNAs, non-coding RNAs, lipids, and proteins [78–81]. miRNAs of EVs from the adipose tissue might act as novel forms of adipokine to facilitate diverse intercellular communication [82, 83]. Obesity and obesity-associated comorbidities may be due to the adipose tissue and liver cross-talk dysregulation mediated by EVs [84]. For example, EV-associated miRNAs from BAT are able to regulate gene expression in the liver [85]. Lean mice exhibit glucose intolerance and insulin resistance after the injection of adipose tissue-derived EVs from mice with obesity [86]. Researchers have found that BAT-EVs preferentially accumulate in the liver after intravenous injection [87]. Furthermore, BAT-EVs target liver metabolism more specifically and efficiently than WAT-EVs [85]. Thus, reducing the expression of miR-143 in adipose tissue with obesity, especially in BAT, may be a more promising target for the treatment of obesity with miR-143.

MiR-143KO is against diet-induced obesity by promoting BAT thermogenesis and inhibiting WAT adipogenesis

For a long time, the primary function of miR-143 was thought to promote adipogenesis of white adipocytes [12, 14, 15, 17, 64, 88, 89]. However, most of the findings are cross-sectional in nature, which do not show the impact of miR-143 on obesity. Our latest research fills the gap in the role of miR-143 in the development of obesity [57]. We construct global miR-143KO mice by using CRISPR/Cas9 technology. Although miR-143KO showed neither phenotypic abnormalities nor energy imbalance, and changes in BAT thermogenesis in mice fed an ND under normal conditions. As cold exposure stimulates stronger body temperature in miR-143KO mice [59], we speculate that miR-143 in adipose tissue acts as a stress miRNA upon metabolic challenge just like miR-21 [90]. Then, we evaluated the role of miR-143 in an HFD-induced obesity model. Surprisingly, the increase in body weight, fat mass, rectal temperature and energy expenditure of KO mice was significantly decreased during HFD feeding compared with WT mice. In addition, improvements in insulin sensitivity and glucose tolerance were also observed in miR-143KO mice. Activating BAT thermogenesis is an important strategy of against obesity, which is mediated by Uncoupling protein 1 (UCP1) protein located in mitochondria [91, 92]. We found that AC9 is a new target of miR-143 in brown adipocytes, and miR-143 promotes the expression of UCP1 by inhibiting adenylate cyclase 9 (AC9) [93], and improves the number and function of mitochondria in BAT, while the mechanism needs further study [59]. AC9 is a physiologically and clinically relevant effector of β_2-adrenergic receptor (AR) signaling in particular [94, 95], and it also regulates cAMP production [95, 96]. More recent research found that BAT thermogenesis occurs through β_2-AR signaling in humans [97], and AC9 inactivation increases weight gain and adipose tissue volume in mice with the treatment of an atherogenic diet [98]. Whether AC9 is sufficient and/or necessary for UCP1 induction thermogenesis needs more research.

In addition, our study confirmed that miR-143KO inhibit the differentiation of white adipocytes and fat synthesis and promote lipolysis in WAT [59]. The inhibition of miR-143KO on fat synthesis may be through the inhibition of fatty acid synthase protein expression through AMPK signaling pathway [99–101]. And miR-143KO significantly inhibited the differentiation of white adipocytes by promoting MEK5-PPARγ signaling pathway, which further verified previous studies [17]. The target gene of miR-143 regulating fat synthesis and lipolysis has not been found yet, which needs further research. At the same time, adipose tissue-specific knockout mice are the focus of the next study on the function of miR-143.

OBESITY AFFECTS THE EXPRESSION OF MIR-143 IN ADIPOCYTES THROUGH IMMUNE CYTOKINES

The immune system is a critical regulator of metabolic homeostasis. Adipose tissue is heterogeneous, and the function of adipose tissue is dynamically regulated by communication between adipocytes and other cell types, like macrophage [92, 102]. The enlargement of the adipose tissue during obesity is accompanied by the development of chronic low-grade inflammation of the adipose tissue, which includes infiltration of macrophages into the adipose tissue and increased levels of cytokines [103, 104]. The miR-143 expression in the BAT of mice (a population including ND-fed and HFD-fed mice) exhibited a statistically significant inverse relationship with tumor necrosis factor α (TNFα) and interleukin 6 (IL-6) expression in the BAT [93]. In adipocytes, miR-143 may be involved in the response of adipocytes to obesity-induced macrophage infiltration and cytokines secretion, as treatment of TNF-α [14] and LPS or IL-6 [93] to differentiated 3T3-L1 adipocytes or primary brown adipocytes reduced the expression of miR-143. Further details of the effect of TNF-α treatment on the decline of miR-143 in white adipocytes have not been clearly studied. IL-6 is a well-known cytokine activator of thermogenesis [105, 106]. More importantly, IL-6 treatment reduced the expression of miR-143 and increased the expression of *Ucp1* mRNA in brown adipocytes, while miR-143KO also enhanced the levels of IL-6 [93]. The above results indicate that there is a mutual inhibition between miR-143 and IL-6 in brown adipocytes.

Obesity-associated pro-inflammatory changes in WAT can contribute to the development of metabolic diseases. WAT with obesity is characterized by increased accumulation of $CD4^+$ T helper type 1 (Th1) cells, cytotoxic $CD8^+$ T cells, pro-inflammatory classically activated macrophages, and decreased abundance of regulatory T cell (Treg), Group 2 innate lymphoid cell (ILC2), and eosinophils (Eos) [104]. miR-143 is found to affect the secretion of immune cytokines in some immune cells. For example, miR-143 overexpression increases the differentiation of central memory T $CD8^+$ cells and pro-inflammatory cytokine secretion [107], while miR-143 is downregulated during T helper 9 (Th9) cell differentiation, and its overexpression inhibited Th9 differentiation, proliferation, and IL-9 production [108]. However, up to now, the function of miR-143 in characterized immune cells of WAT with obesity has not been reported. Therefore, the role of miR-143 in immune cells and how immune cells regulate the expression of miR-143 in adipocytes are the focuses of further research.

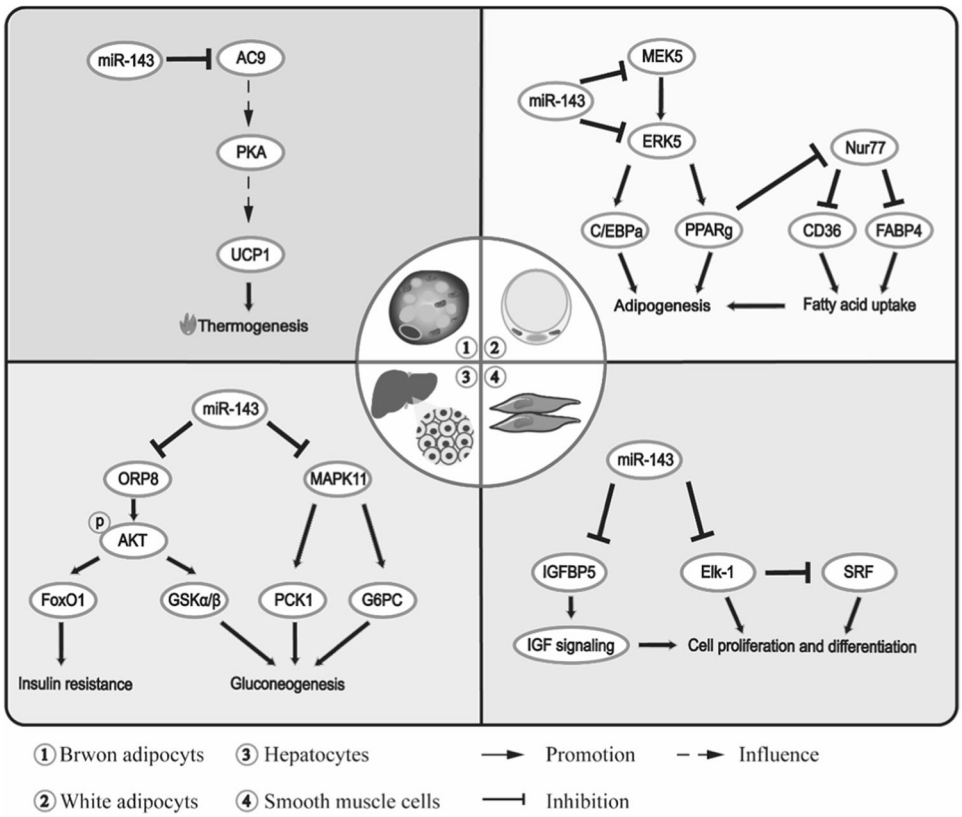

Fig. 2 Schematic illustration of miR-143 regulating brown adipocyte, white adipocyte, liver cell, and smooth muscle cell function. In brown adipocytes, miR-143 targets AC9 to inhibit thermogenesis by decreased the expression of UCP1. In white adipocytes, miR-143 targets MEK5 and ERK5 to inhibit adipogenesis by inhibiting the expression of PPARγ and C/EBPα. PPARγ promotes the ubiquitination and degradation of Nur77, which in turn leads to the loss of Nur77's transcriptional inhibition of CD36 and FABP4, thereby promoting fatty acid uptake and cell proliferation. In hepatocytes, miR-143 targets ORP8 and contributes to the development of obesity-induced insulin resistance. MiR-143 can also target MAPK11, and inhibits gluconeogenesis by repressing the activity of PCK1 and G6PC. In smooth muscle cells, miR-143 targets IGFBP5 and Elk-1 to affect cell proliferation and differentiation.

MIR-143 IS INVOLVED IN THE REGULATION OF BODY TEMPERATURE

In recent years, brown or beige adipocyte has attracted extensive attention because of their unique thermogenic function as an important target for the prevention and treatment of obesity and its complications [109]. There is increasing evidence to suggest that specific miRNAs in brown or beige adipocytes can regulate thermogenesis and confront against obesity [110, 111]. miR-143 is highly expressed in adipose tissue, and the expression of miR-143 in BAT is even higher than that in WAT [18]. It has been reported that cold exposure and CL316,243 (CL) treatment, which are classic stimuli known to induce thermogenesis of BAT, significantly reduce the expression level of circulating miR-143 [112]. We confirmed that low-dose LPS can also promote body temperature and thermogenesis of BAT by reducing the level of miR-143 [93]. However, the mechanism of miR-143 in regulating thermogenesis has not been fully exploited. Moreover, the upregulated miR-143 is found in THP-1-derived macrophages and peripheral blood mononuclear cells (PBMCs) after heat exposure and in turn targets endogenous pyrogens including IL-6, IL6ST, TLR2, PGE2, and TNF to complete a negative feedback mechanism, which may be crucial to prevent pathological hyperthermia [113]. In this report, they also defined miR-143 as a temperature-sensitive miRNA [113]. Recent studies have found that IL-27–IL-27Rα signaling plays a critical role in inducing thermogenesis, protecting against diet-induced obesity, and ameliorating insulin resistance [114]. The regulatory effect of immune cytokines on thermogenesis is further emphasized. Thus, under physiological and pathophysiological conditions, the effect of miR-143 on the cross-talk of adipocytes and immune cells is an important direction for future research.

THE CURRENT GAP BETWEEN MIR-143 AND OBESITY AND THE CLINICAL SIGNIFICANCE OF MIR-143

Although previous studies have reported a strong correlation between obesity and miR-143, there is a lack of evidence that miR-143 directly controlled the development of obesity. Interestingly, our latest study found that global miR-143KO mice showed a significant reduction in increased body weight, fat mass, liver, and adipose tissue weight (including BAT and WAT), and increased glucose utilization and energy expenditure during HFD-induced obesity [57, 59]. Our study demonstrated that miR-143KO can resist diet-induced obesity in vivo. We summarize the functions and regulatory pathways of miR-143 in white adipocytes, brown adipocytes, hepatocytes, and smooth muscle cells (Fig. 2). Unfortunately, to date, the mechanism of miR-143 in BAT has rarely been illustrated, though BAT is a promising anti-obesity target. And in the current studies, obesity-induced changes in miR-143 in tissues were described, but it still remains unclear how miR-143 work in fat dysfunction and by which regulatory pathways. Furthermore, tissue-specific miR-143KO mice are urgently needed to validate the contribution of miR-143 functions in different tissues (liver, muscle, and adipose tissue) to obesity.

Obesity-related circulating miRNAs, an endocrine factor that promotes communication between metabolic organs and tissues [85] while having good stability [115], may be the most important

indicators of potential non-invasive biomarkers for the management of obesity and related metabolic disorders [73]. Several specific miRNAs, such as miR-132 and miR-17-5p [116], are known to be differentially expressed in patients with obesity as compared with healthy individuals and are potential biomarker candidates. According to the current data, circulating miR-143 may not be suitable as a marker for obesity, due to inconsistent results from different research works, and that the downregulation of circulating miR-143 was not effective in reducing obesity in mice, although it alleviated insulin resistance [62].

Since the discovery of miRNA in the 1990s [117], miRNAs have emerged as attractive therapeutic agents for various diseases, including obesity. Two miRNA-based therapeutic tools have shown promise in preclinical studies and clinical trials: miRNA mimics and anti-miRNA oligonucleotides (inhibitors). To date, the miRNA-targeted therapeutics for metabolic disorders that have reached phase I clinical trials are antimiR-103 and anti-miR-107 (known as RG-125/AZD4076), which are intended to treat type 2 diabetes mellitus with non-alcoholic fatty liver disease (NAFLD) [118] and non-alcoholic steatohepatitis (NASH) [119]. miR-143 inhibitors may be a potential way in the treatment of obesity, since knock out of miR-143 reduced HFD-induced obesity, but it still has a long way off Another important question is how to deliver miR-143 inhibitors more efficiently and specifically to adipose tissue.

CONCLUDING REMARKS AND PROSPECTIVE

Studies have shown that miR-143 is stably and highly expressed in WAT and BAT and is downregulated as obesity occurs. This could be due to the intrinsic homeostasis regulation mechanism, which inhibits adipogenesis and promotes thermogenesis by reducing miR-143 to resist obesity. Circulating miRNAs derived from adipose tissues have been proposed as important endocrine factors in whole-body metabolic control, providing new insight into cross-organ communications. Although the expression of WAT-derived and circulating miR-143 in patients and mice with obesity is still controversial, it is confirmed that miR-143 is downregulated in the BAT of mice with obesity, indicating the important role of miR-143 in the BAT in anti-obesity. Throughout the research history of miR-143, it is not difficult to find that, in addition to our recent reports, there is almost no information on the regulatory role of miR-143 in fat mobilization, including lipid transport, lipolysis, and thermogenesis. Further study in this field and a complete description of miR-143 regulatory function in adipose tissue is an important theoretical basis for guiding miR-143 to obesity treatment.

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AUTHOR CONTRIBUTIONS

JL, HW, and DZ drafted the manuscript. JX, JL, XC, TC, QX, and JS collected the data and organized the references. XR and YZ participated in the study design. All of the authors have read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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