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Are microRNAs the Molecular Link Between Metabolic Syndrome and Alzheimer's Disease?

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Abstract Alzheimer's disease (AD) is the most common cause of dementia in people over 65 years of age. At present, treatment options for AD address only its symptoms, and there are no available treatments for the prevention or delay of the disease process. Several preclinical and epidemiological studies have linked metabolic risk factors such as hypertension, obesity, dyslipidemia, and diabetes to the pathogenesis of AD. However, the molecular mechanisms that underlie this relationship are not fully understood. Considering that less than 1 % of cases of AD are attributable to genetic factors, the identification of new molecular targets linking metabolic risk factors to neuropathological processes is necessary for improving the diagnosis and treatment of AD. The dysregulation of microRNAs (miRNAs), small non-coding RNAs that regulate several biological processes, has been implicated in the development of different pathologies. In this review, we summarize some of the relevant evidence that points to the role of miRNAs in metabolic syndrome (MetS) and AD and propose that miRNAs may be a molecular link in the complex relationship between both diseases.

Keywords Alzheimer's disease · Metabolic syndrome · microRNA · Lifestyle

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Introduction

Alzheimer's disease (AD) is the most common type of dementia, in which the death or malfunction of neurons causes changes in memory, behavior, and cognition. In AD, this dysfunction results in an impaired ability to carry out such basic functions as walking and swallowing and is ultimately lethal [1]. At present, AD has no cure or preventive treatment [2, 3]. Late-onset AD (LOAD) occurs in individuals over the age of 65 and is reported in greater than 90 % of Alzheimer's cases [4]. Several of the risk factors associated with LOAD have been classified as genetic or non-genetic factors. The strongest genetic risk factor for AD is related to the apolipoprotein E (APOE) gene, which can confer an increased probability of developing LOAD. The presence of the ε4 allele of the APOE gene not only dose-dependently increases the risk for AD but also lowers the age of onset [5]. However, many factors other than genetics contribute to the development of AD.

Preclinical evidence with experimental animal models suggests that the relationship between cardiometabolic risk factor and AD is robust and clear, including spontaneous-induced experimental type 2 diabetes (T2DM), leading to AD-like pathology [6–8], induction of hypertension by angiotensin II infusion, and promoting AD lesions [9], hypercholesterolemia [10], and obesity [11]. On the other hand, clinical and epidemiological evidence indicates that the clusters of metabolic syndrome (MetS) such as hypertension [12], dyslipidemia [13], obesity [14], and T2DM [15] in a separate manner

promote development of mild cognitive impairment (MCI), dementia, and AD, even considering some contradictions between studies [16], given the difficulties of the homogenization of the sample populations.

Early work indicates that T2DM is associated with a two- to threefold increase in the relative risk for AD, independent of the risk for vascular dementia [17]. In a global manner, patients with MCI and MetS had a higher risk of progression to dementia compared with patients with MCI alone [18–20]. A growing body of epidemiological evidence has allowed the development of a pathophysiological model termed "metabolic-cognitive syndrome" that aims to understand the complex relationship between metabolic disorders and cognitive disturbances and thereby generate therapeutic strategies against MetS that could help prevent or ameliorate the cognitive impairment observed in patients with AD or other cognitive disturbances [18, 21–23]. Despite a wealth of evidence supporting this relationship, the molecular mechanisms underlying metabolic-cognitive syndrome are not fully understood.

Considering that less than 1 % of cases of AD are attributable to genetic factors [1], the identification of new molecular targets linking metabolic risk factors to neuropathological processes is necessary for improving the diagnosis and treatment of the disease. As AD and MetS are multifactorial pathologies, multiple mechanisms have been proposed in base to the etiological overlap observed. In this context, it has been suggested a role for inflammation in the etiology of MCI and AD [24]. Oxidative stress could also precede the onset of clinical and pathological AD symptoms and MetS [25]. Amyloidosis is another interesting hypothesis which is common to diabetes mellitus and AD [26]. The amylin aggregates observed in the pancreas are morphologically similar to the amyloid fibrils of AD, and both present neurotoxicity [27] and contains APOE [28].

We previously discussed how deregulation in several signaling pathway, including leptin, angiotensin, Wnt, and others, could explain the interesting crossroad between MetS and AD [29]; Now, we want to expand this work view including the role of microRNAs (miRNAs) as a molecular link between MetS and AD.

miRNAs are small endogenous RNAs, approximately 22 nucleotides (nt) in length, that have emerged as important post-transcriptional regulators of different protein-coding genes [30, 31]. The study of miRNAs is relatively new, but these small molecules have an important impact in most biological processes. The development of techniques such as gene amplification, gene sequencing, and microarray analysis has allowed the expression profiles of a large number of miRNAs in human diseases, including metabolic disorders [32], obesity [33], T2DM [34], hypertension [35], and cardiovascular disease [36], to be established. Because several of those "metabolic miRNAs" have been shown to be altered in AD patients (Table 1), it is possible that miRNAs might constitute a molecular link that explains the functional relationship between metabolic risk factors and the development of AD. Additionally, a series of preclinical studies show that the metabolic signals produced in peripheral tissues like insulin or leptin regulate the expression of miRNAs in several brain regions, and the metabolic distress observed in MetS alters the expression of miRNAs related to human AD.

Importantly, the understanding that the risk factors associated to MetS and AD are lifestyle dependent, such as poor nutrition and a lack of exercise, and that miRNAs respond to changes in diet and physical activity could open new therapeutic avenues to the prevention and diagnosis of AD.

MicroRNA Biogenesis and Function

Precursor forms of miRNAs, which are hundreds of nt in length, are processed to reach their mature forms, which in turn are subsequently loaded in the miRNA-induced silencing complex (miRISC). This finely orchestrated process may be subject to regulation at different levels to control the function of miRNAs and gene expression [38–40]. We review some basics of the miRNA biogenetic pathway and discuss the unique functional modalities of miRNAs that can help to understand their possible role as a molecular link between MetS and AD.

miRNA Transcription

The transcription of miRNA generates a primary miRNA transcript (pri-miRNA), from either individual genes containing their own promoters (intergenic) or intragenically from spliced portions of protein-coding genes (intronic or exonic). The transcription of intragenic miRNAs is dependent on the regulatory elements of the host gene promoter. For that reason, intronic miRNAs are normally co-transcribed with their host gene, and pri-miRNA results from the splicing of the host gene transcript precursor. In many cases, this co-transcription is related to the cooperative function of the gene host products and the miRNA [41, 42]. In other cases, the co-transcription results in the silencing of the host in a negative feedback loop [43].

miRNAs are almost exclusively transcribed by RNA polymerase II (RNA Pol II) and their expression is thus subject to the same types of transcriptional control as other cellular genes including RNA Pol II-associated transcription factors and epigenetic regulators. One of the best described examples of transcription factors that regulate miRNA expression corresponds to the p53 tumor suppressor protein that regulates the expression of stress response genes including miR-34 family as the most prevalent p53-induced miRNAs [44]. It is very interesting to note that p53/miR-34 axes are downregulated in cancer [45] but are upregulated in neuropathologies including AD [46–48] which is consistent with the inverse occurrence of both diseases [49–53]. In the same logic, the axis p53/miR-34 has been described to be upregulated in clusters of MetS such

Table 1 Human miRNAs associated to AD and component of MetS

Alzheimer	T2dm	Hypertension	Obesity	Fatty Liver
hsa-mir-21	hsa-mir-21	hsa-mir-21	hsa-mir-21	hsa-mir-21
hsa-mir-103a-1	hsa-mir-103a-1	hsa-mir-103a-1		
hsa-mir-103a-2	hsa-mir-103a-2	hsa-mir-103a-2		
hsa-mir-17		hsa-mir-17	hsa-mir-17	
hsa-mir-107	hsa-mir-107		hsa-mir-107	
hsa-mir-20a		hsa-mir-20a		
hsa-mir-146a	hsa-mir-146a			
hsa-mir-144	hsa-mir-144			
	hsa-mir-143		hsa-mir-143	
		hsa-mir-122		hsa-mir-122
hsa-mir-106b	hsa-mir-486	hsa-mir-1-1	hsa-mir-132	hsa-mir-451
hsa-mir-101-1	hsa-mir-20b	hsa-mir-1-2	hsa-mir-18a	hsa-mir-10b
hsa-mir-590	hsa-mir-24-1	hsa-mir-133a-1	hsa-mir-30e	hsa-mir-34a
hsa-mir-128-1	hsa-mir-24-2	hsa-mir-133a-2	hsa-mir-146b	
hsa-mir-128-2	hsa-mir-15a	hsa-mir-155	hsa-mir-221	
hsa-mir-137	hsa-mir-126	Hsa-mir-208b		
hsa-mir-181c	hsa-mir-191	hsa-mir-204		
hsa-mir-9-1	hsa-mir-197	hsa-mir-637		
hsa-mir-9-2	hsa-mir-223	hsa-mir-133a-1		
hsa-mir-9-3	hsa-mir-320a	hsa-mir-637		
hsa-mir-137	hsa-mir-483	hsa-mir-296		
hsa-mir-181c	hsa-mir-99a	Hsa-mir-133b		
hsa-mir-29a		hsa-let-7e		
hsa-mir-29b-1		hsa-mir-328		
hsa-mir-29b-2		hsa-mir-150		
hsa-mir-124-1		hsa-mir-424		
hsa-mir-124-2		hsa-mir-503		
hsa-mir-124-3		hsa-mir-145		
hsa-mir-125b-1				
hsa-mir-125b-2				
hsa-mir-195				
hsa-mir-153-1				
hsa-mir-153-2				
hsa-mir-34c				

miRNAs associated to each disease were obtained from HMDD v2.0 which is a database that curated experiment-supported evidence for human microRNA (miRNA) and disease associations [37]. In red, miR-21, which is associated to AD and all the diseases of MetS. In blue, miRNAs associated to AD and other two components of MetS. In green, miRNAs associated to AD and one component of MetS. In yellow, miRNAs associate between components of MetS but not with AD. In white, miRNAs without association between AD and MetS

as non-alcoholic fatty liver disease (NAFLD) [54] which support the idea that regulation of miRNAs is part of the pathological mechanism that associates the occurrence of MetS and AD (Fig. 1).

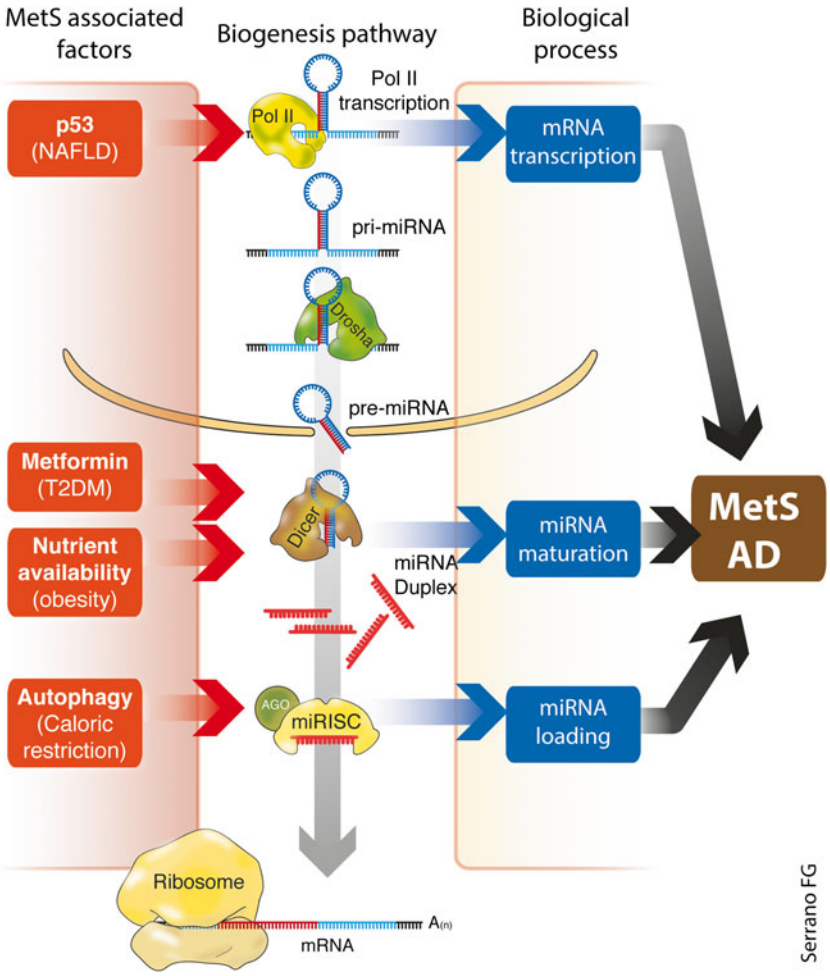


Fig. 1 MiRNA biogenesis and their regulation with MetS-associated factors. The miRNA biogenesis pathway produces pri-miRNA transcripts by RNA polymerase II (*Pol II*) from miRNA genes. Next, the Drosha microprocessor complex processes pri-miRNA transcripts into pre-miRNAs. Pre-miRNAs are exported from the nucleus via exportin 5 and subsequently cleaved by Dicer, and the miRNA/miRNA* duplex is unwound via Argonaute (*AGO*) and loaded into the miRNA-induced silencing complex (*miRISC*). The binding of target mRNAs to miRNAs in RISC is followed by the inhibition of translation and/or mRNA degradation. The miRNA biogenesis pathway may be subject to regulation at different levels to control the function of miRNAs and thus gene expression. In the figure, we show some examples of environmental (external) factors related to MetS that control the expression of miRNA levels through different mechanisms. At the transcription level, the transcription factor p53 controls the expression of miR-34 cluster in response to a diet that generates non-alcoholic fatty liver disease (*NAFLD*). At the processing level, metabolic interventions like fasting or obesity regulate Dicer expression, thereby increasing the processing and generation of mature miRNAs. Finally, at the miRNA loading level, metabolic alterations that regulate the autophagy process affect the stability of AGO and the transcriptional repression of several miRNA targets. The biological consequence or output of this regulation is related to MetS and possibly to AD progression

miRNA Processing

For most miRNAs, the processing of pri-miRNAs to the mature form involves the sequential cropping of nuclear and cytosolic complexes in a process known as the canonical pathway. Once transcribed, the pri-miRNA are recognized by the nuclear microprocessor complex, which generates a shorter stem loop precursor-miRNA (pre-miRNA) that is ~60–70-nt long [55, 56]. The microprocessor complex is composed of two core proteins, DiGeorge Syndrome Critical Region 8 (DGCR8), which contains a RNA-binding domain that recognizes the pri-miRNA and binds to Drosha, a class II RNase III enzyme that cleaves double-stranded RNA in a staggered manner and creates a 2-nt overhang on the 3′ end of its products [57]. This overhang is recognized by exportin 5, which transports the pre-miRNA to the cytoplasm in a GTP-dependent fashion [58–60]. In the cytoplasm, the pre-miRNA is processed by Dicer, a class III RNase III, into a ~22-nt-long miRNA/*miRNA duplex [61].

Any modulation of the miRNA processing proteins has a significant effect on the levels of miRNA produced by the canonical pathway and, consequently, on the biological processes in which they are involved. For example, mice deficient in Dicer do not survive beyond E8.5 [62], and tissue-specific Dicer deletion results in developmental defects in several organs, including the brain [63–66]. Conditional knockout (KO)

of Dicer in the brain of adult mice results in a progressive neurodegeneration, reduced brain size, neuroinflammation, apoptosis, hyperphosphorylation of endogenous tau protein, and impaired dendritic spine morphology similar to that observed in AD brains [63, 67, 68]. A recent study shows that the expression of Dicer in the hypothalamus is regulated by nutrient availability (Fig. 1). Fasting caused specific upregulation of Dicer mRNA levels, and obesity generates a decrease in Dicer expression [69]. Importantly, conditional deletion of Dicer in hypothalamic neurons resulted in obesity, hyperleptinemia, defective glucose metabolism, and alterations in the pituitary–adrenal axis which was paralleled by a neuron degenerative process [69].

These evidences suggest that any external factor that has the ability to regulate Dicer-dependent miRNA expression has the potential to affect neuronal pathological process associated to MetS and AD (Fig. 1).

miRISC Assembly

To control the expression of their targets, the 22-nt-long miRNA/*miRNA duplex needs to be associated with several proteins that conform the miRISC, where it is separated into its mature strand and its complementary strand, the latter of which is degraded in most cases [70]. The core proteins of the miRISC are Dicer, Argonaute (AGO), and TAR RNA binding protein (TRBP), a double-stranded RNA binding protein that is required for the recruitment of AGO to the miRNA bound by Dicer [71]. AGO proteins function as effectors by recruiting factors that induce translational repression, mRNA deadenylation, and mRNA decay [72].

Altering the expression or the activity of different components of miRISC alters miRNA-mediated silencing without affecting miRNA expression or processing. For example, in primary rat hippocampal neurons, AGO2 silencing generates an increase in the protein levels of the amyloid precursor protein (APP). However, no significant alteration of APP mRNA was observed, suggesting that the APP translation is regulated by an AGO2/miRNA pathway [73].

The stability and activity of AGO are regulated by several modifications including prolyl 4-hydroxylation, phosphorylation, poly(ADP-ribosyl)ation, proteasome-mediated degradation, and autophagy [74]. In particular, it has been reported that the homeostatic turnover of unloaded AGO proteins (miRNA-free) is mediated by autophagy [75, 76] which corresponds to a catabolic mechanism that involves degradation of unnecessary or dysfunctional cellular components through the actions of lysosomes [77]. Inhibition of autophagy at the level of autophagosome biogenesis generates an increase in the unloaded AGO levels with a decrease in the transcriptional repression of several miRNA targets [76].

These evidences have implications for human diseases linked to misregulated autophagy and miRNA levels, like MetS [78, 79] and AD [80, 81] (Fig. 1).

miRNA Target Recognition and Functional Modalities

In the miRISC, miRNA functions as a guide by base pairing with its target mRNAs. The initial bases of the miRNA sequence play an important role in defining the mRNA targets. Bases 2–7, known as the miRNA "seed," are responsible for the definition of target specificity [82]. With few exceptions, most of the miRNA recognition elements (MRE) are located within the 3′UTR of the targeted mRNA [31].

Considering that the miRNA–mRNA binding site is short, each miRNA has the potential to regulate many genes as its targets, while one gene may be targeted by many miRNAs [31]. In this sense, the same miRNA could regulate different biological process in function of their target context (Fig. 2a). For example, miR-34a regulate the postprandial metabolic responses by targeting the hepatic co-receptor β-Klotho [83] but in hippocampus contribute to the mood regulation through

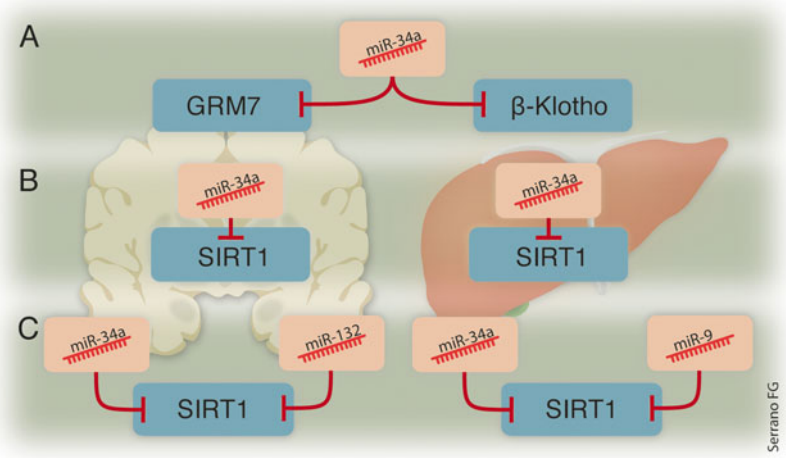


Fig. 2 Functional modalities of miRNAs. **a** miRNAs can control the transcription of tissue-specific or tissue-enriched targets, affecting biological process associated to brain or periphery, respectively. **b** miRNAs can control the transcription of targets ubiquitously expressed and probably have a more general role in several tissues and associated diseases. **c** Convergence of two or more miRNAs in the regulation of the same targets induces an increase in the transcriptional repression

the regulation of metabotropic glutamate receptor 7 [84]. Some of the targets are ubiquitously expressed and probably have a more general role in several tissues and associated diseases (Fig. 2b). For example, miR-34a has been described to be upregulated in both the liver of obese models [85] and the brain of aged mice [86]. Parts of the phenotypes, observed in both tissues, are related to the repression of their target. Silent information regulator 1 (SIRT1) which is a NAD-dependent deacetylase is critically involved in diverse cellular processes including MetS, cancer, aging, and neuroprotection [87, 88].

Another layer of complexity is related to the convergent action of different miRNAs on a common target (Fig. 2c). Continuing with the example of SIRT1, the repression mediated by miR-34a could be reinforced by additional miRNAs [89] including the brain-enriched miR-132 [90] or the action of miR-9 in brain [91] and peripheral tissues [92]. The convergence of two or more co-expressed miRNAs on a given target normally results in an increased degree of translational repression [93, 94].

All these characteristics are important to understand that the regulation of miRNAs is part of the mechanism underlying the development of human diseases. The identification of the noxious stimulus, risk factors, and signaling pathways that affect their biogenesis and function in both, brain, and peripheral tissues could contribute to understand the close association between AD and conditions like MetS.

miRNAs and Metabolic Syndrome

MetS is defined by a combination of metabolic disorders that are used to identify patients at increased risk for cardiovascular disease (CVD), T2DM, and all-cause mortality. The epidemiological concept of MetS originated from the observation that several metabolic risk factors often coincide in patients at high risk for CVD, namely visceral obesity, dyslipidemia, hypertension, NAFLD, and insulin resistance [95, 96]. The worldwide prevalence of MetS is increasing and is currently estimated to be approximately 25 %, largely as a result of the increasing rates of obesity and sedentary lifestyles [97].

Metabolic homeostasis is driven by gene expression programs that respond to cues such as cholesterol, lipids, leptin, glucose, and insulin. This response is mediated by a series of transcription factors including LXRs, sterol regulatory element-binding proteins (SREBPs), proliferator-activated receptors (PPARs), carbohydrate response element-binding protein (CHREBP), CCAAT-enhancer-binding protein (C/EBP), and forkhead box protein O1 (FOXO1). Recently, a series of studies has described the role of miRNAs in the control of metabolic homeostasis and metabolic disorders [32]. In this section, we highlight some examples of miRNAs deregulated in peripheral tissues and the consequential phenotype associated to MetS.

miRNA in Blood Lipid Disorder

Altered lipid levels and hypercholesterolemia represent a critical risk factor for cardiometabolic diseases prevalent in the developed world, such as MetS [32]. Additionally, alterations in cholesterol and lipid metabolism result in major neurodegenerative disorders, including AD [98]. Several miRNAs have been shown to post-transcriptionally regulate the expression of key genes involved in lipid homeostasis. One of the best characterized is miR-33, which acts in coordination with their host gene, SREBP, to increase the intracellular levels of cholesterol, primarily through the transcriptional repression of the ATP-binding cassette transporters 1 (ABCA1) [99], which mediates an essential step in the formation of high-density lipoprotein (HDL or "good cholesterol") [100]. Low HDL levels are strongly associated with risk for CVD [101]. Interestingly, a high-carbohydrate diet increases the levels of SREBP and miR-33 and decreases the levels of the ABCA1 transporter in liver of non-human primates. This could explain the low HDL levels observed in individuals suffering from MetS [102]. In addition to the regulation of genes involved in cholesterol efflux, the list of predicted miR-33a/b targets includes genes that promote fatty acid β-oxidation and negative regulators of SREBPs. This reflects an integrated network of functional interactions between the SREBP transcription factors and their intronic miRNAs to regulate cholesterol and lipid homeostasis [32]. It is important to note that in the brain, ABCA1 acts to lipidate APOE, which is essential for its interaction with Aβ and subsequent clearance, and a growing body of evidence suggests that ABCA1 plays a critical role in Aβ metabolism and accumulation [103]. Considering that ABCA1 transporter is regulated by several miRNAs that respond to metabolic signals is important to study the possible role of brain miRNAs in the regulation of ABCA1 transporter and other regulators of lipid homeostasis in the progression of AD.

miRNA in Obesity

Adipose tissue expansion generates insulin resistance and hyperlipidemia, thereby causing detrimental steatosis in other tissues. Several profiling studies reveal that miRNAs are differentially expressed in the adipose tissue of obese individuals and in mouse models of obesity [104]. For example, miR-103 and miR-107, which are upregulated in adipogenesis, are significantly downregulated in adipocytes from a mouse model of diet-induced obesity [105]. These miRNAs have been proposed to regulate the insulin response through the repression of caveolin 1 (CAV1), a critical regulator of the insulin receptor [106] (Fig. 3d). Another validated target of miR-103/107 is

Dicer (Fig. 3d), a critical enzyme in the biogenetic pathway of miRNAs (Fig. 1). Therefore, the dietary regulation of these miRNAs can generate additional modifications to the full collection of miRNAs in the genome (miRNome), thereby affecting other biological functions that contribute to the development of MetS. The same concept is suggested for AD, because as we will see later, miR-103/107 are downregulated in early stages of AD patients and in the brain of animal models supplemented with a high-fat diet (HFD).

miRNA in NAFLD

Being overweight or obese triggers pathologies such as NAFLD, which is defined as the excess accumulation of hepatic triglycerides and fatty acids and is identified as the hepatic manifestation of MetS [107]. The increased hepatic expression of miR-34a and the subsequently reduced expression of SIRT1 expression have been observed in the NAFLD model [85]. Because the use of natural activators of SIRT1, such as resveratrol, has proven to reduce hepatosteatosis in mice with diet-induced obesity [108], it has been proposed that miR-34a, through the regulation of SIRT1, could be a new therapeutic target for the treatment of NAFLD and other obesity-related diseases.

Another NAFLD-related miRNA is miR-122, which is the most abundant miRNA in the liver and regulates metabolic pathways such as cholesterol biosynthesis, fatty acid synthesis, and oxidation [109]. Studies in patients with NAFLD showed that hepatic and serum miR-122 levels were associated with hepatic steatosis and fibrosis [110–112]. Part of the mechanism whereby miR-122 participates in the development of NAFLD involves the repression of prolyl 4-hydroxylase subunit α-1 (P4H41), a key enzyme in collagen synthesis and, thus, the progression of fibrosis [113] (Fig. 3e).

miRNA and Insulin Signaling

Insulin resistance is a condition in which cells from different tissues do not respond adequately to the normal actions of the hormone insulin and is the most prevalent metabolic dysfunction of all of the MetS risk factors [114]. Many studies have established that miRNAs play significant roles in multiple aspects of insulin signaling [32]. For example, the co-expression of miR-124a and miR-375 regulates insulin exocytosis partly through the regulation of their target Myotrophin, a protein that participates in vesicular fusion [115].

Other miRNAs regulate insulin response by targeting proteins that promote signaling, such as miR-29 a/b, which targets caveolin 2 [116], or miR-126, which represses insulin receptor substrate 1 (IRS1), an adapter protein that plays a key role in signal transduction between the insulin receptor and the phosphoinositide 3-kinase pathway [117] (Fig. 3c).

miRNA and Hypertension

Arterial hypertension (HTA) is a common systemic condition when the individuals have consistent blood pressure measurements exceeding 140/90 mmHg [118]. To date, the main events and system involucrate in pathogenesis of HTA include salt-sensitive theory, abnormal activation of renin-angiotensin system (RAS), and renal fibrosis [119]. The role of miRNAs has been recently described in hypertension and also in other cardiovascular diseases as a putative biomarker of disease risk and progression [120–122]. For example, a recent study shows that hypertensive patients showed a significantly lower miR-9 and miR-126 expression levels compared with healthy controls [123]. Genetics studies show that some polymorphisms influence the expression of miRNAs and the disease pathogenesis. For example, the rs4705342 single nucleotide polymorphism in miR-143 promoter is associated with a decrease in their expression and genetic susceptibility to essential hypertension [124]. In the same line, single nucleotide polymorphisms (SNPs) located in the MRE in RAS genes can influence blood pressure and risk of myocardial infarction [125].

miRNAs can contribute to the development of HTA through the regulation of several component of the renin-angiotensin system in vascular smooth muscle cells. The treatment with angiotensin II generates a robust change in the expression of several miRNAs including miR-483-3p which, in turn, is able to regulate the expression of four different RAS genes including angiotensinogen and angiotensin-converting enzyme 1 (ACE-1) proteins in vascular smooth muscle cells [126] (Fig. 3f).

MicroRNAs Studies in AD

AD is the most frequent form of dementia in the elderly. It is a neurodegenerative disorder that it is characterized by neuron destruction and synaptic loss, which result in a progressive decline in memory and other cognitive functions [2]. The two core histopathological hallmarks of AD are amyloid plaques (senile plaques) and neurofibrillary tangles. Amyloid plaques are formed by the deposition of the Aβ peptides generated by proteolytic cleavage from the full-length APP through the amyloidogenic pathway. In this process, APP is sequentially cleaved by β-secretase (BACE1) and the γ-secretase complex. The cleavage of APP by α-secretase occurs within the Aβ peptide containing region, precluding the formation of this peptide (non-amyloidogenic pathway). The toxicity of the Aβ peptide is dependent on its conformational state and length. Small oligomers of Aβ can be more toxic than mature fibrils, and $A\beta_{1–42}$ peptide aggregates more readily than does $A\beta_{1–40}$ [127]. The ratio of these

two isoforms is influenced by the pattern of cleavage from APP by the α, β, and γ secretases [128].

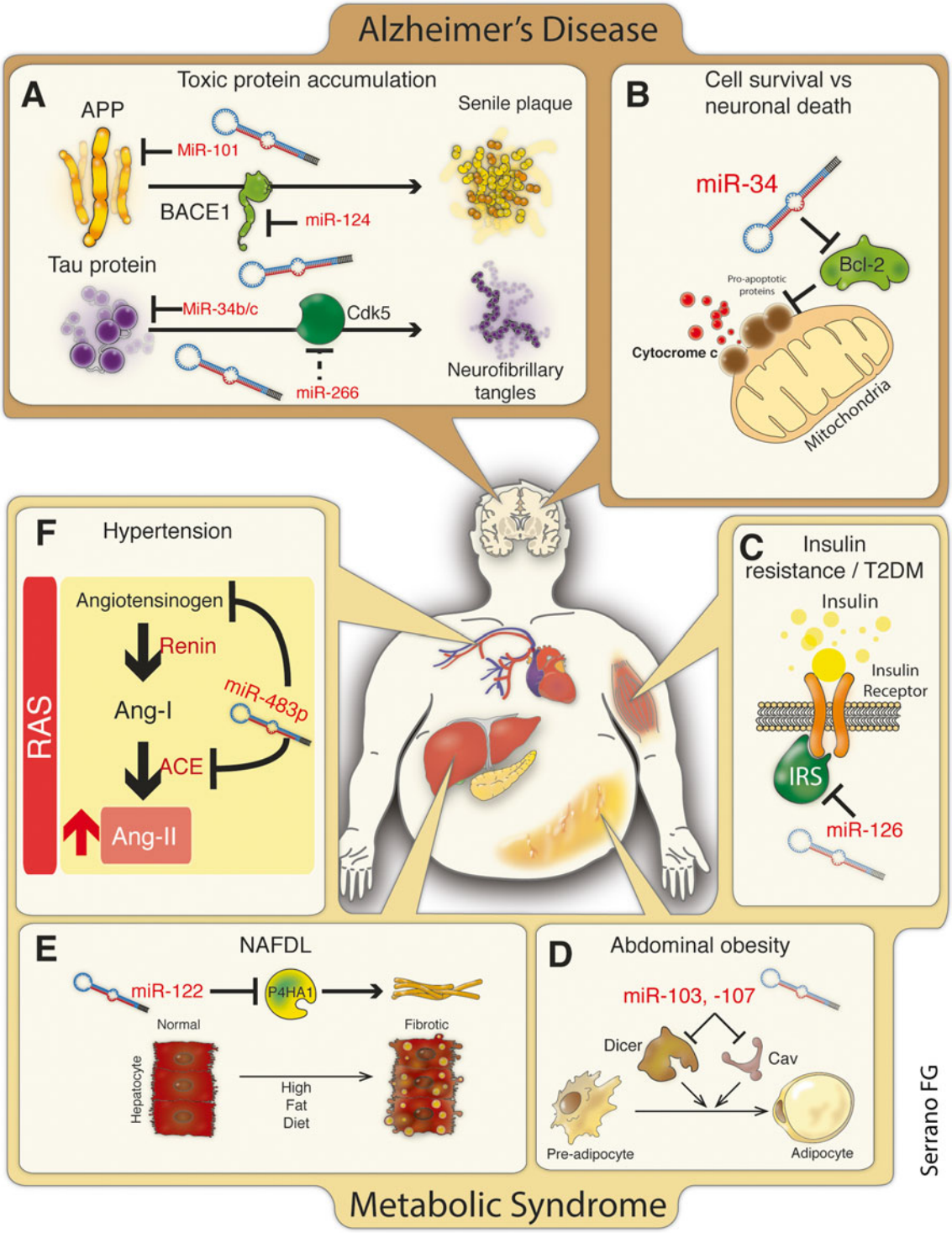
Another hallmark of AD is the neurofibrillary tangles formed by *tau*, a microtubule-associated protein. During neurodegeneration, tau becomes highly phosphorylated, causing conformational changes that result in disassociation from the microtubule aggregation [129]. Therefore, the balance between tau kinases and phosphatases is vital for fine-tuning the phosphorylation state of tau to regulate its biological activity.

Considering the complex molecular network that is involved in the development of AD and the poor diagnostic tools that are currently available, the identification of molecular clues with a clear relationship to the onset and development of the disease is fundamental. Thus, several studies have attempted to generate a miRNA profile in different models of AD. Studies carried out in tissue of human patients, AD animal models, or cell cultures have shown significant changes in subpopulations of miRNAs with respect to their matched controls; however, the changes observed in individual miRNAs have been inconsistent. One remarkable example is miR-9, a brain-enriched miRNA consistently altered in several profiling studies. However, post-mortem samples of human hippocampus have shown both increased [130] and decreased [131] miR-9 levels. Similar studies in the cortex have shown the same inconsistencies [132, 133]. These results may be explained by the use of different experimental approaches or the degree of disease progression. Interestingly, in primary mouse hippocampal neurons, treatment with $A\beta_{1-42}$ has been reported to decrease the levels of miR-9 [134, 135], suggesting that miR-9 deregulation in response to an insult such as Aβ may be an important factor that contributes to the cascade of events leading to AD.

Another important approach for understanding the role of the misregulation of miRNAs in AD is the identification of the miRNA targets implicated in the accumulation of toxic proteins (Fig. 3a) or proteins that promote or inhibit cell survival (for example anti-apoptotic proteins such as Bcl2) (Fig. 3b). miRNAs can regulate these proteins either directly, by interacting with the 3′UTR region of their mRNA, or indirectly, by regulating the mRNA of proteins that affect their expression, processing, or function. For example, miR-101, which has been reported to be reduced in AD cortex [135, 136], possesses two MRE in the APP 3′UTR. In vitro validation of this direct regulation was performed by luciferase assay and gain of function of miR-101 in primary rat hippocampal neurons and human cell cultures [137], suggesting that the downregulation of miR-101 generates an increase in APP levels and contributes to the development of AD (Fig. 3a). Conversely, several miRNAs have been described to regulate proteins that participate in APP processing, including BACE1 [133, 138, 139] (Fig. 3a). Thus, the loss or gain of function of these miRNA controls the generation of Aβ independently of the changes in APP expression. Similar studies have examined the miRNAs regulating tau expression (miR-34 family) [140] and the proteins involved in the hyperphosphorylation of tau observed in AD (for example, miR-26b indirectly affects cytoplasmic export of cyclin-dependent kinase 5 (Cdk5), a major tau kinase [141]) (Fig. 3a).

The miRNome has been shown to be affected during the progression of AD; further, miRNAs have demonstrated their potential as non-invasive biomarkers from blood and serum for a wide variety of human pathologies [142]. Recent studies have sought to establish whether the changes in miRNA expression described in neurons of AD models or patients correlate with the expression of peripheral miRNAs that were obtained from peripheral cells such as platelets or mononuclear cells [143–145] or with that of circulating miRNAs [146, 147] and whether they could potentially act as biomarkers for AD. Some miRNAs were consistently identified in AD, including some let-7 family members, miR-9, miR-181, and miR-29 (Fig. 3f). These miRNAs seem to be involved in processes that have previously been associated with AD, such as inflammation and immunological response [148]. Although the concept is very attractive, extensive validation and follow-up studies in larger cohorts of patients are needed before an analysis of miRNAs can be applied as a diagnostic tool in the clinic.

Fig. 3 miRNA overview in MetS and AD. Research into the specific activity of miRNA in several tissues suggests an important role in the generation of metabolic disorders associated with MetS and the histopathological hallmarks of AD. **a** Toxic protein accumulation. miRNAs can regulate the generation of toxic protein directly by repressing APP and tau or indirectly by repressing the proteins associated with the pathogenic process, such as BACE1 or Cdk5. **b** Cell survival. Several miRNAs regulate the expression of anti-apoptotic proteins such as Bcl2 and influence cell survival processes. In this example, miR-34, a miRNA related to MetS and AD, represses the expression of Bcl2 and induces mitochondrial pathways of apoptosis. **c** Insulin resistance. miRNAs regulate multiple aspects of insulin signaling such as insulin secretion, insulin sensitivity, and regulation of glucose uptake in target tissues. Here, miR-126 regulates the expression of IRS1, which has a key role in signal transduction between insulin receptors and intracellular pathways. **d** Abdominal obesity. miR-103 and miR-107 are upregulated in adipogenesis and significantly downregulated in adipocytes in mouse models of diet-induced obesity. These miRNAs regulate insulin sensitivity by repressing caveolin 1 (*CAV1*), a critical regulator of the insulin receptor. Another important target is Dicer, which can potentially induce the maturation of several additional miRNAs. **e** Non-alcoholic fatty liver disease (*NAFLD*). NAFLD is a hepatic manifestation of MetS and is characterized by the excess accumulation of hepatic triglycerides and fatty acids, hepatic steatosis, and fibrosis. MiR-122 participates in the development of NAFLD by repressing Prolyl 4-hydroxylase subunit alpha-1 (*P4H41*), a key enzyme in collagen synthesis. **f** Hypertension. The increase in angiotensin II generates a robust change in the expression of several miRNAs including miR-483-3p which in turn is able to regulate the expression of different renin angiotensin system genes including angiotensinogen and angiotensin-converting enzyme 1 (*ACE-1*) proteins in vascular smooth muscle cells



microRNAs as a Molecular Link Between MetS and AD

In a practical exercise, you simple can start to enumerate the coincidental characteristics observed in two pathological conditions to try to establish a relationship. In that sense, we are able to highlight several links between MetS and AD, for example inflammation [149], amyloidosis [150], and Wnt signaling imbalance [29], to name just a few. We can do the same with miRNAs, and we can start to compare tables in miRNA-disease database and try to find some coincidences. The last release of the Human miRNA Disease Database V2.0

(HMDD, June 20, 2013) includes experimental-supported evidence for 572 human miRNA associated to 378 diseases, reported in 3,511 papers [37]. For AD, the database includes 33 miRNAs, for hypertension 24, obesity 9, T2DM 20, and NAFLD 5. In Table 1, a cluster of coincidental miRNAs that are deregulated in AD and one or more component of the MetS is described. The obvious conclusion is that all these miRNAs are ideal examples of how miRNAs are in fact a molecular link between AD and MetS, but a coincidental observation does not always implicate a direct relationship. In fact, miR-21, miR-17, miR-20a, and 146a are between the top ten miRNAs with the biggest disease spectrum width (DSW) [37] which is a parameter that evaluates the effect of a miRNA in human diseases [151]. That means that those miRNAs with high DSW are, in fact, altered in several human diseases. In the case of miR-21, which has the biggest DSW, their deregulation was reported in 123 human diseases of a total of 378, including all types of cancer, several infections like HIV, and of course AD. In conclusion, those miRNAs are important markers of a general state of disease but coincidentally do not give evidence of causality.

The other problem of use coincident in the regulation of miRNA, to establish a relation of MetS and AD, is related to the up- or downregulation observed for a particular miRNA in a given condition. For example, if we use the data in the literature, we can assume that a miRNA that is upregulated in AD and MetS is a better candidate than a miRNA that shows opposite regulation (up and down). This is not necessarily true if we consider the phenomenon of resistance observed in AD, in which the levels of metabolic signals like insulin and leptin are different in plasma in relation to cerebrospinal fluid (CSF) or brain, and therefore, the effect on the expression of miRNAs could be different to that of peripheral tissues.

To understand whether miRNAs are part of the epidemiologic associations between MetS and AD, we discuss a series of preclinical studies, showing that metabolic manipulations induce changes in the expression of miRNAs related to AD in different brain areas. The deregulation of metabolic signals observed in MetS as well as its ability to cross the blood–brain barrier (BBB) are fundamental to understand the impact in the brain function, miRNA regulation, and the possible link with AD.

Metabolic Manipulations and miRNA Deregulations in the Brain

Leptin is an adipocyte-derived cytokine involved in long-term regulation of energy intake and expenditure, body weight, and neuroendocrine functions in mammals [152]. In the nonobese condition, energy intake increases leptin secretion and, in the brain, leptin induces a negative feedback on energy intake via stimulating the expression of anorexigenic neuropeptides. However, leptin has different effects depending upon the developmental stage. Peripheral leptin is able to enter CSF and the CNS (crossing the BBB and choroid plexus), and subsequently, in the CNS, leptin interacts with specific areas of the brain such as the hypothalamus and hippocampus [153, 154]. Besides leptin transport into the CNS and CSF, several studies indicated that leptin can also be produced in human and rodent brains, for example in the hypothalamus, cortex, and cerebellum [155–157). Besides a role in energy intake, the presence of leptin receptors in specific regions of the brain illustrates its potential for being involved in multiple mechanisms related to brain function and structure in many rodent models [158–161]. The effects of leptin on brain structure are determined by its influence on neurogenesis, axon growth, synaptogenesis, and dendritic morphology, which occur during both pre-and postnatal life and are important for the establishment of hypothalamic, hippocampal, and cortical pathways [162, 163].

The role of leptin in the regulation of miRNA expression has been described previously in peripheral tissues. One of the most commonly studied miRNAs is miR-26b, which is downregulated in the adipose tissue of obese models (high leptin peripheral levels) and adipocytes treated with leptin [164]. Obesity induces lower brain leptin levels or an attenuated leptin response (leptin resistance), due to impaired transport of peripheral leptin into the brain [165]. Similarly, in the brain of AD patients, leptin levels are reduced which is associated to weight loss and cognitive decline observed in the intermediated and advanced stages of AD [166]. In accordance with this observation, the levels of miR-26b were reported to be significantly elevated in human postmortem brains, starting from early stages of AD (Braak III), and it has been suggested that contribute to the progression of the disease by regulating the hyperphosphorylation of tau through the regulation of this target retinoblastoma protein (Rb1) [141]. Recently, the group of Ghribi describes the upregulation of miR-26b [167] and the concomitant reduction of leptin levels [168] in the brain cortex of rabbits fed with a diet supplemented with 2 % cholesterol, which induce the development of full-blown AD pathology, including cortical Aβ deposits and tangles, and other pathological markers also seen in human AD brains [169–174]. Additionally, they describe the deregulation of other miRNAs previously reported to be altered in human AD samples, including miR-125b, miR-98, miR-107, and miR-30, along with three members of the let-7 family [167]. This suggests that the reduction of central levels of leptin by a metabolic distress, like high cholesterol intake, modulates the expression of miRNAs related to AD in brain and could contribute to the progression of the disease.

Another interesting miRNA regulated by leptin is the brain-specific miR-132, which has been related to synaptic plasticity, neuronal outgrowth, integration of newborn neurons in the dentate gyrus, and it shapes synaptic structure. In the hippocampus of the obesity model *db/db* mice, which is deficient in leptin receptor and the leptin signaling is impaired, the levels of miR-132 are 60 % lower than the wild-type (wt) mice, and treatment of dissociated hippocampal cultures with leptin increased their expression [175]. These animals display cognitive impairments as well as abnormal synaptic structures, which is similar to the phenotype observed in several neurodegenerative diseases. In AD, consistent with the decrease in leptin levels, miR-132 is described to be downregulated in several brain areas of LOAD patients [90, 176–178]. The role of miR-132 in AD could be attributable to their well-known targets related to synaptic plasticity like p250GAP [179], but other relevant targets include tau, EP300, SIRT1, and members of the FOX family of transcription factors [90].

These findings show that leptin not only regulates the expression of miRNAs with a well-known role in metabolic homeostasis in peripheral tissues and brain (miR-26b) but also shows that leptin regulates the expression of brain-specific miRNA whose role is more associated with synaptic regulation as well as pathological processes associated to AD (miR-132).

Leptin regulates the expression of miRNAs in other brain areas like hypothalamus. In the obese *ob/ob* mice model, lacking the leptin gene expression, the hypothalamic neural organization and circuitry are impaired, and interestingly, the neuronal development and metabolic phenotype can be rescue by supplementation with leptin. In male adult obese *ob/ob* mice, the expression of several miRNA was affected compare to the wt mice [180]. The more affected miRNA correspond to miR-200a, which is also upregulated in the hypothalamus of the *db/db* mice. The intraperitoneal administration by 11 days of leptin reduces miR-200a to levels observed in the wt mice [180]. miR-200a has been observed to increase in the hippocampus and prefrontal cortex of LOAD patients [90] and also in the brain of 6-month-old APP swe/PSΔE9 transgenic mice [181]. Considering the leptin resistance observed in LOAD patients is possible to speculate that this pathological process can influence the expression of miR-200a and other miRNAs in the hippocampus of LOAD patients.

Other dietary manipulations, known for generate metabolic alterations and cognitive deficit, have been studied for their role in miRNA regulation in the rat hypothalamus. These studies show that a HFD after weaning increases the expression of several miRNAs, compared to rat reared with a normal diet [182, 183]. One of the interesting findings of this work is that some miRNAs, like miR-200a, show a decrease in their levels during the first week of the HFD but displayed an increase in the chronic period, when obesity is clearly established and hypothalamic insulin, leptin, and inflammation signaling are primarily disturbed. Although the emphasis in AD is often placed on the hippocampus and other brain structures directly involved in cognition and memory, the hypothalamus is clearly involved in AD. Significant atrophy has been identified in the hypothalamus of AD subjects by magnetic resonance volumetric analysis [184]. Also, pathological alterations consistent with AD, including neurofibrillary tangles and amyloid plaques, have been found in the hypothalamus of postmortem AD brains [185, 186]. Therefore, understanding how the hypothalamic miRNAs are affected in response to metabolic distress, like leptin resistance, may offer new insights into the metabolic and cognitive dysfunction associated with AD.

Geekiyanage and Chan showed that a decrease in the levels of miR-137, miR-181c, and miR-9 occurred in brain cortices of wt male mice fed with a HFD for a period of 5 months [187]. The levels of miR-137, miR-181c, and miR-9 are also decreased in AD autopsy brain samples. Interestingly, these miRNAs target a serine palmitoyltransferase protein (SPT) that has been shown to be upregulated in patients with sporadic AD; however, the mRNA level of SPT has not been shown to be altered, suggesting that it is subject to a mechanism of post-transcriptional regulation. SPT is a critical enzyme in the de novo synthesis of ceramides, which promotes BACE1 and γ-secretase mislocation to lipid rafts and therefore promotes the formation of Aβ [188, 189]. The connection of this misregulated miRNA to AD and MetS is strengthened by a posterior study in which the expression levels of miR-137, miR-181c, and miR-9 were also downregulated in the blood serum of probable AD patients and in male wt mice fed a HFD [146].

In contrast to a HFD, the consumption of a low-fat diet, calorie restriction (CR), and maintenance of metabolic function result in preserved cognition, decreased oxidative stress, preserved brain structure, and reduced inflammatory signaling [190], which are essential for reducing the risk of AD [191]. The regulation of miRNAs may be a potential mechanism underlying these beneficial effects of a low-fat diet. Khanna et al. found that the levels of miR-34a, miR-30e, and miR-181-a-1* are significantly lower in brain tissue samples from old mice fed a calorie-restricted diet, i.e., 60 % of their normal ad libitum caloric intake, compared with mice on the usual ad libitum diet [192]. Interestingly, miR-34a are increased in the brain of AD mice models [193] and also in the liver of dietary and genetic obese mice [85, 106].

Physical activity is a necessary complement to diet control, losing weight, and treating MetS. Exercise benefits not only the musculoskeletal and cardiovascular systems but also the brain. It has been clearly established in controlled studies that regular vigorous exercise improves mood and cognition [194]. In fact, voluntary exercise ameliorates HFD-induced memory deficits and Aβ deposition in APP transgenic mice [195]. It has been established that part of the beneficial effects of

exercise in skeletal muscle is attributed to miRNA regulation [196]; however, the evidence of miRNA responsive to exercise in brain is scarce. In the work of Mojtahedi, the brain levels of miR-124 were shown to increase in an exercise intensity-dependent manner [197]. This is interesting because the expression of miR-124 is downregulated in the brains of patients with AD [130, 198]. Furthermore, it has been suggested that miR-124 may target BACE1 and thus reduce AD-related cell death [138] (Fig. 2a). In a more recent study, the effect of physical activity on the miRNA expression was evaluated in the hippocampus of the spontaneous senescence-accelerated P8 mouse model (SAMP8) which is currently considered a model of AD [199]. In 8-month-old SAMP8 sedentary mice, the authors observe 18 altered miRNA (of the 84 miRNA tested) compared to the control strain. Among them, miR-30e-5p, miR-125b-5p, and miR-128-3p have also been reported to be altered in post-mortem human AD hippocampus [130, 131]. Interestingly, these miRNA are responsive to physical activity and change their expression in the AD mice model after voluntary exercise [199]. Bioinformatic analysis indicate that these exercise-responsive miRNAs are involved in the regulation of several biological process including PI-3-kinase, Akt, insulin, and mTOR signaling pathways; all of which are modulated in the brain by exercise [200–202].

Additional studies in animal models of AD are needed to explore the effect of physical activity on miRNA regulation in the brain and further determine the molecular mechanisms behind the beneficial effects of exercise on cognitive processes.

Drug Therapy of MetS and Their Potential Role in AD

The first-line treatment for MetS is change of lifestyle. However, physicians frequently begin a treatment with medication if the MetS biomarkers do not improve within in 3 to 6 months after initiating lifestyle changes. Generally, the individual disorders that comprise the MetS are treated separately. Considering the evidence that demonstrates that improving the metabolic conditions may prevent AD, it was suggested that the use of these drugs medications could also be useful in preventing neurodegenerative conditions such as AD.

For example, statins, a class of hypolipidemic drugs, have been proposed as potential agents for the treatment or prevention of AD [203, 204]. Data from animal models studies suggest that atorvastatin may reduce the Aβ [205] and BACE1 protein levels [206] and would be of possible benefit in preventing AD. Several studies have attempted to determine the mechanism of action through which statins appear to regulate the development of AD. One avenue explored was the ability of statins to lower cholesterol levels; however, statins possess a number of pleiotropic effects (cholesterol-independent) that have been extensively discussed [207]. Recently, a new mechanism of action of statins involving the regulation of miRNAs has been identified. Simvastatin and atorvastatin induce miR-33 expression, resulting in the reduced expression of sterol transporters and decreased cholesterol efflux [208]. Interestingly, lovastatin is also able to induce the expression of miR-33 and reduces the miR-9 levels in xenograft models of medulloblastoma, a highly malignant primary brain tumor that originates in the cerebellum [209]. Although miR-33 has not been associated with AD, the fact that a drug such as lovastatin, which is capable of crossing the BBB [210], can generate such changes in brain miRNome could explain why the drug treatment of MetS has been suggested as a tool for preventing AD (Fig. 4).

Along the same lines, the oral anti-diabetic drug metformin alters the miRNA levels in several tissues [211–213]. Because metformin can increase the levels of Dicer [214], the enzyme

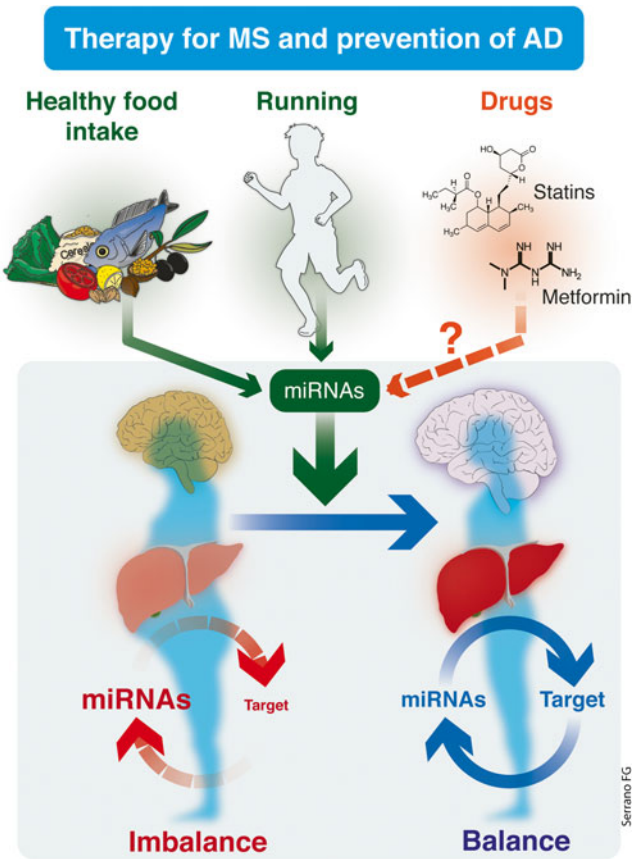


Fig. 4 MetS therapies and their possible impact on AD prevention, through miRNA regulation. Physical activity like running and diet control (e.g., calorie restriction, Mediterranean diet) have been shown to be fundamental in the treatment of MetS through the regulation of several miRNAs in peripheral tissues (liver, adipocytes, vasculature, etc.) and may be important in the prevention of AD by their effects in brain miRNAs that targets protein related to APP processing and survival proteins. Medications for the treatment of individual disorders that compose MetS (e.g., metformin, statins, ARBs) modify miRNAs in peripheral tissues and have the ability to cross the BBB, which suggest a possible role in the regulation of brain miRNAs related to AD progression

responsible for the generation of most of the mature miRNAs (Fig. 1), and is capable of crossing the BBB [215], it is tempting to speculate that some of the controversial roles attributed to metformin in AD [216–218] may be partly dependent on the modulation of miRNAs in the brain (Fig. 4).

Other drugs, such as angiotensin II type 1 receptor antagonists (ARBs), that are used to treat hypertension have been linked to AD [219], but their role in the regulation of miRNAs has not been explored. These drugs can also cross the BBB [220], so more research is necessary to explore the possible regulation of miRNAs that are related to AD.

Concluding Remarks

The concept of "metabolic-cognitive syndrome" emerges from epidemiological and basic research in patients with MetS and cognitive impairment of degenerative or vascular origin [23]. We propose that the *miRNAs may act as a molecular link between MetS and AD*, may play a role in the complex relationship between metabolic disorders and cognitive disturbances, and may be useful in the generation of therapeutic strategies against MetS that could help prevent or ameliorate the cognitive decline observed in AD and other pathologies. In both animal models and patients with MetS or AD, altered expression levels of different miRNAs have been observed as a consequence of changes at different stages of biogenetic processes, including transcription, processing, and miRISC function (Fig. 1). Importantly, metabolic manipulations generate signals that alter the expression of miRNAs in both peripheral tissues and the brain, inducing changes conducting to MetS and AD through the regulation of ubiquitously expressed target reflecting a common mechanism (ABC1 transporter related to impaired cholesterol homeostasis observed in MetS and AD) or tissue-specific targets that control particular characteristic of each disease (for example, p250GAP related to synaptic loss observed in AD or β-Klotho related to impaired postprandial responses in patients with steatosis) (Fig. 2).

More directed experiments that confirm our hypothesis are required, for example, the use of the obese Zucker rats (ZDF) which possess a (*fa/fa*) mutation and leptin receptor deficiency and develop all the hallmarks of MetS [221] is ideally suited for this purpose. These animals show impairment of synaptic plasticity [222, 223], spatial memory, and learning [224] and even show an increase in brain mRNA levels of APOE [225], protein aggregation, and p-tau levels [226, 227] which correspond to classic markers of AD. The study of miRNAs that change their expression in different brain areas in response to metabolic deterioration could identify key biomarkers that helps to develop diagnostic tools and to prevent the cognitive decline in early stages of the metabolic-cognitive syndrome.

Additionally, the use of specific viral delivered miRNA oligomers in the brain that prevent the metabolic-induced change of their levels and restore the cognitive impairment without changes in the metabolic status of the animal might confirm the critical role of miRNAs as a molecular link between MetS and AD.

Lifestyle changes, such as a calorie-restricted diet or increased physical activity, have a positive impact on the expression of the miRNAs that control the proteins involved in APP processing and plaque formation, such as BACE1, suggesting that this is a potential therapeutic approach to prevent deleterious processes that lead towards the development of MetS and AD (Fig. 4). Conversely, the use of medications or drugs to combat the various components of metabolic syndrome may potentially affect the expression of miRNAs in the brain because they can cross the BBB. These unexpected side effects have not been explored in depth, and further research is needed to establish whether this modulation of brain miRNAs can be beneficial or detrimental to the development of AD and other pathologies such as brain cancer. Finally, altered circulating miRNA profiles have already been linked to disease states, including metabolic disorders associated with MetS and AD, and may provide important biomarkers for disease. The use of miRNAs as a molecular link between MetS and AD may provide insight into the initiation and development of these diseases and may offer new therapeutic avenues for diagnostic tests and prevention.

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