MicroRNAs in Human Adipose Tissue Physiology

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In recent years, there has been a large amount of evidence on the role of microRNA (miRNA) in regulating adipose tissue physiology. Indeed, miRNAs control critical steps in adipocyte differentiation, proliferation and browning, as well as lipolysis, lipogenesis and adipokine secretion. Overnutrition leads to a significant change in the adipocyte miRNOME, resulting in adipose tissue dysfunction. Moreover, via secreted mediators, dysfunctional adipocytes may impair the function of other organs and tissues contributing to the development of obesity related compications.

microRNA (miRNA) gene expresion adipose tissue obesity adipogenesis adipose tissue browning adipokines

1. Background

According to worldwide statistics, the number of obese individuals has tripled in the last 30 years, and it is estimated that in 2025, they will constitute approximately 15% of the world adult population. However, it is not obesity itself but obesity-related complications that affect virtually all organs in the body and significantly deteriorate quality of life, constituting a severe social and economic problem [1]. The development of obesity-related complications is related to the dysfunction of adipose tissue. The excessive accumulation of lipids changes the adipocyte metabolism, leading, among other things, to dysfunction of the mitochondria and the associated endoplasmic reticulum stress [2]. These phenomena influence adipocyte transcriptional activity and thus the profile of substances secreted by adipose tissue (adipokines), which affects the functioning of tissues and organs throughout the body in an endocrine manner. While the effects of obesity-related adipose tissue dysfunction are already known, the knowledge of the underlying mechanisms is still insufficient.

In recent years, there has been much interest in the potential role of microRNA (miRNA) in regulating gene expression in adipose tissue [3][4]. miRNAs are single-stranded noncoding RNAs of 17–25 nucleotides in length (on average 22). Although miRNAs do not have open reading frames (they do not encode proteins), they can perform regulatory functions in the cell. It has been shown, for example, that miRNAs located in the cell nucleus can regulate gene transcription both directly—acting as transcriptional cofactors and participating in the mRNA maturation process—and indirectly—by influencing the chromatin structure by participating in histone methylation and acetylation [5].

In vitro studies and animal models of obesity have shown that some miRNAs regulate adipogenesis and browning of adipose tissue [4]. Moreover, the targeted overexpression or ablation of particular miRNAs in white adipose tissue results in enhanced mitochondrial biogenesis and a subsequent decrease in insulin resistance, an improvement in the plasma lipid profile and a reduction in fatty liver markers in mice with diet-induced obesity (DIO) [6][7]. There is evidence that miRNAs can also regulate the function of adipocytes in humans, and obesity may lead to a change in the miRNA profile in adipose tissue [8][9].

2. Role of microRNAs in Adipogenesis

2.1. miRNA in the Regulation of White Adipogenesis

White adipose tissue (WAT) not only constitutes a significant energy depot in the human body but also secretes numerous mediators that can affect the function of distant organs. Complex interactions between different signaling pathways and transcription factors determine the process of multipotent mesenchymal stem cell (MSC) differentiation to white preadipocytes followed by growth arrest induced by contact inhibition. Next, adipogenic stimuli promote cell cycle reentry and synchronous cell division. This process depends on the induction of transcription factors, which are members of the CCAAT/enhancer-binding protein (C/EBP) family. Subsequently, C/EBPβ activates the transcription of the major transcriptional inducers of adipogenic gene expression: *C/EBPA* and peroxisome-proliferator-activated receptor γ (*PPARG*), as well as several other transcription factors responsible for the terminal differentiation of preadipocytes into lipid-storing mature adipocytes [10]. Two key signaling pathways involved in MSC differentiation toward adipocytes are the Wingless (Wnt)/β-catenin and the transforming growth factor β (TGFβ)/bone morphogenetic proteins (BMP)/Smad pathways. Activated Wnt/β-catenin signaling stimulates osteogenic gene expression; however, its inhibition induces adipogenic differentiation via the induction of adipogenic-related genes, including the abovementioned *PPARG* and *C/EBPA*. The interaction between β-catenin and PPARγ results in β-catenin degradation with the subsequent inhibition of Wnt/β-catenin signaling and bone formation, promoting adipogenesis. Similarly, BMP/Smad signaling favors adipogenesis by increasing the expression of *PPARG*, while the TGFβ/Smad pathway exerts inhibitory effects on adipogenesis [11][12]. The proper regulation of adipocyte development and turnover assures adipose tissue homeostasis, which is seriously disturbed in the course of obesity.

The inhibition of enzymes involved in miRNA biogenesis, such as Drosha and Dicer, depresses the differentiation of human MSCs into adipocytes, which supports a role for miRNAs in adipocyte development [13]. Subsequently, several miRNAs have been found to be regulators of human adipocyte differentiation [4]. WAT undergoes dynamic changes to adapt to the body's energy balance to maintain its energy storage role. In excess energy intake, WAT augments its capacity to store energy by increasing lipid accumulation and differentiation of preadipocytes to mature adipocytes. The remodeling of WAT in response to the excess of nutrients is accompanied by changes in the WAT miRNOME, with several miRNAs being up- and downregulated [14]. Moreover, several adipocyte-selective miRNAs implicated in adipocyte proliferation and differentiation in normal-weight individuals are differentially expressed in adipose tissues of obese subjects [8][9][15].

miRNAs are implicated in the regulation of the critical signaling pathways related to adipogenesis. For instance, miR-9-5p, by targeting the 3'UTR of Wnt3a (a Wnt ligand) and reducing its expression, inhibits Wnt/β-catenin signaling and promotes the differentiation of rat MSCs toward adipocytes [16]. The expression of miR-9-5p is significantly increased in visceral adipose tissue (VAT) compared to subcutaneous adipose tissue (SAT) in obese patients, suggesting that the upregulation of this miRNA can be involved in the pathogenesis of obesity in humans [9]. High serum miR-9 levels are also considered as a marker of poor prognosis in diabetic nephropathy [17]. A similar effect exerts miR-210, which targets the T cell-specific transcription factor 7-like 2 (TCF7L2) responsible for triggering the downstream responsive genes of the Wnt pathway, as previously shown in 3T3-L1 murine preadipocytes [18]. This miRNA was, in turn, upregulated in the SAT of obese patients, compared to the SAT of normal-weight individuals, while weight loss led to a significant decrease in its expression [8][9]. Moreover, the expression of miR-210 was upregulated in the SAT of obese individuals with normal glucose tolerance, compared to those diagnosed with type 2 diabetes mellitus (T2DM), suggesting its protective role in the development of obesity-related adipose tissue dysfunction [19]. However, in patients with T2DM, serum miR-210 concentration may serve as a diagnostic biomarker of diabetic retinopathy patients and may have the ability to predict disease development and severity [20].

In turn, miR-21 was found to positively regulate adipogenesis in human adipose-derived stromal cells (hADSCs) by binding and neutralizing TGFβ1—an inhibitor of adipogenesis [21]. The upregulation of miR-21 in the adipose tissue of obese subjects has been consistently reported in several studies [9][22][23], while its serum levels correlate negatively with body mass index, waist circumference and insulin levels [24]. Another miRNA targeting TGFβ/Smad is miR-199a-5p, which promotes the adipogenic differentiation of human bone marrow stromal cells (BMSCs) [25]. Obesity is associated with increased miR-199a-5p levels in VAT and in sera [19][26]. However, metabolically healthy obese individuals have lower miR-199a-5p expression in SAT compared to obese patients diagnosed with T2DM [8]. The regulation of adipogenesis can also be obtained by miRNAs acting on TGFβ/Smad-independent pathways, as shown in the case of miR-143 targeting extracellular-signal-regulated kinase 5 (ERK5) [27]. The regulatory role of this miRNA during adipogenesis depends on the differentiation stage that it acts on. If miR-143 is overexpressed during the clonal expansion stage, it inhibits the adipogenic differentiation of adipose tissue-derived stromal cells (ADSC). On the contrary, miR-143 overexpression during the growth arrest stage or terminal differentiation stage promotes adipocyte differentiation [28]. The expression of this miRNA is upregulated in the sera of obese individuals and decreased in the adipose tissue of previously obese patients after successful weight loss [29].

Several other miRNAs have been shown to inhibit MSC differentiation towards osteoblasts and, therefore, to promote adipogenesis. This takes place in the case of miR-204 and miR-637, which target members of the Wnt/β-catenin signaling pathway: runt-related transcription factor 2 (RUNX2) and osterix (OSX), respectively [30][31]. The increased expression of miR-204 characterizes VAT in human obesity and impairs mitochondrial biogenesis and the development of brown adipose tissue (BAT) in rodents [9][15]. Obesity-related changes in miR-637 expression in human adipose tissue have not been reported to date; however, its serum levels increase during dietary weight loss intervention [32].

In turn, miR-27b and miR-130a, by interfering with PPARγ and miR-31 by targeting C/EBPα, were found to favor the osteogenic differentiation of MSCs [33][34][35]. Moreover, miR-130a can suppress MSC differentiation towards adipocytes via interfering with adenomatosis polyposis coli downregulated 1 (*APCDD1*), encoding an inhibitor of the Wnt signaling pathway [36]. Consistently, decreased levels of this miRNA accompany human preadipocyte differentiation [8][23][37]. However, while the decreased expression of miR-27b was found in the SAT of obese patients with T2DM and VAT, and individuals with non-alcoholic steatohepatitis (NASH), the SAT of metabolically healthy obese individuals was characterized by increased levels of miR-27b, and weight loss did not influence its expression [9][15][22][38]. In turn, obese patients with polycystic ovary syndrome (PCOS) tended to exhibit decreased serum miR-27b levels [39]. Data on obesity-induced changes in miR-130a are inconsistent; in some studies, obesity was associated with increased miR-130a levels in SAT and in sera, while in others, it was associated with its downregulation. However, it should be noted that while Nardelli et al. measured the expression of both miR-130a isoforms (3p and 5p), in the study by Wang et al., only the miR-130a-5p level was assessed [15][22][40]. In turn, miR-31-5p was found to be upregulated in the VAT compared to the SAT of obese adult individuals and in the sera of obese adolescents [9][41].

miR-181a is an example of another miRNA regulating adipogenesis by targeting PPARγ; however, miR-181a suppression decreased the expression of PPARγ in porcine primary preadipocytes [42]. The role of this miRNA in the pathogenesis of obesity and related complications in humans is less clear. Ortega et al. found that increased miR-181a expression is a hallmark of preadipocytes originating from the SAT of obese subjects, compared to normal-weight individuals, while Kloting et al. observed its upregulated levels in the SAT of T2DM patients compared to obese subjects without metabolic complications of obesity [8][19]. Moreover, miR-181a expression was significantly elevated in the serum of patients with non-alcoholic fatty liver disease (NAFLD), suggesting it can serve as a disease marker [43]. However, in other studies, miR-181a expression was downregulated in the SAT of metabolically healthy obese patients and VAT of obese individuals with NASH [38][44].

In addition to the direct interaction with PPARγ mRNA, miRNA can regulate adipogenesis by targeting proteins involved in the regulation of PPARγ activity. For instance, miR-146b has been found to promote preadipocyte differentiation via interaction with Sirt1, the NAD-dependent deacetylase, known as a PPARγ inhibitor [45]. Human obesity is associated with the upregulated expression of miR-146b in SAT and sera, which significantly decreases after weight loss [9][46][47]. Interestingly, a high miR-146b serum concentration is a T2DM predictor in obese adolescents, while lower levels are observed exclusively in the VAT of patients with NASH and pericellular fibrosis but are not changed between NASH and non-NASH NAFLD patients [38][47].

The decreased expression of *SIRT1* correlates negatively with the expression of several other miRNAs in the adipose tissues of obese patients, including those involved in pro-inflammatory responses (miR-22-3p), the inhibition of adipose tissue browning (miR-34a-5p) and the activation of white adipogenesis (miR-181a-3p), suggesting that the interaction between miRNAs and SIRT1 constitutes a critical regulatory mechanism in adipocyte homeostasis [42][44][48][49].

Given that a single miRNA targets several mRNAs, its regulatory influence on adipocyte differentiation can be exerted by triggering different cellular pathways. For instance, in different experimental conditions, miR-103 was found to promote adipogenesis via (i) targeting retinoic acid-induced protein 14 (RAI14) in the early stages of adipogenesis; (ii) activation of the protein kinase B/mammalian target of a rapamycin signaling pathway (AKT/mTOR pathway); and (iii) reversing the anti-adipogenic effects of myocyte enhancer factor 2D (MEFD2), which is a transcription factor that negatively regulates preadipocyte differentiation by downregulating the expression of multiple adipocyte markers (e.g., PPARγ and C/EBPα) [50][51]. However, in humans, obesity seems to have little influence on miR-103 expression in adipose tissue, and thus its isoform, miR-103a-3p, is even recommended as a reference for the analysis of miRNA expression in adipocytes [52]. On the contrary, miR-103, together with miR-107, can promote endoplasmic reticulum stress-mediated apoptosis in murine preadipocytes by targeting the Wnt3a/β-catenin/activating transcription factor 6 (ATF6) signaling pathway [53]. The expression of miR-107 was downregulated in the SAT of obese individuals compared to normal-weight subjects and in the VAT of those diagnosed with NASH [22][38][54]. Moreover, miR-107 SAT levels decreased after bariatric surgery, suggesting persistent, obesity-related adipose tissue dysfunction [9]. In turn, elevated miR-103/miR-107 serum levels are a predictor of insulin resistance in obese adolescents [55].

For many years, BAT has been thought to play a marginal role in adult energy homeostasis. However, recent research has increased our understanding of the mechanisms involved in the development and activation of brown adipocytes and their contribution to metabolic health. It has been revealed that miRNAs also play a significant role in regulating these processes.

2.2. miRNA in Regulation of Brown Adipogenesis and Thermogenesis

The proper development and activity of BAT enable higher metabolic rates and can protect against the development of obesity. The brown adipocytes present in the human body can be of distinct developmental origins. The classical or constitutive brown adipose tissue (cBAT) expands during embryogenesis, and recruitable BAT (rBAT, alternatively called beige or brite) emerges postnatally within WAT in the adipose tissue browning process (described in the following section). The activation of adaptive thermogenesis to maintain the normal body temperature is the primary role of cBAT. This is feasible due to the high content of mitochondrial uncoupling proteins (UCPs) responsible for the uncoupling of electron transport from the production of chemical energy in the form of adenosine triphosphate (ATP). The change in the balance of electrons and protons across the mitochondrial membrane leads to energy loss as heat is essential to preserve the normal body temperature [56].

In addition to the general regulators of adipogenesis common with white adipocyte development, the expression of thermogenic genes in brown and beige adipocytes requires additional transcriptional factors, including peroxisome PPARγ coactivator 1 α (PGC1α), PR domain containing 16 (PRDM16) and forkhead box C2 (FOXC2) (reviewed in [57]). Several miRNAs have been reported to regulate brown adipogenesis and, subsequently, the BAT thermogenic program. Therefore, the up- or downregulation of these miRNAs may influence the effectiveness of thermogenesis, which affects whole-body energy expenditure and glucose uptake, and insulin sensitivity [58]. Since miRNAs

involved in brown adipogenesis also frequently participate in regulation of thermogenic pathways, they will be discussed together in the following sections.

3. microRNA in the Regulation of Adipose Tissue Function

3.1. Lipolysis/Lipogenesis

Fatty acids (FA) are stored in adipocytes in the form of triacylglycerol (TAG) in lipid droplets and mobilized during lipolysis—the catabolic process leading to the breakdown of TAG into glycerol and non-esterified fatty acids (NEFA) for internal or systemic energy use. The basal lipolytic activity of adipocytes is determined by genetic variance, sex, age, physical activity, location of the fat depot, etc., and controlled by multiple factors. Lipolysis is, therefore, a dynamic process involving the assembly and disassembly of protein complexes on the surface of lipid droplets and is regulated by two major opposing hormonal signals, catecholamines and insulin. Since the proteins involved in lipolysis are multifunctional enzymes, lipolysis can mediate homeostatic metabolic signals at the cellular level and participate in interorgan communication. Among the recently identified mediators of lipolysis, such as adipokines, structural membrane proteins, atrial natriuretic peptides, AMPK and mitogen-activated protein kinase (MAPK), are also several miRNAs [59].

An example of miRNAs involved in regulating adipose tissue storage capacity is the miR-181 family, which, as mentioned above, also plays a significant role in the regulation of adipogenesis. On the one hand, the overexpression of miR-181a leads to the downregulation of key lipolytic genes: hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), leading to the accelerated accumulation of lipid droplets in vitro in porcine primary preadipocytes [42]. On the other hand, miR-181a decreases the expression of genes involved in lipid synthesis and increases the expression of genes involved in β-oxidation via targeting isocitrate dehydrogenase 1 (IDH1, an enzyme in the tricarboxylic acid cycle) and PPARα; therefore, miR-181a transgenic mice exhibit less lipid accumulation as compared with their wild-type littermates [43][60]. This two-directional effect of miR-181a on lipolysis and lipogenesis may partially explain previously described discrepancies regarding the relationship of this miRNA with the development of obesity and its complications in humans [8][19][38][43][44].

miR-143 is another example of a small-noncoding RNA involved both in the regulation of adipogenesis (see previous sections) and lipid metabolism, since its inhibition leads to the downregulation of adipogenic marker genes (including HSL and PPARγ) and subsequent triglyceride accumulation in subcutaneous preadipocytes [25].

Two miRNAs, miR-33a and miR-33b, encoded by the intronic sequences of the genes of sterol regulatory element-binding proteins (SREBPs) 1 and 2, are also implicated in the regulation of cellular cholesterol and fatty acid metabolism [61]. miR-33b, when overexpressed in porcine preadipocytes, via interaction with PPARγ and C/EBPα, attenuates lipid accumulation in vitro [62]. In turn, the genetic ablation of miR-33 in mice leads to enhanced lipid uptake and impaired lipolysis in WAT, which results in the expansion of adipose tissue depots [63]. This effect of miR-33b on adipose tissue can result from its interaction with the HMGA2 (High Mobility Group AT-Hook 2) transcription factor involved in the regulation of preadipocyte proliferation and differentiation [61]. During obesity,

both miR-33a and miR-33b are upregulated in VAT in metabolically healthy individuals, while miR-33a is selectively upregulated in patients diagnosed with NAFLD compared to those with NASH [9][38]. This finding is consistent with the fact that the serum miR-33a level is an independent predictor of liver steatosis and inflammation in patients after liver transplantation [64].

miR-425 is another example of an adipocyte lipogenesis and lipolysis regulator. By targeting Cab39, an upstream co-activator of AMPK, miR-425 inhibits intracellular lipolysis and lipid oxidation. This mechanism, together with its ability to interact with mitogen-activated protein kinase 14 (Mapk14) and enhance adipocyte differentiation, determines excessive fat accumulation and the development of obesity in experimental animals with miR-425 overexpression. In turn, miR-425 silencing prevents mice from developing obesity, despite a high-fat diet [65]. Accordingly, in humans, weight loss is associated with the downregulation of miR-425 expression in SAT; however, 3-month lifestyle intervention in T2DM patients was associated with the upregulation of serum miR-425 levels [9][66].

Even though miR-128 exerts a similar effect on preadipocyte differentiation by binding PPARγ, interaction with the SERTA domain containing 2 (Sertad2) can promote lipolysis (measured by HSL and ATGL levels) in 3T3-L1 preadipocytes [67]. The proadipogenic effect seems to be dominant in vivo since human obesity is associated with upregulated miR-128 levels in SAT, which decrease after bariatric surgery [9][22].

ATGL and its co-activator comparative gene identification 58 (CGI-58) are major targets of miR-124a. Subsequently, the ectopic expression of this miRNA in murine preadipocytes leads to reduced lipolysis and increased cellular TAG accumulation [68]. Although the role of miR-124a in the development of human obesity has not been confirmed, it plays a significant role in pancreatic beta cell development and regulation of insulin secretion, and thus its aberrant expression is implicated in the pathogenesis of T2DM [69]. Similarly, miR-145 can inhibit lipolysis in murine preadipocytes by interfering with CGI-58 and forkhead box o1 (FOXO1—another activator of lipolytic activity) [70]. Even though it has not been verified whether gain and loss of function of miR-145 in adipose tissue affect lipolysis and adiposity in vivo, in humans, obesity is associated with its increased expression in SAT, while NAFLD is also associated with its increased expression in VAT [19][22][38]. However, it should be mentioned that the 5p isoform (miR-145-5p) was found to be downregulated in the SAT of morbidly obese individuals, while its serum concentrations are decreased in the course of T2DM and prediabetes [15][71].

As demonstrated, miRNAs, both directly (by interacting with the mRNA of enzymes essential for lipolysis and lipogenesis) and indirectly (by targeting regulators of cellular metabolism, such as PPAR), can influence lipid metabolism and cell lipid storage capacity and thus affect the organism’s ability to accumulate adipose tissue. This action frequently results from their simultaneous effect on adipocyte differentiation and proliferation.

In addition to being involved in the regulation of adipocyte storage capacity, miRNAs mediate other functions of adipose tissue, including the secretion of adipokines.

3.2. Adiponectin

Adiponectin, encoded by *ADIPOQ*, is a protein hormone almost exclusively produced in adipose tissue that exhibits favorable metabolic effects, including anti-inflammatory, anti-oxidative and insulin-sensitizing effects. Adiponectin levels measured in the serum and adipose tissue of obese individuals are significantly lower than those in normal-weight subjects and correlate negatively with obesity-related complications [72][73]. There are several lines of evidence that miRNAs are implicated in the obesity-related downregulation of *ADIPOQ* expression.

miR-378, in addition to being a positive regulator of brown adipogenesis, also plays a role in regulating *ADIPOQ* transcriptional activity. Its overexpression in 3T3-L1 cells leads to a significant decrease in adiponectin mRNA and protein levels, which can be reversed by adding the miRNA-378 inhibitor. Accordingly, miR-378 levels were found to be higher, while adiponectin mRNA levels were found to be lower, in the WAT of diabetic ob/ob mice than wild-type animals [74]. However, its role in the development of human obesity requires further investigation since in human VAT, miR-378 levels correlated positively with *ADIPOQ* expression [75].

In addition to directly targeting *ADIPOQ* mRNA, miRNA can indirectly regulate adiponectin expression by binding key transcription factors. This takes place in the case of miR-144 and FOXO1. miR-144 targets *FoxO1* mRNA, thus reducing its expression and inhibiting its promotional effect on adiponectin, thereby alleviating the inhibitory effect of adiponectin on adipogenesis in porcine preadipocytes [76]. In human obesity, serum miR-144 is a marker of insulin resistance, and its levels are elevated in SAT and decrease after weight loss intervention [9][77][78].

Moreover, miRNAs (e.g., miR-221 and miR-218) play a pivotal role in the post-transcriptional regulation of adiponectin receptors (AdipoR) that mediate adiponectin's pleiotropic effects in peripheral tissues. Since adiponectin synthesis is reduced in the course of obesity, the induction of AdipoRs via miRNAs could potentially enhance adiponectin's beneficial effects and ameliorate obesity-associated insulin resistance and diabetes [79][80].

3.3. Inflammation

Chronic overnutrition, manifested by the excessive accumulation of lipids, impairs adipocyte metabolism, leading to mitochondrial dysfunction that contributes to endoplasmic reticulum stress, hypoxia and cell hypertrophy. These pathological changes activate the expression of genes encoding cytokines, chemokines and adhesion molecules in adipose tissue, which attracts infiltrating immune cells (different subsets of T cells and macrophages) that contribute to the production of pro-inflammatory cytokines. Pro-inflammatory mediators (e.g., tumor necrosis factor-alpha, TNFα and interleukins (IL) 1 and 6) impair adipose tissue function in an auto- and paracrine manner but also influence other tissues, contributing to the development of insulin resistance and other components of metabolic syndrome [81]. There is mounting evidence that this chronic, low-grade inflammation, called metaflammation, is under the epigenetic control of miRNAs, and conversely, the inflammation of the adipose tissue leads to the dysregulation of miRNA expression. Accordingly, the miRNA panel of adipose tissue in genetically obese ob/ob mice resembles that of TNFα-treated 3T3-L1 preadipocytes, suggesting that obesity leads to the spontaneous conversion of the miRNA profile to a pro-inflammatory one [54].

The effects of miRNAs on the inflammatory response in adipose tissue can be twofold: stimulating and inhibiting. For instance, the overexpression of miR-132 in primary human adipose-derived stem cells leads to an increase in the production of IL8 and monocyte chemoattractant protein-1 (MCP1), while the overexpression of miR-126 in human adipocyte progenitor cells leads to the downregulation of MCP1 [82][83]. In turn, the exposure of human differentiated adipocytes to miR-145, miR-26a and miR-let-7d results in the downregulation of TNFα synthesis in the case of miR-26a and let-7d, and upregulation in the case of miR-145 [84].

miR-30a is an example of an miRNA triggering anti-inflammatory responses in adipose tissue. By targeting the signal transducer and activator of transcription 1 (*STAT1*), miR-30a opposes the actions of interferon γ (IFNγ), resulting in increased insulin sensitivity in DIO mice [85]. Moreover, members of the MiR-30 family are involved in the polarization of macrophages towards the M2 (anti-inflammatory) phenotype. HFD causes the hypermethylation of MiR-30 genes via the activation of AMPK and delta-like ligand 4 (DLL4)-Notch signaling, leading to their downregulation and the exacerbation of inflammation and insulin resistance in an animal model of obesity [86]. Human obesity is associated with decreased miR-30a expression in SAT but with elevated serum levels [15][87].

miR-17 (by blocking *STAT3* and apoptosis signal-regulating kinase 1—*ASK1* expression) can also suppress pro-inflammatory responses [88][89]. Its overexpression reduces the secretion of IL1β, IL6 and TNFα in lipopolysaccharide-stimulated macrophages, preventing macrophage-mediated adipose tissue inflammation and improving insulin resistance [89]. Notably, miR-17 levels are reduced in the VAT and sera of obese individuals [90].

In turn, the overexpression of miR-27a enhances the polarization of macrophages towards a pro-inflammatory phenotype (M1) by targeting PPARγ. Conversely, miR-27a knockout reduces cytokine (e.g., IL10) expression in activated macrophages [91]. Moreover, HFD leads to increased MiR-27a serum levels, which correlates with increased adiposity and insulin resistance. However, in miR-27a knockout animals, cytokine levels are within the normal range, despite being fed an HFD [92].

The pro-inflammatory environment in adipose tissue contributes to the dysregulation of adipogenesis, since pro-inflammatory cytokines (e.g., TNFα) can downregulate the expression of key adipogenic factors, e.g., *PPARG*, *C/EBPA* and *FABP4*. There is evidence that miRNA participates in this process: for instance, TNFα, via activation of the nuclear factor κB pathway, induces the expression of miR-130 (an inhibitor of adipocyte differentiation) in murine adipocytes [93]. Moreover, HFD triggers miR-130b activation in adipose tissue, which, via targeting PPARγ, polarizes macrophages to express the M1 phenotype, exacerbating inflammation and insulin resistance [94].

Moreover, the influence of pro-inflammatory cytokines on miRNA expression in adipocytes can be miRNA specific. While the treatment of human mature adipocytes with TNFα and IL6 leads to a significant elevation in miR-335 expression, in a culture of adipose tissue-derived MSCs from obese subjects, the expression of miR-221 correlates negatively with *TNFA* mRNA levels [95][96].

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