Shortcuts to a functional adipose tissue: The role of small non-coding RNAs

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ABSTRACT

Metabolic diseases such as type 2 diabetes are a major public health issue worldwide. These diseases are often linked to a dysfunctional adipose tissue. Fat is a large, heterogenic, pleiotropic and rather complex tissue. It is found in virtually all cavities of the human body, shows unique plasticity among tissues, and harbors many cell types in addition to its main functional unit – the adipocyte. Adipose tissue function varies depending on the localization of the fat depot, the cell composition of the tissue and the energy status of the organism. While the white adipose tissue (WAT) serves as the main site for triglyceride storage and acts as an important endocrine organ, the brown adipose tissue (BAT) is responsible for thermogenesis. Beige adipocytes can also appear in WAT depots to sustain heat production upon certain conditions, and it is becoming clear that adipose tissue depots can switch phenotypes depending on cell autonomous and non-autonomous stimuli. To maintain such degree of plasticity and respond adequately to changes in the energy balance, three basic processes need to be properly functioning in the adipose tissue: i) adipogenesis and adipocyte turnover, ii) metabolism, and iii) signaling. Here we review the fundamental role of small non-coding RNAs (sncRNAs) in these processes, with focus on microRNAs, and demonstrate their importance in adipose tissue function and whole body metabolic control in mammals.

1. Metabolic diseases

Obesity statistics are alarming. According to the World Health Organization (WHO), more than 1.9 billion adults were overweight in 2014, and more than half a billion were obese. Once an exclusive issue of high-income countries, obesity is now prevalent in the developing world and has been considered a global epidemic [1]. This is extremely worrisome given that obesity represents one of the most important risk factors for chronic diseases, including type 2 diabetes (T2D), cardiovascular diseases and cancer – the leading causes of mortality and morbidity worldwide [2]. When appearing together, these diseases are classified as a broader syndrome often referred to as the "metabolic syndrome" [3].

The increase in the prevalence of obesity is due to many factors including genetics, diet, sedentarism and issues concerning the psychological, socioeconomic, or educational status of the individual [4].

Simplistically, obesity appears when there is a positive energetic balance, *i.e.* when energy consumption (food intake) overcomes energy expenditure [5,6]. The definition and classification of obesity is still a subject of debate. The WHO divides individuals into four categories based on their body mass index (BMI, kg/m^2): underweight BMI < 18.50, normal weight BMI=18.50–24.99, overweight=BMI 25.00–29.99, and obese BMI≥30.00 [7]. This sole parameter often creates confusion regarding the risk of metabolic diseases, since individuals can be classified as overweight or obese but do not display increased risk of mortality nor any metabolic alteration [8,9]. Moreover, in some cases even a negative association between BMI and mortality - in particular cardiovascular mortality – is found [10]. To avoid misdiagnosis, supporting clinical information needs to be taken into consideration, such as patient's life history (*e.g.* addictive behavior or body weight oscillation) and localization of excessive fat mass (*e.g.* upper body or lower body) [8,11,12]. When considering the latter, obesity can be further classified into an android syndrome (*i.e.* male-type or apple-shaped), where fat is deposited preferentially in intra-abdominal regions (*i.e.* visceral white adipose tissue - vWAT), and a gynoid syndrome (*i.e.* female-type or pear-shaped), where fat is deposited over the gluteofemoral region (*i.e.* subcutaneous white adipose tissue - sWAT) [13,14]. The first has been more commonly linked to comorbidities such as hypertension, dyslipidemia, and T2D [15–17], while the second confers a neutral or even protective effect against metabolic diseases [17,18]. To account for these differences, parameters like waist-to-hip ratio, magnetic resonance imaging or dual-energy X-ray absorptiometry [19,20] have been used as bona fide predictors of metabolic diseases and as useful parameters for researchers to understand how fat accumulation determines the risk of these diseases [12,21,22].

The pleiotropic nature of fat depots has been extensively explored in mice. For example, transplantation of sWAT from donor mice into the intra-abdominal region of a host mouse improves metabolism by reducing body weight and overall fat mass, increasing insulin sensitivity and whole body glucose uptake [23], and alleviating diet-induced glucose intolerance and inflammation [24,25]. Interestingly, these effects are minor when sWAT is transplanted into the subcutaneous cavity and no effect is observed when vWAT is transplanted to the intra-abdominal area [23–25], indicating that the differences between depots are determined by intrinsic characteristics as well as by anatomical localization. This is particularly highlighted in patients with lipodystrophy, where the pattern of fat accumulation differs from normal. These patients exhibit a degree of adipose tissue atrophy (whereas some depots can be hypertrophic), and often end up accumulating fat in non-adipose organs such as liver, heart, and skeletal muscle – a phenomenon that is causally linked to the metabolic syndrome [26–28]. Lipodystrophy can be classified according to fat loss topography (*e.g.* general or partial) or cause (*e.g.* congenital or acquired) [29,30]. The most prevalent form of lipodystrophy is acquired by patients with HIV undergoing antiretroviral treatment [31,32]. For instance, the highly active antiretroviral treatment (*i.e.* a combination of at least three antiretroviral drugs) inhibits mitochondrial DNA polymerase-γ causing mitochondrial toxicity, and the use of protease inhibitors up-regulates genes that inhibit adipocyte differentiation and down-regulates pro-adipogenic transcriptional factors such as PPAR-γ, C/EBP-α and SREBP-1, as well as genes involved in lipid metabolism [26,33,34]. These alterations are observed in white adipocytes, mainly in the subcutaneous depot either from the upper (*e.g.* face and shoulder) and/or lower body (*e.g.* gluteal and femoral). Additionally, HIV patients can also exhibit increased fat accumulation in breast, cervical, dorsocervical and visceral depots [35,36]. Importantly, these patients have a higher risk to develop insulin resistance and cardiovascular disease, and appear to age prematurely [37–39]. Therefore, abnormal changes in adipose tissue accumulation, independently of fat gain or loss, impact on the risk of metabolic diseases, a feature that highlights the importance of adipose tissue to whole body metabolic control.

2. The etiopathogenesis of metabolic diseases

Insulin resistance is a common feature of metabolic diseases and represents the main cause of T2D [40]. Like for obesity, the prevalence of T2D in the world is extremely high (8.8% of the world's population) and is rapidly growing [41]. In 2015, T2D killed approximately 5 million people [42]. The causes of T2D involve both genetic [43] and environmental factors that progressively lead to insulin resistance, glucose intolerance, and ultimately beta-cell failure [44,45]. Several reports support the notion that excess lipids continuously released from visceral fat into the portal vein in obese patients is a major trigger of T2D [46,47]. These lipids expose the liver to incremental amounts of free fat acids (FFAs), inducing hepatic insulin resistance and affecting gluconeogenesis [46,48]. Interestingly, like mentioned above, despite the association between T2D and obesity, some morbidly obese individuals as classified by BMI are significantly more glucose tolerant than leaner individuals [49]. Again, this apparent paradox might be explained by changes in the pattern of fat accumulation, since increased adipose tissue expandability and plasticity, particularly of subcutaneous depots, is linked to metabolic health [50,51]. In essence, the proposed model evokes that every individual has a limited capacity for fat storage, and when this limit is reached, either by obesity or impaired adipocyte function, excess lipids accumulate ectopically, causing lipotoxicity, inflammation, tissue dysfunction and disease [52–54].

At the molecular level, FFAs are usually taken up by cells and esterified into long chain acyl CoA molecules [55]. The bulk of these metabolites are directed to beta-oxidation, but a small portion can be converted into two lipid intermediates: diacylglycerols and ceramides [56]. In excess, these intermediates can activate kinases such as Jun amino-terminal kinase (JNK), IκB kinase (IKK), and protein kinase C (PKC) [57–60], which in turn phosphorylate the insulin receptor substrate-1 (IRS1) in serine and inhibit insulin signaling downstream of the insulin receptor [60–62]. Furthermore, lipids can signal through toll-like receptors or G protein-coupled receptors to cause insulin resistance or affect insulin secretion [63,64]. Additionally, excessive adipocyte hypertrophy without proper neovascularization creates a pseudohypoxic state in the adipose tissue [65,66]. Altogether, these stimuli lead to the infiltration of immune cells into the adipose tissue [67,68]. Within the tissue, monocytes differentiate into either anti-inflammatory M2 or pro-inflammatory M1 macrophages depending on the niche [69]. M1 macrophages are more commonly present in adipose tissue under obesogenic conditions, when they are activated by fatty acids and adipocyte-derived factors, and release a variety of pro-inflammatory cytokines that signal locally or systemically to cause insulin resistance through the activation of the same group of kinases and similar mechanisms as mentioned above [70,71].

Interleukin 1 beta (IL-1β) is one such pro-inflammatory cytokine synthesized and released from M1 macrophages in the context of obesity [72,73]. IL-1β production and secretion is controlled by the inflammasome and contributes directly to establishment of insulin resistance [74–76]. Supporting this notion, Ehses et al. treated type 2 diabetic Goto-Kakizaki rats with IL-1 receptor antagonist and observed an improvement in insulin sensitivity and glucose tolerance [77]. M1 macrophages also produce tumor necrosis factor alpha (TNF-α) [78,79]. TNF-α acts in cells within the adipose tissue and in non-adipose tissues to inhibit the tyrosine phosphorylation of IRS1 and therefore its activation [80,81]. Moreover, it modifies the pattern of adipocyte differentiation [82,83] while inducing lipolysis, which in turn increases the levels of FFAs and creates a "pro-inflammatory vicious cycle" [84,85]. In addition to causing lipotoxicity, as mentioned before, FFAs stimulate the synthesis of pro-inflammatory cytokines through the toll-like receptor-4 (TLR4) pathway [86,87]. IL-6 is also involved in the pathophysiology of obesity, but its role is more complex. It is

increased in adipose tissue and in circulation with obesity [88,89], and *in vitro* studies using adipocytes or hepatocytes chronically exposed with high levels of IL-6 show that this cytokine impairs insulin signaling [90–92]. However, transient or acute increases in IL-6 levels in healthy or type 2 diabetic patients, either by exogenous infusion or exercise, have been associated with beneficial effects, which include increased insulin sensitivity and improved glucose uptake [93–95]. Moreover, while brown adipose tissue (BAT) transplantation from a wild type donor mouse to a wild type recipient mouse improves glucose tolerance, insulin sensitivity, and decreases fat mass, when BAT isolated from a IL-6 knockout mouse is used for the transplantation these effects are lost [96]. Indeed, the period of exposure and the source of IL-6 determine its effects. While an acute increase can be beneficial, chronic exposure (as in obesity) is often deleterious [97].

Sustained cellular exposure to energetic substrates such as FFAs and glucose, in addition to systemic inflammation, also modifies the redox state of the cell and induces oxidative stress. During obesity, antioxidants enzymes [*e.g.* superoxide dismutase (SOD) and glutathione peroxidase (GPX)] cannot cope with the accumulation of reactive oxygen species (ROS) [*e.g.* superoxide (O_2-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-)] [98,99], particularly in the mitochondria [100,101]. Furthermore, TNF-α stimulates the activity of NADPH oxidase enzymes exacerbating the generation of superoxide [102]. Chronic exposure to ROS alters the expression of glucose transporters and impairs insulin-stimulated glucose uptake [103]. Interestingly, rats fed a high-fat diet are not insulin resistant when administered with the exogenous antioxidant SS31 [104,105]. In contrast, antioxidant administration (a combination of vitamin C and E) blunts the induction of an endogenous antioxidant response and the amelioration of parameters of insulin sensitivity when healthy, non-obese people are subjected to exercise [106].

Changes in the metabolic status of the adipocyte also affect the production and secretion of adipocyte-derived factors often named adipokines. Many adipokines have been described, including the cytokines mentioned above, but two adipocyte-specific molecules are worth citing: leptin and adiponectin [107]. Leptin was the first identified adipokine. Its coding gene (*Lep* or *ob*) was found to create a phenotype of massive obesity and infertility when mutated in homozygosis in mice [108]. Leptin is secreted by adipocytes in response to a positive energy balance, and acts primarily in the brain to inhibit food intake and promote energy expenditure [109,110]. Furthermore, leptin plays a role in immunity, energy portioning and lipid storage, as well as bone homeostasis [111]. Adiponectin is also expressed exclusively by adipocytes and acts as an anti-diabetic, cardioprotective adipokine. Adiponectin levels are extremely high in circulation (7–10 mg/L) and weight loss reduces these levels [112]. In general, adiponectin acts to improve whole body glucose homeostasis and lipid handling [107]. Adiponectin can also reduce inflammation and it is thought to be beneficial against the metabolic syndrome [107]. However, under certain conditions, adiponectin can hamper osteoblast proliferation and decrease bone mass, which can be detrimental [113].

Together, these studies evidence a complex, yet fundamental role of fatty acids, adipokines and ROS in the etiopathogenesis of metabolic diseases, reinforcing the notion that these molecules act to maintain organismal homeostasis and are required for normal physiology, but can be harmful when in excess.

3. Different types of fat

Fat is a simplistic name for a rather complex tissue that exhibits heterogeneous morphology, contains many different cell types, shows distinct functions, and localizes in all compartments of the body. The characteristic unit of the adipose tissue is the adipocyte – a cell that is specialized in storing triglycerides. In addition to adipocytes, the adipose tissue hosts stem cells, preadipocytes, fibroblasts, endothelial cells, macrophages, and other immune system cells [114]. The adipose

tissue has been historically classified in two sub-classes: white (WAT) and brown (BAT). This classification is based on morphological and molecular signatures that take into account cell structure, color, localization, vascularization, gene expression and function [115].

Adipocytes in WAT are composed by a single large unilocular lipid droplet in the cytoplasm and a peripheral nucleus [116]. The vascular network of WAT is dense, providing enough substrate and oxygen delivery and facilitating the access of hormones, adipokines and other signaling molecules [117]. In humans, WAT depots are located in between visceral organs (vWAT; *e.g.* epicardial, mesenteric, omental, retroperitoneal, and gonadal depots), and in the subcutaneous compartment (sWAT; *e.g.* abdominal, gluteal, and femoral depots) [116]. Rodents have a similar pattern of WAT distribution with slight differences [118]. As mentioned before, vWAT differs from sWAT in several aspects despite being both categorized as WAT. For example, in sWAT, lipolysis is more efficiently inhibited by insulin, while the vWAT displays a great lipolytic response to catecholamines and lower response to insulin [119–121]. Furthermore, vWAT produces and releases more of the pro-inflammatory molecules that are associated with insulin resistance and T2D [88,122,123]. It also expresses angiotensinogen – a precursor of angiotensin II - providing a mechanistic link to cardiovascular disease [124]. On the other hand, sWAT shows a more plastic, intermediate phenotype that confers it vWAT-like or BAT-like characteristics depending on the condition [125,126]. This aspect will be discussed later in this section.

Undoubtedly, one of the main functions of WAT is to store energy and mobilize nutrients in periods of negative energy balance. In addition, WAT has many other important roles: i) protecting organs such as eyes, gut and body parts such as heels, pads and gluteus from mechanical stress; ii) conferring insulation and thermoregulation [127]; iii) protecting the organism from lipotoxicity [128]; iv) being a major reservoir of mesenchymal stem cells [129] and immune system cells (*e.g.* macrophages and T cells) [130]; and v) functioning as an important endocrine organ [117]. WAT undergoes massive expansion and contraction in response to chronic alterations in energy balance, accounting for as little as 5% of the body mass in extremely lean athletes [131] or as much as 65% of the body mass in obese individuals [132], corresponding to the largest tissue of the body. Moreover, in most mammals, the WAT can completely regenerate itself following lipectomy [133–135]. This striking degree of plasticity is unique among the organs of adult mammals. At the cellular level, adipose tissue expansion is driven by both hypertrophy and hyperplasia of adipocytes [136–138]. Even in nonexpanding fat, the pool of adipocytes frequently renews itself to compensate for adipocyte death, with approximately 10% of adipocytes renewed annually in humans and 1–5% of adipocytes being replaced each day in mice [139,140]. This is thought to be mainly accounted for by *de novo* adipocyte differentiation of a pool of committed adipocyte precursors (preadipocytes) existing within the adipose tissue.

In contrast to WAT, BAT is specialized in burning calories to produce heat. Brown adipocytes contain multiple lipid droplets (multilocular), display a large number of mitochondria with high respiration rates, and uniquely express uncoupling protein 1 (UCP1) - a transmembrane protein that dissipates heat by uncoupling the respiratory chain and allowing for substrate oxidation with low ATP production rate [141–146]. BAT is highly vascularized and innervated [147]. This innervation is important to the activation of a thermogenic program that involves catecholamine signaling, nutrient mobilization and activation of UCP1 by FFA [148]. In rodents, BAT concentrates mainly in an interscapular depot, but can also be found in smaller fat pads in other anatomical regions (such as perirenal and perivascular) or within the skeletal muscle [146]. In humans, the existence of BAT was described for the first time in 1902 by Shinkishi Hatai [149]. The BAT described by Hatai was located under the sternocleidomastoid and trapezius muscles and ran laterally and in parallel to the neck (Hatai, 1902). Later on, Juliet Heaton (1972) observed the presence of BAT in

adult humans – "it is localized in the neck, along the spinal cord, particularly in the para-aortic area, around the heart and infradiaphragmatic depots in the perirenal area"[150]. She added that during the first decade of life there is a wide distribution of active brown fat, but this distribution disappears gradually with age. More recently, discoveries showed that adult humans maintain an active pool of brown adipocytes located around the supra-clavicular and cervical regions of the body [151–160].

In both rodents and humans, adipocytes with brown characteristics can also be found within WAT (particularly in sWAT) in response to cold exposure, beta-adrenergic stimulation, exercise or caloric restriction [146,158,161–164]. Like classic (or preformed) brown adipocytes, these cells express UCP1, exhibit multilocular lipid droplets, and produce large amounts of heat. Due to their inducible/recruitable characteristics and their distinct developmental origin, these adipocytes are often distinguished from the other types by the name of inducible brown, brite (brown-in-white) or beige adipocytes.

The expression of UCP1 confers to brown and beige adipocytes the unique capacity of dissipating more heat per gram of tissue than any other cell in the body of a mammal [165–167], contributing to nearly 50% of the total oxygen consumption of a rat in the cold [168]. Ucp1 knockout mice develop obesity even under thermoneutrality due to impairment of diet-induced thermogenesis [169]. In humans, studies demonstrate that BAT-mediated cold activation increases energy expenditure by up to 28% [170–173] and diet-induced thermogenesis by 32% in young men [174]. It is also estimated that 50–100 mL of BAT can increase energy expenditure by 150–300 kcal a day in cold exposed healthy men [173]. Interestingly, the amount of functional BAT or beige fat in adult humans and rodents is inversely correlated with adiposity and age, which raises the possibility of promoting brown adipogenesis to prolong metabolic healthspan and prevent obesity [146,157,175–178].

UCP1–expressing adipocytes are also a "metabolic sink" for glucose and triglycerides, as they are responsible for clearing up to 75% and 50% of the total glucose and triglycerides from circulation in cold exposed mice [179,180]. Although still debatable, recent studies have demonstrated that BAT activation in humans can contribute to the clearance of glucose from the circulation [reviewed by [179]]. These findings point to the potential of activating and/or recruiting brown or beige adipocytes to induce energy expenditure and improve glucose control. In practice, this could be achieved by the recruitment of newly formed UCP1-expressing cells from adipogenic precursor cells or by the induction of UCP1 expression in differentiated adipocytes. Both mechanisms have been shown to effectively induce energy expenditure and limit weight gain in mice when stimulated by pharmacological or genetic interventions [181,182].

The functional identity of UCP1-expressing adipocytes is determined by both cell autonomous and cell non-autonomous mechanisms. Transcriptional regulators such as PRDM16 (PR domain containing 16), PGC1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha), and C/EBPβ (CCAAT/enhancer-binding protein beta) [183–186] are among the players required for the commitment and differentiation of brown or beige cells. Cold exposure, exercise, cancer cachexia, caloric restriction, or a rich social and physical environment are among the environmental cues that promote brown/beige fat activation and/or recruitment in mammals [161,162,184,187,188]. These conditions affect the expression of key transcriptional and post-transcriptional regulators in preadipocytes or in differentiated adipocytes, pushing these cells towards the activation of a brown-like gene expression signature, which in turn leads to UCP1 expression, mitochondrial biogenesis and energy dissipation. Some of these external cues are determined by endocrine function, i.e. by hormones or metabolites that are secreted in the circulation or locally, such as catecholamines, fibroblast growth factors (FGF), bone morphogenetic proteins (BMP), growth/differentiation factor 5 (GDF5), natriuretic peptides, prostaglandins, vascular endothelial growth factor (VEGF),

and β-aminoisobutyric acid [reviewed by [179]]. For instance, the thermogenic effects of exercise have been linked to the recruitment of beige adipocytes by circulating molecules such as irisin, IL-6 and meteorin-like [161,189,190]. Some tumors also secrete molecules like IL-6 and PTHrP to induce beige adipocyte recruitment in WAT, a phenomenon that leads to cancer cachexia [187,191]. Interestingly, the appearance of beige adipocytes in WAT after cold exposure or exercise requires the involvement of eosinophils and M2 macrophages, placing the immune system as a key regulator of adipocyte fate [189,192].

The developmental origin of precursor cells also plays a role in adipocyte functional determination [193–196]. In a groundbreaking study, Seale et al., 2008 demonstrated that brown but not white adipocytes arise from progenitor cells expressing Myf5 (myogenic factor 5), sharing a common precursor lineage with myoblasts [197]. Moreover, they found that the transcription regulator PRDM16 is essential for brown fat fate determination [197]. Indeed, different fat depots have different precursors with intrinsic characteristics that confer phenotypical differences to the adipose tissue [196,198,199], but these characteristics are not sufficient to ultimately determine the phenotype of the adipocyte upon differentiation. For example, white adipocytes located at the dorsal-anterior region in mice also derive from Myf5 progenitors [200,201]. Differences in adipocyte characteristics can even be determined after differentiation. Rosenwald et al., 2013 showed that white adipocytes within sWAT have a bi-potential to be white or brown depending on the stimulus [126]. They also revealed that beige adipocytes rapidly acquire white-like characteristics upon removal of external stimuli without passing through an intermediate precursor stage [126,202]. Understanding the mechanisms underlying the functional heterogeneity of adipocytes and fat depots has been a major goal of the field. Only by seeking this goal we will be able to manipulate fat cells to help people with metabolic diseases to better handle substrates and adjust their energy balance. Small non-coding RNAs (sncRNAs) appear as essential molecules in this context and therefore will be explored in details during this Review.

4. Small non-coding RNAs (sncRNAs)

The central dogma of molecular biology postulates that the genetic information contained in the DNA is transcribed into messenger molecules (e.g. messenger RNA - mRNA), which are in turn translated into proteins that exert function [203,204]. This affirmation is not untruthful but is rather incomplete. The discovery of an abundant class of regulatory non-coding RNAs (ncRNAs) opened too many exceptions to the dogma and revolutionized molecular biology as we know it [205,206].

SncRNAs is a sub-class of ncRNAs with maximum length of 199-nt and is further classified into at least 25 different types of molecules based on length, structure, precursor, processing machinery, organism expression, tissue expression and function [207] (Table 1). Most sncRNAs are involved in fine tuning gene expression by interacting with target mRNA or with proteins involved in mRNA translation [208,209], and in some cases, they can interact with the chromatin to cause genomic rearrangements or epigenetic modifications [210–214].

Despite the wide variety of sncRNAs and their function in the cell, the literature has largely focused on the role of sncRNAs in RNA interference (RNAi) - a process where sncRNA molecules inhibit gene expression and/or translation by targeting mRNAs [215]. The process of RNA-mediated silencing was first observed in experiments using plants and viruses, where scientists found transcriptional inhibition by exogenous antisense RNA [216–218]. Later on, elegant experiments performed by Craig Mello, Andrew Fire and colleagues identified the mechanisms underlying such phenomenon [219]. In brief, they found that injection of C. elegans with double-stranded RNA (dsRNA) efficiently silences endogenous genes that share complementary sequences with the exogenous RNA. Remarkably, the effect was found to be transgenerational and not to occur when single stranded mRNA or

Table 1

Summary of types of sncRNAs with potential or described function across the animal kingdom. (?), function not well defined.

Name	Abbrev	Class	Length (nt)	Function	Ref
C/D snoRNA-derived RNA snRNA	C/D sdRNA	snRNA	17–19, 27	Post-transcriptional gene repression, processing of pre-rRNA	[352,353]
Centromere repeat-associated sRNA	crasiRNA	chRNA	34–42	Heterochromatin formation	[354,207]
Double-strand break induced sRNA	diRNA	DSB	21	DNA double-strand break repair	[355–357]
Endogenous small interfering RNA	endo-siRNA	siRNA	21–26	Inhibition of retrotransposition, pos-transcriptional gene repression	[358,359]
Exogenous small interfering RNA	exo-siRNA	siRNA	21	Gene silencing, anti-viral	[360,361]
H/ACA snoRNA-derived RNA snRNA	H/ACA sdRNA	snRNA	20–24	Post-transcriptional gene repression, alternative splicing	[362–364]
microRNA	miRNA	miRNA	19–22	Post-transcriptional gene repression	[221,365]
miRNA-offset RNAs	moRNA	miRNA	19–22	Post-transcriptional gene repression	[367,368]
Promoter-associated small RNAs	PASRs		18–200	Transcriptional regulation	[369,370]
Piwi interacting RNA or repeat-associated siRNA	piRNA or rasiRNA	piRNA	25–33	Germline post-transcriptional gene repression, transposon regulation, chromatin modification	[230,242,371]
Pyknon	Pyknon	miRNA/siRNA	16–22	Post-transcriptional gene repression	[372]
Small nuclear RNA or small Cajal-body RNA	snRNA or scaRNA		128	Pseudouridylation of U2 spliceosomal RNA (?)	[374,375]
Splice site-associated small RNA	spliRNA	CAsRNA	17–18	Involved in regulating epigenomic modifications and transcription (?)	[376]
Stem-bulge RNA	sbRNA	Y RNA	67–133	RNA quality control, chromosomal replication	[377,378]
Small NF90-associated RNA	SNAR			Remain to be established	[379,380]
Small vault RNA	svRNA	vRNA	22–37	Post-transcriptional gene regulation	[381,382]
Telomere-specific sRNA	tel-sRNA	chrRNA	24	Epigenetic regulation	[385]
Transcription initiation sRNA	tiRNA	CAsRNA	18	Transcriptional regulation	[369,386]
tRNA derived halves	tRH	tDR	30–35	Post-transcriptional gene repression	[387,388]
tRNA-derived fragments	tRF	tDR	20	Post-transcriptional gene repression, translational repression	[389,390]
Transcriptional start-site-miRNA	TSS-miRNA	miRNA	20–90	Post-transcriptional gene repression	[369,391]
Unusually small RNA	usRNA	miRNA	15–17	Post-transcriptional gene regulation	[392]
Y RNA-derived small RNAs Y RNA	yDR	Y RNA	24–25, 30	Ro-RNA particle to control RNA quality (?) and chromosomal replication	[393,394]

antisense RNA is administered. The biological and technological implications of these findings were immediately noticed and studies were designed to understand the role of ncRNAs in essentially all the tree of life. This was further motivated by the identification of endogenous ncRNAs with potential regulatory roles. In 1993, studies from the Ruvkun and the Ambros labs independently identified *lin-4* as a tiny ncRNA that controlled developmental timing in *C. elegans* [220,221]. In a series of genetic and biochemical experiments, they found that the locus of *lin-4* coded for two small RNAs of approximately 22 and 61 nt, in which the sequence of the former was contained in the latter. They also identified in these molecules complementary sequences to the 3′-untranslated region (3'-UTR) of the *lin-14* mRNA – a gene that was known to genetically interact with *lin-4* [220,221]. The authors predicted that *lin-4* could regulate *lin-14* translation through RNA-RNA interaction and anticipated a mechanism that would be characterized only several years later. Pushed by the discovery of RNAi as an endogenous and evolutionarily conserved biological process in the late 1990s, Ambros, Ruvkun and many others went on to identify similar tiny ncRNAs in different species across kingdoms and named them microRNAs (miRNAs) [220–224].

As of today, many other endogenous sncRNAs with silencing activity have been identified and functionally characterized. Didactically, the most studied ones compose three sub-classes: i) piwi-RNAs (piRNA); ii) endogenous small interference RNAs (endo-siRNAs) and iii) miRNAs. The first group is found in both invertebrates and vertebrates, where they are essential for fertility [225–229]. They are considered the longest sncRNA of the three classes, ranging from 25 to 33 nt in length [230]. PiRNAs can be found in the nucleus, where they regulate epigenetic and post-transcriptional gene silencing of retrotransposons [231,232], or in the cytoplasm, where they target the 3'-UTR of target mRNAs to promote decay [233]. Despite elegant studies in the topic [234,235], the mechanism of piRNA biogenesis in most species is not fully understood. What is clear is that this mechanism differs from the canonical processing of siRNAs and miRNAs since it is DICER-independent (see more below) [236].

Instead, piRNAs interact with PIWI-clade proteins, which determine their processing and mediate gene silencing [230,236].

Endo-siRNAs are found mainly in plants and lower animals that do not have antibody or cell-mediated immunity (*e.g.* fungi, insects and nematodes), where their main function is to serve as a defense against viral infections [237,238]. Nonetheless, endo-siRNAs can also regulate gene expression in mouse oocytes or stem cells [239,240]. They derive from long dsRNA molecules such as intergenic repetitive elements, pseudogenes, and endo-siRNA clusters [241]. Endo-siRNA processing varies slightly across different species, but in all of them the long dsRNA is processed by the type III endoribonuclease DICER to generate 20–25 bp siRNA duplexes that are unwinded and loaded into the RNA-induced silencing complex (RISC) where proteins of the Argonaute family (AGO) are located [241]. The RISC complex loaded with the siRNA is guided to its target mRNA by perfect sequence complementarity, therefore directing the mRNA to degradation [241].

MiRNAs are the most studied class of sncRNAs. They differ in many aspects from piRNAs and endo-siRNAs, like in their tendency to be conserved in sequence across the evolutionary spectrum and their function as essential regulatory molecules in most cell types [207,242]. They are similar in length and share some components of the processing/silencing machinery with siRNAs, particularly at the dicing step and downstream, but also differ in many ways [207,242]. There are nuances when comparing the miRNA processing pathway across organisms, although in general this process is highly conserved. To avoid confusion, we will describe here the mammalian pathway unless stated otherwise (Fig. 1).

MiRNA primary transcripts (pri-miRNAs) are classified as intergenic or intronic according to the genomic location where they are expressed. Intergenic pri-miRNAs are transcribed as independent transcription units, whereas intronic pri-miRNAs are processed from introns of their host transcripts [243,244]. In general, pri-miRNAs are transcribed by the RNA polymerase II and are 5'-capped and 3'-polyadenylated [245]. In some cases, like for the cluster of miRNAs expressed in the human chromosome 19, a common pri-miRNA
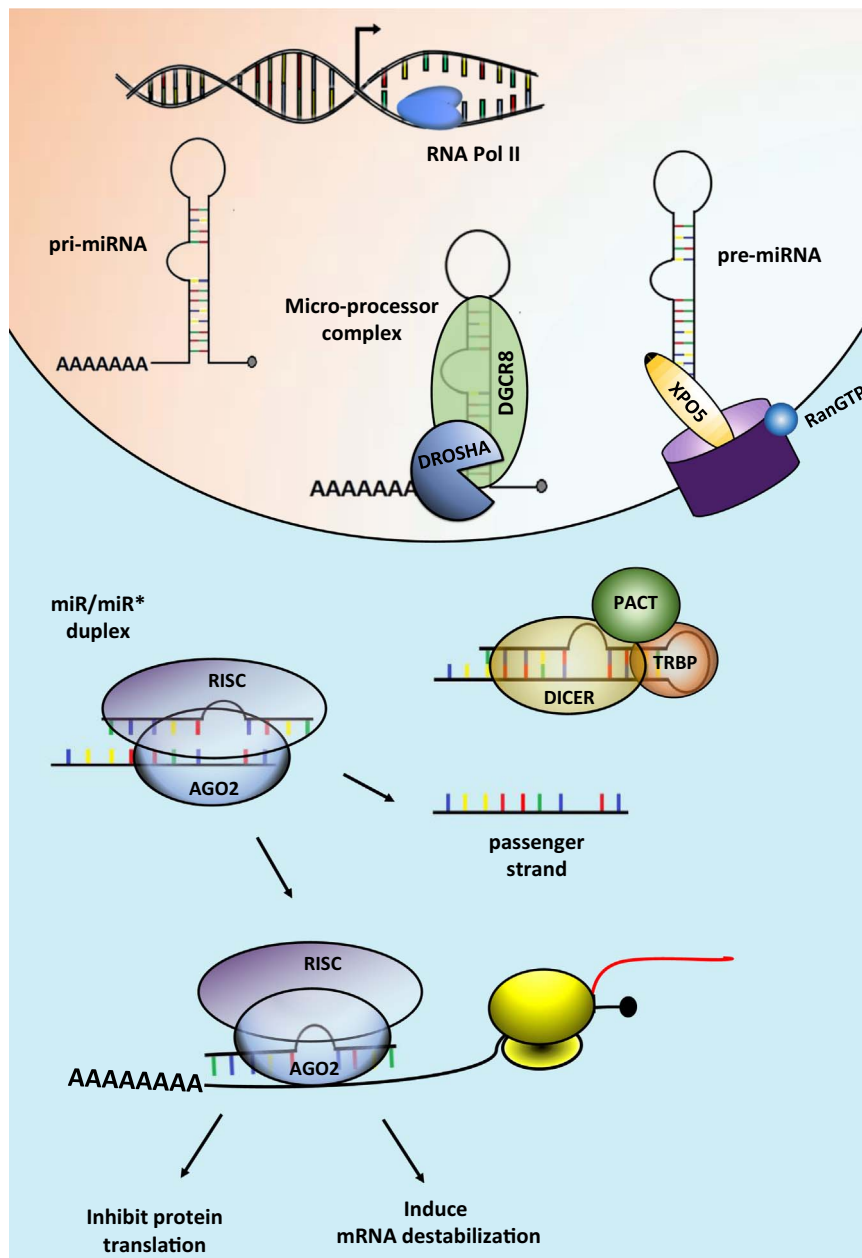
Fig. 1. *The miRNA processing pathway.* miRNA genes are transcribed by RNA polymerase II (RNA Pol II) or III into primary miRNAs (pri-miRNA). In the nucleus, the pri-miRNA is cleaved by the microprocessor complex, comprised by the RNase III enzyme DROSHA and its partner DGCR8. This step will originate a precursor hairpin (pre-miRNA), which is exported to the cytoplasm by Exportin-5 (XPO5). In the cytoplasm, DICER and its partners TRBP and PACT cleaves the pre-miRNA hairpin into mature miRNA (19–22 nt). The mature miRNA will be incorporated with Argonaute 2 (AGO2) into the RNA-induced silencing complex (RISC) and will guide the RISC to silence the target mRNA by destabilizing it and/or inhibiting its translation.

element is transcribed by RNA polymerase class III [246]. Pri-miRNAs are characterized by a hairpin structure that is recognized and processed by the microprocessing complex in the nucleus. This complex contains DROSHA, a type III endoribonuclease that cleaves the two strands of the hairpin at the stem approximately 22 bp away from the terminal loop, and DiGeorge syndrome critical region protein 8 (DGCR8), a dsRNA-binding protein that ensures efficient and accurate processing by DROSHA [245]. This step gives rise to pre-miRNAs, which are exported to the cytoplasm by exportin proteins (*e.g.* XPO5 or Exportin-5) - a class of RanGTP-dependent dsRNA-binding proteins [247,248].

In the cytoplasm, DICER processes the pre-miRNA at the loop to generate miRNA duplexes of approximately 22 bp with two base overhang on the 3'end [249,250]. To do so accurately, DICER interacts with the HIV-1 TAR RNA binding protein (TRBP) and the Protein

ACTivator of the interferon-induced protein kinase (PACT) [251]. The miRNA duplex is then unwinded and loaded into the RISC, where one of the strands binds to the target mRNA (the guide strand) and mediate gene silencing. The other strand is called passenger (or miRNA*) and is often degraded, although some miRNAs* are capable of down-regulating different [252] or the same gene as the guide miRNA strand [253]. What determines strand preference and whether a strand will be functionally active or be degraded is still a matter of study, but evidence demonstrates that the thermodynamic characteristic of the duplex and the position of the stem-loop in the pre-miRNA play a role in this process [250,254–256]. Moreover, differences in the precursor transcript structure (*e.g.* mismatches, bulges, symmetrical and asymmetrical internal loops) determine the length diversity among miRNAs, often called isomiRs [257–259].

Once loaded in the RISC, the miRNA recognizes the target mRNA

using 6–8 complementary nucleotides (the seed region) at its 5'-end, leading to translation inhibition and in some cases mRNA destabilization [260]. Recently though, Broughton et al. observed that sequences away from the seed are necessary for proper miRNA-target interaction in *C. elegans* [261]. Due to the short length of the seed and imperfect targeting mechanism, one miRNA can fine tune the expression of hundreds of targets, while one target can be regulated by multiple miRNAs in a combinatorial manner [262]. Thus, miRNAs take part in complex gene network regulation, where different members of the same network can be commonly targeted by one or more miRNAs [263–265]. Thousands of miRNAs have been identified in humans [262], some ubiquitously expressed and some enriched in a cell- or time-enriched fashion [266–268]. Altogether, miRNA-mediated silencing constitutes one of the most important mechanisms of gene expression regulation of animals [269]. It is predicted that about 30% of the human mRNA is targeted by miRNAs [262]. Not surprisingly, miRNAs are involved in essentially all biological processes and dysregulation of miRNA expression is linked to a wide variety of human diseases [270]. At the cellular level, miRNAs appear to confer cell robustness in response to different environmental stimuli [271,272]. Thus, miRNA dysregulation impairs cell fate decisions [273,274], affects metabolic processes [275], and increases stress sensitivity [271]. In adult tissues, this often results in dysfunction and disease [276,277].

5. sncRNAs in the adipose tissue

The adipose tissue expresses a wide variety of sncRNAs with relatively high abundance. In a mouse differentiated adipocyte cell line, 68% of the sncRNA pool consist of miRNAs (our unpublished data). Given the enrichment of miRNAs in adipocytes and since the vast majority of the data on sncRNAs in adipose tissue refers to these molecules, they will be the focus of this Review. Nevertheless, we will discuss the potential role of other sncRNA species later on in topic 7.

When over 600 miRNAs were measured in mouse inguinal sWAT using RT-qPCR, 265 were detected with relative abundance [271]. Each one of these individual miRNAs is expected to exhibit its own mode of regulation that can be impacted by disease or metabolic alterations, as we will give examples in this Review. At the genomic level, the miRNA genes can undergo epigenetic modifications resulting in aberrant pri-miRNA expression through DNA methylation or histone modification [278]. Transcription factors can also influence pri-miRNA expression [279], and this form of regulation helps setting tissue specificity and pattern expression during development. For example, the transcription factor p53 stimulates pri-miR-34 expression by directly binding to its promoter region [280], while ERα inhibits pri-miR-221 serving as a transcriptional repressor [281]. Furthermore, there are critical nodes of regulation that affect the expression of a broader range of miRNAs and can have a wider impact. One such node is the miRNA processing pathway.

We and others have demonstrated that the expression of components of the miRNA processing pathway in adipose tissue is highly susceptible to regulation, particularly at the level of DICER (dicing step) [178,271]. We found that aging leads to down-regulation of approximately 50% of all miRNAs expressed in sWAT of mice – a phenomenon that is linked to a parallel down-regulation of Dicer in adipocytes and preadipocytes, but not in other adipose tissue cells or non-adipose tissues [271]. General down-regulation of miRNAs and decreased *DICER1* levels with aging are also found in human pre-adipocytes [271]. In humans, *DICER1* levels are lower in subcutaneous fat depots of patients with partial lipodystrophy when compared to healthy individuals, and this is associated with "whitening" and dysfunction of the tissue [39,271]. Moreover, obesity and progeria have a global impact on miRNA expression in mouse BAT [178]. In conditions of diet- and genetically-induced obesity, these changes are associated with down-regulation of Dicer [178]. Importantly, a modest

reduction in BAT Dicer levels (25%) results in down-regulation of more than 75% of the most highly expressed miRNAs in the tissue [178], indicating that Dicer is a rate-limiting enzyme in miRNA processing in brown fat. These results evidence an important aspect of the miRNA processing pathway in the adipose tissue – the fact that minor expression changes in its components exert a major impact on miRNA expression. Nonetheless, not all the miRNAs are sensitive to this type of regulation and some are in one fat depot but not in others. This is consistent with the notion that each miRNA has its own mode of regulation, and context may determine whether changes in the miRNA processing machinery will affect the expression of the mature miRNA.

6. Adipose tissue miRNAs and adipose tissue function

Evidence that miRNAs are important for adipose tissue function came from studies using gain- or loss-of-function approaches to manipulate components of the miRNA processing machinery or individual miRNAs. Initial studies using tissue culture indicated a necessary role for miRNAs in preadipocyte differentiation and adipocyte fate determination [282–284]. The *in vivo* experiments came to support this notion and also demonstrate that adipocyte miRNAs play an important role in organismal homeostasis. For example, adipocyte-specific Dicer knockout mice (AdicerKO) exhibit a phenotype that resembles humans with partial lipodystrophy, *i.e.* atrophy of WAT, hypertrophy and "whitening" of BAT, insulin resistance, dyslipidemia, impaired resistance to oxidative stress and premature aging [274,285]. Furthermore, these mice are refractory to many of the beneficial effects exerted by caloric restriction, such as improved oxidative metabolism and increased mitochondrial biogenesis in adipocytes, reduced inflammation in adipose tissue, and increased whole body insulin sensitivity [285]. Similarly, adipocyte-specific DGCR8 knockout mice (ADGCR8KO) show alterations in fat distribution, "whitening" of BAT, and insulin resistance [286]. Thus, miRNA deficiency leads to impairment of basic functions of adipocytes, such as differentiation and fate, metabolism, and signaling. This impacts on adipose tissue characteristics, cellularity and size, which in turn leads to abnormal fat accumulation and results in the metabolic syndrome. As much as it was found that global changes in miRNA biogenesis are important for adipose tissue function in a rather complex manner in the context of the metabolic syndrome (see discussion below in topic 8), the contribution of individual miRNAs to the phenotype is undeniable. We will therefore describe the mode of regulation and function of specific miRNAs in a discrete manner, as they were first identified. Some examples will be provided in the text below, but a comprehensive compilation of miRNAs with reported function in the adipose tissue is presented in Table 2. Didactically, we divided miRNAs in three topics, according to their function: a) adipogenesis, b) metabolism and c) signaling. We believe that these three cellular processes are hallmarks of a properly functional adipose tissue, and defects in any one of these processes can lead to metabolic diseases (Fig. 2).

6.1. miRNAs involved in adipogenesis

The adipogenic process is very tightly regulated [139,287]. The total number of adipocytes is determined in the period from childhood to adolescence and is maintained constant during adulthood, in lean and obese individuals [139,287]. Nonetheless, in 8.3 years, approximately 50% of the pool of adipocytes of an adult human is renewed [139,287]. Adipocyte turnover is sustained by adipose-derived stem cells (ADSCs) and preadipocytes [288]. ADSCs are similar to stem cells derived from the bone marrow, *i.e.* they are both multipotent and can differentiate into a variety of cell types, such as osteoblasts, chondrocytes, myocytes, and adipocytes (white or brown) [288–290]. Preadipocytes are one step down in the commitment path to the adipogenic lineage, and given their high proliferation rate are usually the main source of newly formed adipocytes [291].

Table 2

Compilation of studies that implicate miRNAs in adipose tissue biology. Up, up-regulated. Down, down-regulated. Co, co-regulated. ND, not determined. A, 6.1. miRNAs involved in adipogenesis. B, 6.2. miRNAs and adipocyte metabolism. C, 6.3. miRNAs involved in signaling.

miRNA	Expression changes				Function				Ref
	Species	Direction	Condition	Tissue	Topic	Phenotypic Association	Relation	Target Gene	
miR-100	Human	Down	T2D	WAT and blood	A	Adipogenesis	Induces	IGF1R and MTOR	[395]
miR-103	Mouse	Up/down/down	Adipocyte differentiation/obesity/TNF-α incubation	3T3-L1 and isolated adipocytes	A	Adipogenesis	Induces	ND	[396]
miR-124	Mouse	Up	Insulin incubation	3T3-L1	A	Adipogenesis	Induces	Dlx5	[397]
miR-130	Human/mouse	Down/down	Adipocyte differentiation/obesity	Primary preadipocytes, 3T3-L1 and sWAT	A	Adipogenesis	Inhibits	PPARγ	[398]
miR-138	Human	Down	Adipocyte differentiation	ADSCs	A	Adipogenesis	Inhibits	EID-1	[399]
miR-140	Mouse	–	–	–	A	Adipogenesis	Induces	Neat1 (positive regulation)	[400]
miR-143	Mouse	Up/down/down	Adipocyte differentiation/obesity/TNF-α incubation	3T3-L1 and isolated adipocytes	A	Adipogenesis	Induces	ND	[396]
miR-143	Mouse/human	Up	Obesity/Adipocyte differentiation	vWAT/white preadipocytes	A	Adipogenesis	Induces	Erk5	[401,402]
miR-145	Pig	Up	Adipocyte differentiation	Primary preadipocytes	A	Adipogenesis	Inhibits	IRS1	[403]
miR-146a-5p	Pig	Up	TNF-α incubation	Adipocytes	A	Adipogenesis	Inhibits	IR	[343]
miR-146b	Mouse	Up	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Induces	SIRT1	[404]
miR-17	Pig	Up	Adipocyte differentiation	BMSCs	A	Adipogenesis	Induces	ND	[405]
miR-17~92	Mouse	Up	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Induces	Rb2/p130	[310]
miR-181a	Pig	Up	Obesity	Adipose tissue	A	Adipogenesis	Induces	TNF	[406]
miR-195a	Mouse	Down	Adipocyte differentiation	C3H10T1/2 cells and 3T3-L1	A	Adipogenesis	Inhibits	Zfp423	[407]
miR-199a	Mouse	Down	Adipocyte transdifferentiation	C2C12 myoblasts	A	Adipogenesis	Inhibits	Fatp1	[408]
miR-204-5p	Human	Up	Adipocyte differentiation	ADSCs	A	Adipogenesis	Induces	DVL3	[409]
miR-21	Human	Up	Adipocyte differentiation	ADSCs	A	Adipogenesis	Induces	TGFBR2	[304]
miR-210	Mouse	Up	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Induces	Tcf7l2	[410]
miR-21a-5p	Mouse	Down	Bisphenol A incubation	3T3-L1	A	Adipogenesis	Inhibits	Map2k3	[411]
miR-224-5p	Mouse	Up	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Inhibits	EGR2 and ACSL4	[412]
miR-23a	Mouse	Down	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Inhibits	Stat1	[413]
miR-24	Mouse	Up	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Induces	Mapk7	[414]
miR-27	Mouse	Down/up	Adipocyte differentiation/obesity	ADSCs	A	Adipogenesis	Inhibits	PPARγ and C/EBPalpha	[415,416]
miR-30	Human	Up	Adipocyte differentiation	ADSCs	A	Adipogenesis	Induces	RUNX2	[296]
miR-302a	Mouse	Down	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Inhibits	Pparγ	[417]
miR-33b	Human	Up	Adipocyte differentiation	SGBS cells and preadipocytes	A	Adipogenesis	Inhibits	HMGA2	[418]
miR-363	Rat	Not changed	Adipocyte differentiation	ADSCs	A	Adipogenesis	Inhibits	E2F3	[311]
miR-369-5p	Human	Down	Adipocyte differentiation	MSCs	A	Adipogenesis	Inhibits	FABP4	[419]
miR-375	Mouse	Up	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Induces	ND	[317]
miR-448	Mouse	Up	Adipocyte differentiation	3T3-L1	A	Adipogenesis	Inhibits	Klf5	[420]
miR-519d	Human	Up	Obesity	sWAT	A	Adipogenesis	Induces	PPARA	[421]
miR-540	Rat	Down	Adipocyte differentiation	ADSCs	A	Adipogenesis	Inhibits	Pparγ	[422]
miR-125b-5p	Human	Up	Adipocyte differentiation	SGBS preadipocytes	A	Adipogenesis	Inhibits	MMP11	[423]
miR-1275	Human	Down	Obesity/adipocyte differentiation	MSCs and vWAT	A	Adipogenesis	Inhibits	ELK1	[424,425]
miR-324-3p	Human	Up	Obesity/Adipocyte differentiation	Adipose tissue, MSCs and 3T3-L1	A	Adipogenesis	Induces	CTBP2	[426]
miR-301a	Mouse	Down	Inflammation	3T3-L1 and blood	A	Adipogenesis and inflammation	Inhibits	Pparγ	[427]
miR-128	Human	Up/down	Adipocyte/osteoblast differentiation	MSCs	A	Adipogenesis/osteogenesis	Induces/inhibits	ND	[428]
miR-140-5p	Mouse	Up	Obesity/Adipocyte differentiation	BMSCs, 3T3-L1, and WAT	A	Adipogenesis/osteogenesis	Induces/inhibits	Tgfbr1	[429]
miR-17-5p/106a	Human	Up	Adipocyte differentiation	ADSCs	A	Adipogenesis/osteogenesis	Induce/inhibit	BMP2	[297]
miR-188	Human/mouse	Up	Aging	BMSCs	A	Adipogenesis/osteogenesis	Induces/inhibits	Hdac9 and Rictor	[430]
miR-194	Mouse	Down/up	Adipocyte/osteoblast differentiation	BMSCs and C3H10T1/2 cells	A	Adipogenesis/osteogenesis	Inhibits/induces	Nr2f2	[431]
miR-204/211	Mouse	Up	Adipocyte differentiation	C3H10T1/2 cells	A	Adipogenesis/osteogenesis	Induces/inhibits	RUNX2	[295]

Table 2 (continued)

miRNA	Species	Direction	Condition	Topic	Phenotypic Association	Relation	Target Gene	Ref
		Expression changes		**Function**				
miR-22	Human	Down/up	Adipocyte/osteoblast differentiation	A	Adipogenesis/osteogenesis	Inhibits/induces	HDAC6	[432]
miR-223	Mouse	Up/down	Adipocyte/osteoblast differentiation	A	Adipogenesis/osteogenesis	Induces/inhibits	Fgfr2	[433]
miR-3077-5p	Mouse	Up	Osteoporosis	A	Adipogenesis/osteogenesis	Induces/inhibits	Runx2	[434]
miR-637	Human	Up/down	Adipocyte/osteoblast differentiation	A	Adipogenesis/osteogenesis	Induces/inhibits	OSX	[435]
miR-705	Mouse	Up	Osteoporosis	A	Adipogenesis/osteogenesis	Induces/inhibits	Hoxa10	[434]
miR-145a-5p	Mouse	Down	Obesity	A	Adipogenesis/proliferation	Inhibits/induces	ND	[436]
miR-146b	Human/mouse	Up	Adipocyte differentiation/obesity	A	Adipogenesis/proliferation	Induces/inhibits	KLF7	[437]
miR-196a	Mouse/human	Up	Cold and β-adrenergic stimulation	A	Beige adipogenesis	Induces	Hoxc8	[438]
miR-149-3p	Mouse	Up/down	Fasting/cold	A	Beige adipogenesis and thermogenesis	Inhibits	Prdm16	[439]
miR-193b/ 365	Mouse	Up	BAT vs. WAT	A	Brown adipogenesis	Induces	Runx1t1	[300]
miR-106b/ 93	Mouse	Up	Obesity	A	Brown adipogenesis	Inhibits	ND	[440]
miR-182/203	Mouse	Up	Brown adipogenesis/BAT vs. WAT	A	Brown adipogenesis	Induces	Insig−1 and Pdgfra	[286]
miR-346	Mouse	Down	Dicer KO	A	Brown adipogenesis	Induces	ND	[274]
miR-362	Mouse	Down	Dicer KO	A	Brown adipogenesis	Induces	ND	[274]
miR-378	Human	Up	Eicosapentaenoic acid incubation	A	Brown adipogenesis	Induces	ND	[441]
miR-328	Mouse	Up/down/down	Brown adipogenesis/aging/obesity	A	Brown adipogenesis/myogenesis	Induces/inhibits	Bace1	[178]
miR-133	Mouse	Down	Cold	A	Brown/beige adipogenesis	Inhibits	Prdm16	[305]
miR-155	Mouse	Down/up	Brown adipogenesis/TGFβ incubation	A	Brown/beige adipogenesis	Inhibits	Cebpb	[442]
miR-27	Mouse	Down	Cold and brown adipogenesis	A	Brown/beige adipogenesis	Inhibits	Prdm16, Ppara, Creb, and Pgc1β	[443]
miR-455	Mouse/ human	Up	BAT vs. WAT/cold/BMP7	A	Brown/beige adipogenesis	Induces	Hif1an, Runx1t1 and Necdin	[444]
miR-34a	Mouse	Up	Obesity	A	Brown/beige adipogenesis and thermogenesis	Inhibits	Fgfr1	[345]
let-7	Mouse	Up	Adipocyte differentiation	A	Mitotic clonal expansion and terminal differentiation	Inhibits	Hmga2	[312]
miR-192*	Human	Down	Obesity	A, B	Adipogenesis and lipid accumulation	Inhibits	SCD and ALDH3A2	[445]
miR-34a	Mouse	Up	Obesity/Adipocyte differentiation	A, B	Fat accumulation	Inhibits	ND	[346]
miR-155	Mouse/ human	Up	Obesity and TNF-α incubation	A, C	Adipogenesis	Inhibits	Pparγ	[339]
miR-193b	Human	–	–	B	Adiponectin production	Induces	NFYA	[333,303]
miR-378*/378	Mouse	Co	Ppargc1b coexpression	B	Adiposity/oxidative metabolism	Induces/inhibits	Crat and Med13	[326]
miR-378	Mouse	Up	BAT vs. WAT	B	BAT expansion	Induces	Pde1b	[446]
miR-223	Human	Up	Insulin resistance	B	GLUT4 expression	Inhibits	GLUT4	[335]
miR-93	Human	Up	Insulin resistance, PCOS	B	GLUT4 expression	Inhibits	GLUT4	[319]
miR-10b	Human	Up	Abdominal vs. gluteofemoral	B	Lipolysis	Induces	ND	[447]
miR-124a	Mouse	Down	Fasting	B	Lipolysis	Inhibits	Atgl	[448]
miR-378	Mouse	–	–	B	Lipolysis and energy expenditure	Induces	Akt1 and Scd1	[449]
miR-200b/a/ 429	Mouse	–	–	B	Lipolysis and energy expenditure on HFD	Induces	Eps8, Lhfp, Glis2 and Rps6kb1	[450]
miR-520	Human	Down	Obesity	B	RAB11A expression	Inhibits	RAB11A	[451]
miR-141	Human	Down	Obesity	B	YWHAG expression	Inhibits	YWHAG	[451]
miR-92a	Human	Down	BAT activation	C	BAT activity	Inversely correlates	ND	[349]
miR-221	Human	Up/down	Obesity/adipocyte differentiation	C	BMI	Directly correlates	ADIPOR1 and ETS1	[344,302]
let-7a/d	Human	Down	Obesity	C	CCL2 secretion	Inhibits	ND	[303]
miR-126	Human	Down	Obesity	C	CCL2 secretion	Inhibits	CCL2	[303]

(continued on next page)

Table 2 (*continued*)

| miRNA | Species | Expression changes | | Function | | | | | | |
		Direction	Condition	Tissue	Topic	Phenotypic Association	Relation	Target Gene	Ref
miR-193b	Human	Down	Obesity	sWAT	C	CCL2 secretion	Inhibits	ND	[303]
miR-146b-5p	Human	Down	Obesity	Monocytes	C	Inflammation	Inhibits	*ND*	[336]
miR-146b-5p	Human	Up	Adipocyte differentiation/TNF-α or IL–6 incubation	vHPA	C	Inflammation	Directly correlates	ND	[452]
miR-883b-5p	Mouse/human	Up/down	Adiponectin/obesity	WAT	C	Inflammation	Inhibits	ND	[453]
miR-26b	Mouse/human	Down	Obesity and insulin resistance	vWAT and preadipocytes	C	Insulin signaling	Induces	*Pten*	[454]
miR-320	Mouse	Up	Insulin resistance	3T3-L1	C	Insulin signaling	Inhibits	ND	[455]
miR-26a	Human	Down	Obesity	sWAT	C	Lipolysis and secretion of CCL2 and TNF-α	Inhibits	ND	[303,456]
miR-29b	Human	Down	Obesity/4-HNE	sWAT and ADSCs	C	TNF-α expression	Inhibits	ND	[457]

The pro-adipogenic transcription factors peroxisome proliferator-activated receptor-γ (PPARγ) and CCAAT-enhancer-binding proteins (C/EBPs), as well as the anti-adipogenic signaling cascade triggered by Wnt, BMPs, transforming growth factor beta (TGFβ) or hedgehog participate in the regulation of ADSC commitment into the adipose linage and control adipocyte differentiation [292]. Differentiation and maturation of healthy, functional adipocytes involve the activation of intricate molecular pathways organized in three subsequent steps: i) *commitment*, the stage where ADSCs differentiate into adipocyte precursor cells (including preadipocytes); ii) *mitotic clonal expansion*, which in tissue culture is triggered by confluence and growth arrest; and iii) *terminal differentiation* [293,294]. During the first step of commitment, ADSCs can give rise to two different precursors: a) one that will differentiate into white or beige adipocytes and another that will differentiate into brown adipocytes or myocytes [127]. All these steps have been shown to be regulated by miRNAs.

For instance, a study by Hung et al. showed that incubation of a mesenchymal stem cell line (C3H10T1/2) with adipocyte differentiation medium up-regulates miR-204/211 and down-regulates Runt-related transcription factor 2 (Runx2), an osteogenic transcriptional factor stimulated by Wnt and the BMP pathways. Additionally, over-expression of miR-204 in C3H10T1/2 suppresses *Runx2* expression and stimulates the commitment of these cells to the adipose lineage [295]. In a parallel study, Zaragosi et al. showed that the miR-30 family is highly up-regulated during adipogenesis of ADSCs and revealed that miR-30a and miR-30d can also target *Runx2*, which in turn favors adipocyte differentiation [296]. Similarly, miR-17-5p and miR-106a promote adipogenesis and inhibit osteogenesis of ADSCs by targeting the pro-osteogenic protein BMP2 [297]. Interestingly, adipose tissue miR-17-5p expression is inversely correlated with markers of hyper-glycemia and insulin resistance in humans [298,299].

MiRNAs can also silence myogenic genes to favor adipogenesis. The miR-193b-365 cluster is highly expressed in BAT, where it induces common myogenic/adipogenic precursors to commit and differentiate into brown adipocytes [300]. The miR-193b-365 cluster is induced by PRDM16 [300], a transcriptional coregulator that is necessary for brown/beige adipocyte differentiation [301]. Once up-regulated, miR-193b targets the pro-myogenic factors *Cdon* and *Igfbp5*, inhibiting myogenesis and promoting adipogenesis [300]. More recently, miR-193b (and the seed-related miR-328) was shown to target the β-secretase Bace1 to promote brown adipogenesis [178]. Importantly, miR-193b is down-regulated in subcutaneous adipose tissue of obese individuals [299,302,303].

In addition to inhibiting osteogenic or myogenic commitment to favor adipocyte differentiation, miRNAs can directly silence inhibitors of adipogenesis. For example, miR-21 expression is up-regulated during adipogenic differentiation of ADSCs, which leads to silencing of TGFβ receptor-2, hence suppressing the adipogenic inhibition caused by TGFβ [304]. Moreover, miRNAs can inhibit adipogenesis. MiR-133 targets PRDM16 mRNA in muscle stem cells therefore inhibiting commitment to the brown adipocyte lineage and allowing myogenesis [305]. Thus, miRNAs interact with signaling pathways and transcriptional regulators that are normally involved in developmental control to determine commitment and differentiation of ADSCs.

Once committed, adipogenic precursor cells need to proliferate. During cell proliferation, transition from G1 to S is regulated by the retinoblastoma protein (Rb)/E2F pathway [306]. Cyclin kinase-dependent hyperphosphorylation of Rb releases E2F to transcriptionally activate genes involved in the S phase [306]. The transition between these two phases of the cell cycle is extremely important and dictates whether preadipocytes will in fact reach terminal differentiation [307,308]. During early differentiation, after proliferation and growth-arrest, preadipocytes need to reentry the cell cycle and undergo approximately two rounds of divisions (*i.e.* mitotic clonal expansion) in order to differentiate [307,309]. Like the other steps in adipogenesis, miRNAs also control mitotic expansion.
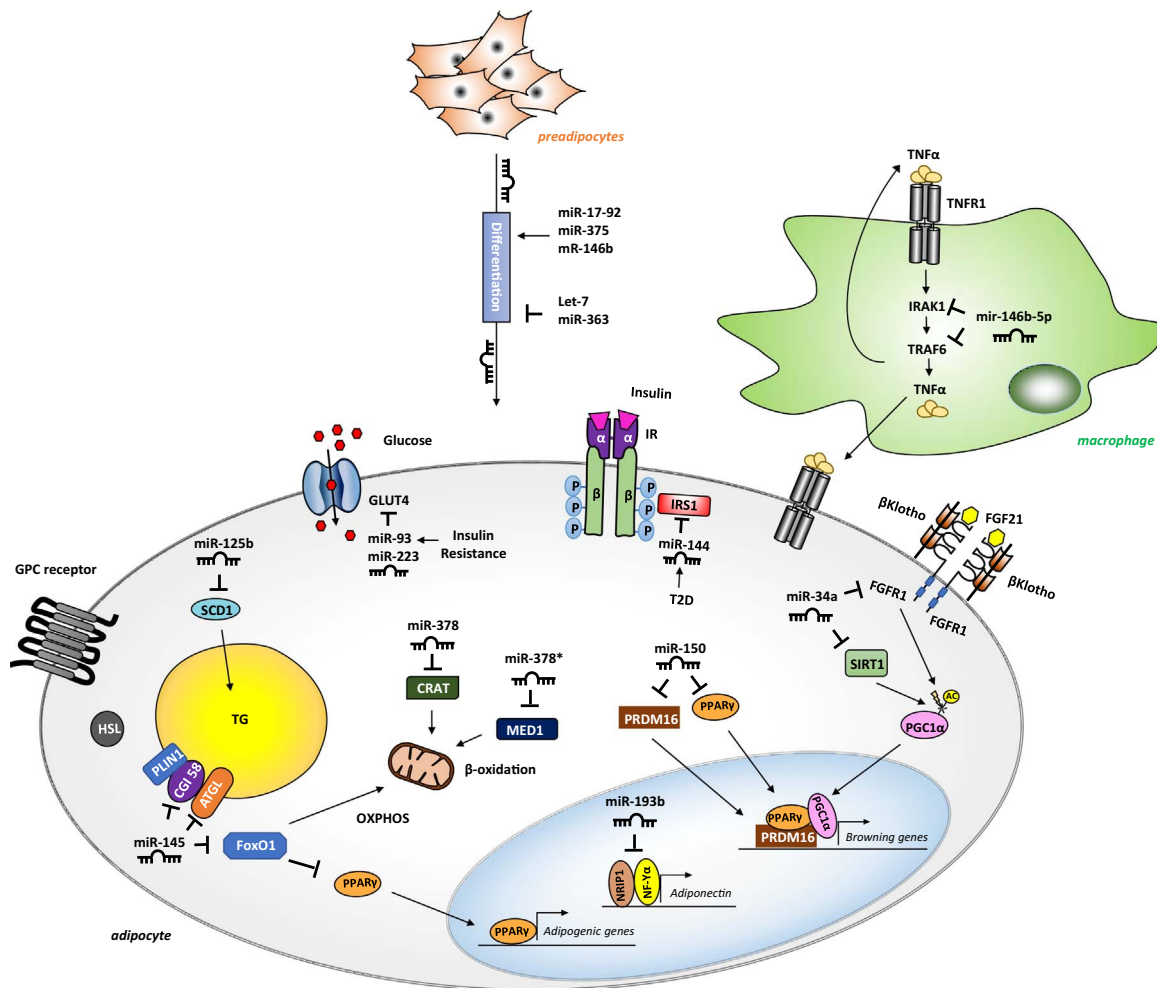
Fig. 2. *Adipocyte function and examples of miRNA-mediated regulation.* MiRNAs are involved in different steps of adipocyte maturation, metabolism and signaling. They regulate adipogenesis (positively: miR-17–92, miR375 and miR-146b; negatively: let-7 and miR-363), glucose uptake (miR-93 and miR-223), lipolysis and β-oxidation (miR-145), triglyceride synthesis (miR-125b), insulin signaling (miR-144), browning (miR-150 and miR-34a), adiponectin synthesis (miR-193b) and inflammation (miR-146b-5p in macrophages).

Wang et al. demonstrated that the expression of the miR-17–92 cluster matches with the time of reentry and exit of the cell cycle. They observed that the miR-17–92 cluster reaches its peak after one day of the adipogenic stimulus in 3T3-L1 preadipocytes, coinciding with the down-regulation of the retinoblastoma-like protein 2 (Rb2/p130) and inducing reentry in the cell cycle [310]. After this, the miR-17–92 cluster is down-regulated and Rb2/p130 expression is increased, exiting cells from the cell cycle for terminal differentiation [310]. In contrast, miRNAs such as the members of the let-7 family (which target the mRNA of high mobility group AT-hook2 protein HMGA2) and miR-363 (which targets E2F3 mRNA) inhibit mitotic clonal expansion and terminal differentiation of adipocytes [311,312].

Fat accumulation characterizes the final stage of adipogenesis. Once the fate of the adipocyte is determined, lipids start accumulating in response to growth factor signaling and a positive energy balance [313–315]. Insulin and PPARγ are the main drivers of adipogenesis at this step [316]. Among the downstream kinases activated by insulin, it is worth mentioning the extracellular signal-regulated kinase (ERK). Tight regulation of ERK is essential for adipocyte differentiation. Whereas activation of ERK during precursor cell proliferation is required for clonal expansion, activation of ERK at the final stages of differentiation inhibits PPARγ and abrogates adipocyte differentiation [315]. Consistent with this notion, miR-375 expression increases with 3T3-L1 adipocyte differentiation to promote lipid accumulation by suppressing ERK1/2 phosphorylation [317].

Taken these studies together, it is safe to affirm that miRNAs play a

role in different aspects of adipocyte development. Not surprisingly, changes in miRNAs involved with adipogenesis have been associated with different metabolic diseases. For example, Roldan et al. observed that miRNAs such as let-7c/d/e (which target HMGA2 and inhibit cell proliferation), miR-23b and mir-27b (which are Wnt activators and PPARγ and TGFβ/Smad repressors), and miR-320, miR-542-5p, miR-140, miR-143, and miR-661 (which are associated in different manners with adipocyte differentiation) are up-regulated in ADSCs of morbidly obese individuals compared to lean individuals [318].

6.2. miRNAs and adipocyte metabolism

Once the adipocyte is terminally differentiated, miRNAs can regulate basic metabolic functions of these cells, including glucose utilization, lipid turnover, and oxidative metabolism [299]. Adipocytes use a large portion of the available blood glucose to maintain their function, particularly brown adipocytes [179]. Chen et al. observed that miR-93 overexpression in adipocytes down-regulates the glucose transporter type 4 (GLUT4) - the main insulin-sensitive glucose transporter in these cells [319]. Importantly, miR-93 expression is higher in adipose tissue of non-obese patients with insulin resistance, and inversely correlates with GLUT4 levels in these individuals [319]. These changes in miRNA-mediated glucose transport capacity in adipose tissue can therefore contribute to the pathogenesis of insulin resistance.

Once taken up by adipocytes, glucose needs to be broken down to

feed the mitochondria with substrates for ATP generation. Little is known about the role of miRNAs in adipocyte glycolysis, but in other tissues the link between glucose utilization and specific miRNAs is well established [320,321,322]. Evidence that miRNAs control glycolysis in adipocytes comes from our study using the AdicerKO mice [285]. Adipocytes lacking Dicer induce anaerobic glycolysis even in conditions when oxidative metabolism is expected to be activated, *i.e.* during caloric restriction [285]. This phenotype is associated with adipocyte mitochondrial dysfunction and suggests that miRNAs are important in adipocytes to control the engagement of adequate metabolic pathways (*i.e.* oxidative vs. glycolytic) in response to changes in nutrient availability [285].

A defective capacity of adipocyte mitochondria to oxidize substrates has been associated with metabolic diseases [323]. The transcription co-activators of the PGC-1 family are key regulators of mitochondrial biogenesis, thermogenesis and glucose and fatty acid metabolism, and are preferentially expressed in tissues with relatively high mitochondrial content such as the BAT [324]. The pre-miR-378 hairpin resides within the first intron of the PCG-1β gene *(Ppargc1b)* and is co-expressed with the host gene in highly oxidative tissues, including the adipose tissue, where they counterbalance each other functions [325,326]. Consistent with a role in fat metabolism, miR-378/378* knockout mice are resistant to diet-induced obesity [326]. miR-378 and miR-378* target the mRNAs of carnitine O-acetyltransferase and MED13, respectively, two important proteins involved in beta-oxidation [326], and therefore inhibit oxidative metabolism.

In anabolic states, intermediates of glycolysis and the tricarboxylic acid (TCA) cycle also serve as building blocks for lipid synthesis [327]. In adipocytes, newly synthesized fatty acids, or FFAs coming from the circulation can be re-esterified into triglycerides for storage, in a process called lipogenesis [327]. A rate-limiting step in lipid synthesis is catalyzed by the stearoyl-CoA desaturase1 (SCD-1). SCD-1 mRNA is a target of miR-125b in mammals, and overexpression of this miRNA in adipocytes reduces triglyceride accumulation [328]. Interestingly, miR-125b is up-regulated in mouse subcutaneous adipose tissue in response to calorie restriction, and its overexpression in preadipocytes confers protection from oxidative stress-induced cell death [271].

One of the main functions of adipocytes is to break down triglycerides to mobilize FFAs and feed the organism in conditions of negative energy balance [327]. This process, called lipolysis, is co-ordinated by nutrient availability, hormones and, importantly, miRNAs [327]. Lin et al. showed that miR-145 control lipolysis rate in mouse adipocytes [329]. They studied KH-type splicing regulatory protein (KSRP) knockout mice [329], which lack an RNA-binding protein that controls the synthesis of a subclass of miRNAs, including miR-145 [330,331]. KSRP$^{-/-}$ mice display higher lipolysis rate in epididymal fat due to up-regulation of forkhead box protein O1 (FOXO1), comparative gene identification-58 (CGI58) and adipose triglyceride lipase (ATGL) [329]. Ectopic expression of miR-145 in 3T3-L1 adipocytes inhibits *Foxo1* and *Cgi58* mRNAs by direct targeting, and thus reduces lipolysis [329]. Using the same mouse model, Chou et al. noted that KSRP$^{-/-}$ mice are leaner due to "browning" of the inguinal sWAT [332]. They found that to be due to down-regulation of miR-150, which targets the mRNAs of PRDM16 and PPARγ [332].

6.3. miRNAs involved in signaling

The adipose tissue is a major site of endocrine regulation. Molecules secreted by the adipocytes and other adipose resident cells signal to the organism to control metabolic function and homeostasis [107]. On the other hand, adipocytes sense the levels of extracellular molecules that inform them of the energy status of the organism [107]. miRNAs control the expression of adipokines and components of signaling pathways, therefore contributing to intercellular communication. For example, adipose tissue miR-193b expression correlates with serum adiponectin levels in humans [333], and as previously mentioned, is

down-regulated in obese individuals [299,302,303]. MiR-193b controls adiponectin by targeting the mRNA of nuclear transcription factor Yα and potentially nuclear receptor interacting protein 1, which are negative regulators of this adipokine [333].

MiRNAs also regulate the crosstalk between adipocytes and immune cells within the adipose tissue. Zhuang et al. showed that miR-223 knockout mice are prone to high fat diet (HFD)-induced adipose tissue inflammation and exhibit systemic insulin resistance. They observed that macrophages from the miR-223$^{-/-}$ mice have a skewed profile towards the pro-inflammatory M1 type and concluded that miR-223 regulates macrophage polarization during obesity [334]. Interestingly, miR-223 expression in human sWAT positively correlates with insulin resistance and TNF-α exposure induces the expression of this miRNA by nearly 2-fold in human differentiated subcutaneous adipocytes [335]. Moreover, overexpression of miR-223 blocks insulin-stimulated glucose uptake and reduces GLUT4 expression in these cells [335]. MiR-146b-5p and miR-155 are two other examples of miRNAs involved with inflammation. MiR-146b-5p is decreased in monocytes from obese patients [336] and increased in adipocytes treated with TNF-α or IL-6 [337], while miR-155 expression levels correlate with the number of macrophages infiltrating human sWAT [298,299]. Consistent with a role in atherosclerosis, miR-155 loss-of-function intensifies the inflammatory response and the uptake of lipids by a macrophage cell line stimulated with oxidized low-density lipoprotein (LDL) [338,339,299]. In contrast, miRNAs can correlate with less inflammation. For instance, the levels of IL-6 in the serum of patients with non-alcoholic steatohepatitis negatively correlate with the adipose tissue expression of three miRNAs (namely miR-149, miR-574-3p, and miR-132) known to target IL-6 mRNA [340].

Some miRNAs are also potent regulators of growth factor signaling. Karolina et al. reported increased miR-144 expression in blood, liver, muscle, and adipose tissue of type 2 diabetic patients [341]. An inverse correlation between miR-144 and insulin receptor substrate 1 (IRS1) expression was observed by these authors [341]. Luciferase assays revealed that miR-144 targets the 3'-UTR of IRS1 mRNA and can therefore regulate insulin signaling [341]. MiR-139-5p also targets IRS1 in murine preadipocytes [342], while miR-146a-5p targets the mRNA of insulin receptor in primary porcine adipocytes [343]. Another miRNA that affects growth factor signaling to control adipose tissue function is miR-34a. MiR-34a is up-regulated in the subcutaneous fat depot of obese people [344] and inhibits beige and brown fat formation in obese mice partially by suppressing the FGF21 signaling pathway [345]. Inhibition of miR-34a in obese mice using systemic administration of lentivirus-expressing antisense miR-34a increases energy expenditure and induces thermogenic capacity in brown and epididymal adipose tissues [345]. In contrast, Lavery et al. showed that miR-34a knockout mice are more susceptible to weight gain under HFD and exhibit an altered macrophage phenotype [346]. It is worth mentioning that the strategies to knock out miR-34a were different between the two studies, indicating a time and/or tissue dependent function for miR-34a.

Finally, miRNAs themselves can act as signaling molecules. MiRNAs are carried in circulation by extracellular vesicles (*e.g.* exosomes) or associated with proteins (*e.g.* lipoproteins) [347]. Adipocytes are the main source of circulating miRNAs in mice (and likely in humans) and these adipocyte-secreted miRNAs can be taken up by other cells where they regulate target gene expression [348]. For instance, adipocyte-secreted miR-99b down-regulates FGF21 in liver [348]. Interestingly, BAT contributes more to the pool of circulating miRNAs than WAT [348], and this secretion is potentiated by beta-adrenergic stimulation and cold exposure [349]. Among the cold stimulated, brown fat secreted miRNAs, circulating levels of miR-92a negatively correlates with BAT activity both in mice and humans [349]. Interestingly, gastric bypass surgery in obese individuals affects the expression of 168 circulating, adipocyte-derived exosomal miRNAs, and components of the insulin signaling pathway are among the most

enriched targets of these differentially expressed miRNAs [350]. Importantly, the expression of ten of these miRNAs correlates with insulin resistance [350]. Hence, miRNAs can act in cell autonomous and non-autonomous manners to regulate adipose tissue function.

7. Perspectives on the role of sncRNAs in adipose tissue

Despite the recent advances, our understanding of how sncRNAs control adipose tissue function is still in its early stages. Publications in PubMed containing the keywords "microRNA" and "adipose" have grown exponentially in the last decade and sum 478 papers as of Dec 31st, 2016 – two thirds of them published in the last 3 years (data not shown). The universe of miRNAs expressed in fat is vast, and so are their targets and interactions. Thus, much more is expected to be unveiled about adipose tissue miRNAs. For what is worth concerning redox biology, almost nothing is known regarding adipose tissue miRNAs, except for indirect links and speculation. ROS down-regulates Dicer in murine preadipocytes and Dicer knockout preadipocytes and young AdicerKO mice are more susceptible to oxidative stress-induced mortality [271]. In contrast, Dicer overexpression in the *C. elegans* intestine (the analog of the mammalian adipose tissue) protects worms from oxidative stress [271]. These phenotypes are partially due to changes in the expression of the lin-4/miR-125 family [271]. The downstream targets of lin-4/miR-125 that confer protection from oxidative damage are yet to be found, and so is the mechanism of how ROS regulate Dicer expression. Indeed, the regulation of miRNA expression in adipose tissue is a fascinating topic for future studies. MiRNAs in adipose tissue are globally regulated by physiological stimuli in a rather unique manner. Dicer is a rate-limiting step in miRNA biogenesis in fat and its dynamic range of regulation is intriguing. Why would adipocytes need to change Dicer expression so dramatically under physiological conditions?

Perhaps the answer to this question relies on the recent discoveries that the adipose tissue is the main source of circulating miRNAs in the mouse and potentially humans. These findings opened up a whole new dimension to the topic. Are adipose-derived circulating miRNAs relevant for physiological control in mammals? It certainly does seem so based on the most recent studies. But which miRNAs contribute to the endocrine functions of the adipose tissue and how? These are questions that remain to be answered.

Finally, miRNAs consist of only 68% of the total sncRNA pool of a murine differentiated adipocyte cell line (our unpublished data). The remaining 32% have not been characterized. Except for one match related to a report of moRNA expression in pig adipose tissue [351] and excluding miRNAs, there is no paper in PubMed associating any of the sncRNAs listed in Table 1 and the adipose tissue. Unraveling this unexplored universe is a fascinating endeavor for future studies.

8. Conclusions

SncRNAs (represented here by the well characterized and abundant class of miRNAs) play a role in a complete range of cellular processes that contribute to adipose tissue function, *i.e.* adipogenesis, metabolism and signaling (Fig. 2). Impaired biogenesis of DICER-dependent sncRNAs (*e.g.* miRNAs, siRNAs) in adipocytes leads to alterations in these processes and results in features of the metabolic syndrome. DICER is a rate limiting protein in the miRNA biogenesis pathway in adipocytes, at least for the majority of the miRNAs expressed in these cells. Given the importance of miRNAs in adipose tissue, DICER up-regulation may represent a key mechanism to accelerate sncRNA production in conditions when these molecules are necessary (as the ones reviewed here). DICER up-regulation may not necessarily increase sncRNA expression, as each sncRNA has its own mode of regulation, but it will allow miRNAs to be expressed rapidly. This will confer a more robust (less noisy) response to stimuli that control, for instance, cell fate, substrate utilization and intercellular communica-

tion. More studies are necessary to determine all the pieces in this complex puzzle, and more importantly, to find strategies to target this pathway to minimize the suffering of patients with metabolic diseases.

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