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MicroRNAs in Metabolic Disease

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Abstract

Alterations in the metabolic control of lipid and glucose homeostasis predispose an individual to develop cardiometabolic diseases such as type 2-diabetes and atherosclerosis. Work over the last years has suggested that miRNAs play an important role in regulating these physiological processes. The contribution of miRNAs in regulating metabolism is exemplified by miR-33, an intronic miRNA encoded in the *Srebp* genes. miR-33 controls cellular cholesterol export and fatty acid degradation while its host genes stimulate cholesterol and fatty acid synthesis. Other miRNAs, such as miR-122, also play a critical role in regulating lipid homeostasis by controlling cholesterol synthesis and lipoprotein secretion in the liver. This review article summarizes the recent findings in the field, highlighting the contribution of miRNAs in regulating lipid and glucose metabolism. We will also discuss how the modulation of specific miRNAs may be a promising strategy to treat metabolic diseases.

MicroRNAs (miRNAs) are small (18–25 nucleotides in length), evolutionarily conserved, non-coding RNAs that have an important function in gene regulation, acting predominantly at the post-transcriptional level[1, 2]. Mature miRNA products are generated from a longer primary miRNA (pri-miRNA) transcript through sequential processing by the ribonucleases DROSHA and DICER. miRNAs typically control the expression of their target genes by imperfect base pairing to the 3'-untranslated regions (3'UTR) of messenger RNAs (mRNAs), thereby inducing repression of their target mRNAs[1, 2]. This inhibitory effect can occur by either transcript destabilization, translational inhibition, or both (more detailed information about miRNA biogenesis, function and targeting activity can be found in recent reviews covering these topics). Importantly, a single miRNA can regulate the expression of hundreds of genes and the expression of a single gene can be regulated by multiple miRNAs. The effect of a particular miRNA on gene expression is likely to be dictated by the relative expression of the miRNA and its target genes which can compete for the binding in their 3'UTRs. Of note, one miRNA often regulates multiple genes that are involved in a

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specific signaling cascade or cellular mechanism, thus making miRNAs potent biological regulators[1, 2]. Since miRNAs have been described in the early 90's as regulators of developmental timing in *Caenorhabditis elegans*, they have been shown to participate in almost every cellular process investigated, including metabolic homeostasis[2–5].

microRNAs as regulators of lipid metabolism

Growing evidence suggests that faulty regulation of lipid metabolism promotes metabolic diseases. In addition to the classical transcriptional regulators, SREBPs and LXRs, several miRNAs have been shown to post-transcriptionally regulate the expression of key genes involved in lipid homeostasis, including miR-122, miR-33, miR-106, miR-758, miR-26, miR-370, miR-378/378*, let-7, miR-27, miR-143, miR34a and miR-335[6–21]. In the present review we will focus our attention on the liver specific *miR-122* and the well-characterized intronic *miR-33*.

miR-122

miR-122 is the most abundant miRNA in the liver, with approximately up to 135,000 copies per human hepatocyte, accounting for ~ 75% of total miRNA expression in this organ [22–25]. miR-122 plays important roles in a wide variety of liver functions ranging from cholesterol metabolism, liver cancer, stress responses, and viral infection to circadian regulation of hepatic genes[7, 23–27]. Two pioneering studies have shown that antisense targeting of miR-122 results in a significant reduction of plasma cholesterol levels[7, 22]. The first study shows that the effect on plasma cholesterol results most likely from decreased expression of many cholesterol biosynthetic genes, including 3-hydroxy-3-methylglutaryl-CoA reductase (*Hmgcr*), the rate-limiting enzyme in the cholesterol biosynthesis pathway[22]. Despite this, the effects of miR-122 on cholesterol biosynthesis are indirect and it is unclear which direct targets of miR-122 mediate them. Interestingly, this study underlines that a miRNA loss-of-function phenotype may be caused by genes that are not directly targeted by the miRNA. The second study implements a similar antisense technology (ASO) against miR-122 in mice and not only confirms the effect on plasma cholesterol, but also reports a significant decrease in plasma triglycerides, as well as decreased hepatic steatosis, in high-fat-diet-fed mice[7]. Furthermore, hepatocytes isolated from ASO-miR-122-treated mice display decreased hepatic fatty acid and sterol synthesis and increased fatty acid oxidation, likely due to the observed increased levels of AMP-activated kinase (AMPK)[7]. Subsequent studies using locked nucleic acid (LNA) chemistry in mice and non-human primates corroborate the reduced plasma cholesterol levels without any apparent liver toxicity[28]. Recently, miR-122 liver-specific knockout and miR-122 germline knockout mice have been shown to have a significant reduction (~30%) in total serum cholesterol and triglyceride (TG) levels and therefore, recapitulate the effects observed with antisense inhibitors of miR-122[23, 25]. Interestingly, the study of Tsai and colleagues also found a significant down-regulation of the microsomal TG transfer protein (MTTP), which is essential for the assembly of lipoproteins[25]. Intriguingly, *Mttp* is not a direct target of miR-122 and the mechanism by which miR-122 regulates its expression is still unknown. Altogether, these results demonstrate that miR-122 plays an important role in regulating serum cholesterol and TG

levels by controlling cholesterol biosynthesis and very-low density lipoprotein (VLDL) secretion in the liver.

In addition, a recent report has also shown that the knockdown of miR-122 results in the regulation of hundreds of mRNAs, of which a disproportionately high fraction accumulates in a circadian fashion[26]. The transcripts associated with these pathways indeed show the strongest time point-specific changes upon miR-122 depletion. The identification of peroxisome proliferator-activated receptor (PPAR) alpha, beta, and gamma and the PPAR alpha coactivator, Smarcd1/Baf60a, as novel targets of miR-122 suggest an involvement of the circadian metabolic regulators of the *Ppar* family in miR-122-mediated metabolic control[26]. Taken together these results suggest that inhibition of miR-122 might be a feasible therapeutic approach. In another study, 46 miRNAs were differentially expressed in humans with nonalcoholic fatty liver disease (NAFLD)[29]. miR-122 was downregulated in NAFLD, and this was correlated with increased expression of lipogenic genes in human livers[29]. Knockdown of miR-122 in HepG2 cells recapitulated the lipogenic gene expression profile observed in individuals with NAFLD. In this case, it seems likely that miR-122 down-regulation is a compensatory mechanism that counters increasing hepatic lipid levels, rather than a causative agent in the development of NAFLD. Future studies should clarify this apparent discrepancy. In line with these observations, some of the above-mentioned reports have also shown that antagonism of miR-122, in both mice and non-human primates, not only lowers low-density lipoproteins (LDL) levels but the levels of high-density lipoproteins (HDL) as well. These *a priori* adverse effects, together with the recently reported increased risk of developing hepatocellular carcinoma[23, 25], challenge the therapeutic approach of miR-122 inhibition for the treatment of metabolic lipid diseases.

miR-33

miR-33 consists of two intronic microRNAs, *miR-33a* and *miR-33b*, which are encoded within the introns of the *Srebp2* and *Srebp1* genes, respectively[6, 15, 16, 19]. While *miR-33a* and *miR-33b* share their target activity, they differ in their pattern of evolutionary conservation. *miR-33a* is encoded within intron 16 of the human *Srebp2* gene and is conserved in many animal species[6, 15, 16, 19]. However, the conservation of *miR-33b*, which is found within intron 17 of the human *Srebp1* gene, is lost in many species including rodents and rabbits. *miR-33a* and *miR-33b* are co-transcribed with their respective host genes, thereby participating in the regulation of physiological processes related to *Srebp2* and *-1*[6, 15, 16, 19]. Indeed, we and others have found that miR-33a and miR-33b regulate intracellular cholesterol and fatty acid homeostasis in concert with their host genes. Specifically, miR-33a has been shown to target genes involved in cholesterol export such as the adenosine tri-phosphate binding cassette (ABC) transporters *Abca1* and *Abcg1*[15, 16, 19] and the endolysosomal transport protein Niemann-Pick C1 (*Npc1*)[19]. In agreement with the regulation of ABCA1 by miR-33, modulation of miR-33a levels results in encompassing effects in cholesterol efflux in macrophages thus suggesting that miR-33 may participate in the regulation of HDL levels *in vivo*. Indeed, three independent studies have demonstrated that endogenous inhibition of miR-33 using different strategies leads to a significant increase in hepatic ABCA1 expression and plasma HDL levels[15, 16, 19], findings that were later confirmed in the *miR-33* knockout mice [30]. Most importantly, anti-miR-33 therapy also

results in increased plasma HDL levels in non-human primates[31]. Interestingly, in the well-characterized model for hypercholesterolemia, *LDLr* knockout mice, anti-miR-33 therapy promotes reverse cholesterol transport (RCT) and atherosclerosis regression[32]. Despite this, the effect of anti-miR-33 therapy on RCT might not be solely due to ABCA1 up-regulation since it has been recently reported that miR-33 also targets two canalicular transporters, *Abcb11* and *Atp8b1*, which regulate bile secretion[33].

In addition to the important role of *miR-33a* and its host gene, *Srebp2*, in regulating cholesterol metabolism, the genomic localization of *miR-33b* in an intron of the *Srebp1* gene, led several groups to study the contribution of miR-33 in controlling additional metabolic pathways such as fatty acid metabolism[6, 10]. Importantly, miR-33a and miR-33b contribute to the regulation of fatty acid metabolism by controlling the expression of carnitine O-octanyl transferase (*Crot*), carnitine palmitoyltransferase 1A (*Cpt1a*), and hydroxyacyl-CoA dehydrogenase-3-ketoacyl-CoA thiolase-enoyl-CoA hydratase (trifunctional protein) β-subunit (*Hadhb*)[6, 10]. CROT and CPT1A regulate the transport of fatty acids to the mitochondria for their degradation and HADHB is directly involved in mitochondrial fatty acid β-oxidation. Interestingly, endogenous inhibition of *miR-33* in human hepatic cells increases the degradation of fatty acids, suggesting that anti-miR-33 therapy may be useful for treating hepatic steatosis by increasing the degradation rate of fatty acids in the liver[6, 10]. In this regard, non-human primates treated with anti-miR-33 oligonucleotides show a significant reduction of plasma VLDL levels[31]. These results could be explained by a reduced lipidation and secretion of ApoB-containing lipoproteins due to the increased fatty acid oxidation that might be occurring in the liver of non-human primates treated with anti-miR-33 oligonucleotides. However, this remains to be addressed.

In addition to the regulation of fatty acid oxidation, miR-33a and miR–33b have also been shown to control the expression of *Ampkα1* and sirtuin 6 (*Sirt6*), which are involved in the regulation of lipid and glucose metabolism[6]. The latter will be discussed in the following section. AMPKα1 regulates key lipogenic enzymes, including HMGCR and ACC. Thus, inhibition of AMPKα1 by miR-33 may increase HMGCR and ACC activity to boost intracellular levels of cholesterol and fatty acids. Altogether, these results suggest a paradigm in which *miR-33a* and *miR-33b* act in concert with their host genes, *Srebp2* and *Srebp1*, to increase intracellular cholesterol and fatty acid levels by balancing transcriptional induction and post-transcriptional repression of lipid metabolism genes. Finally, insulin receptor substrate 2 (*Irs2*), an adaptor protein that controls insulin signaling in the liver, has also been shown to be a miR-33 target, thereby affecting the signaling of a complex downstream network of proteins including protein kinase B (PKB; also known as AKT) phosphorylation and FOXO1 cytoplasmic localization[6]. Collectively, these data indicate that both isoforms of *miR-33* participate in the regulation of relevant pathways that impact three of the primary risk factors of metabolic syndrome, namely insulin resistance, low HDL and high VLDL and suggest that anti-miR-33 therapies may be an attractive approach for treating metabolic diseases.

In contrast to miR-122, miR-33 is less expressed in the liver compared with other tissues such as the brain[16, 21]. However the presence of multiple binding sites in the 3'UTR of some of the key target genes, including *Abca1* and *Crot*, explain why anti-miR-33 therapy is able

to increase their expression in the liver[6, 19]. The role of miR-33 in the brain is under intensive investigation since ABCA1 also plays an important role in regulating Aβ clearance and its expression has been associated with neurological disorders, including Alzheimer's disease[34, 35]. Altogether, these findings show that miR-33 is playing key roles in controlling many physiological processes and much work is necessary to understand the impact of anti-miR-33 therapy in human physiology to rule out possible adverse effects of the chronic treatment with anti-miR-33 oligonucleotides.

Other miRNAs that regulate lipid metabolism

Additional miRNAs (miR-106, miR-758, miR-26, miR-370, miR-378/378*, let-7, miR-27, miR34a and miR-335) have been described to participate in the regulation of lipid metabolism. Among them, miR-758, miR-26 and miR-106b have been shown to regulate cellular cholesterol efflux by targeting ABCA1 in macrophages, hepatocytes and neuronal cell lines, therefore indicating that the post-transcriptional regulation of ABCA1 expression is mediated by multiple miRNAs[12, 18, 36]. miR-370 has been shown to reduce fatty acid β-oxidation via its targeting activity towards *Cpt1a*[11]. In addition, miR-370 appears to participate in the regulation of miR-122 by increasing the expression of lipogenic genes, including *Srebp1* and *Dgat2*[11]. miR-34a targets hepatic sirtuin 1 (*Sirt1*) and interestingly, the expression of miR-34a was inversely correlated with levels of SIRT1 in fatty livers of diet-induced obese mice[37]. Both strands of *miR-378* have been shown to regulate TG synthesis in 3T3-L1 adipocytes, thereby cooperating in the regulation of lipid accumulation during adipogenesis[9]. Interestingly, overexpression of miR378/378* in ST2 cells increases the expression of fatty acid binding protein 4 (*FABP4*), *FASN*, *SCD1*, Kruppel-like factor 15 (*KLF15*), and resistin[9]. Finally, let-7, miR-143, miR-335, miR-27 and miR-103/107 were also reported to control adipocyte differentiation[8, 13, 14, 17, 20, 21].

microRNAs as regulators of glucose metabolism and insulin signaling

Diabetes mellitus is the most common metabolic disorder world-wide and is a major risk factor for cardiovascular disease[38]. Diabetes mellitus is characterized by elevated blood glucose levels due to a lack of insulin-producing pancreatic β-cells (Type 1 diabetes) or insulin resistance in peripheral tissues (Type 2 diabetes)[38]. Plasma glucose levels are tightly controlled by insulin and glucagon. Changes in circulating glucose modulate insulin production by the pancreatic β-cells, leading to an increase in glucose uptake in peripheral tissues, including the muscle and adipose tissue[39]. Moreover, insulin inhibits glucose synthesis and glycogen degradation and stimulates lipid synthesis in the liver[39].

Insulin binds to its receptor (INSR) and stimulates an intracellular signaling pathway involving IRS1 and 2, phosphatidylinositol 3-kinase (PI3K) and AKT[40]. AKT phosphorylates and inactivates forkhead box O1 (FOXO1), a key transcription factor that regulates glucose 6-phosphatase (*G6pc*) and phosphoenolpyruvate carboxykinase (*Pck1*) expression, leading to a significant reduction of glucose production in the liver[41]. Insulin also stimulates the translocation of glucose transporters, such as GLUT-4 in the muscle and adipose tissues, thus promoting glucose clearance[42]. In addition to hormones, miRNAs have emerged as critical regulators of glucose metabolism by regulating insulin production and secretion, as well as insulin sensitivity. The global impact of miRNAs in glucose production

and pancreatic β-cell functions was defined with the generation of pancreas-specific *dicer* knockout mice[43]. These mice survive until birth but fail to grow and die by postnatal day 3. The absence of miRNAs during pancreatic β-cell development causes defective Notch signaling, leading to an increase in cell death and several defects in all pancreatic cell lineages[43]. To solve this problem, Melkman-Zehavi and colleagues developed pancreatic dicer-conditional knockout mice inducible upon treatment with tamoxifen[44]. Inactivation of pancreatic *dicer* expression in adult mice results in enhanced blood glucose and reduced plasma insulin levels[44]. *Dicer*-deficient β-cells show a significant decrease in insulin synthesis and secretion, which is associated with the up-regulation of basic helix-loop-helix family member e22 (*Bhlhe22*) and Sox6, two transcriptional repressors of the *insulin* gene[44]. Interestingly, four miRNAs, including miR-24, miR-26, miR-182 and miR-148 regulate *Bhlhe22* and *Sox6* expression at the post-transcriptional level and are significantly down-regulated in *dicer*-deficient pancreatic β-cells[44].

Besides the studies in *dicer* null mice, several reports have recently shown the critical role of specific miRNAs in regulating insulin production and sensitivity. The importance of some of them will be discussed in the following sections of this review article.

miR-375

miR-375 is one of the most abundant miRNAs in the pancreas and regulates insulin secretion independently of changes in plasma glucose levels[45]. *miR-375* null mice are normoinsulinemic but hyperglycemic and glucose intolerant [46]. These mice also have an increase in the number of pancreatic α-cells and fasting and fed plasma glucagon levels[46]. The increase in plasma glucagon levels results in a significant increase in G6PC and PCK1 expression and glucose production in the liver. miR-375 also regulates the expression of a cluster of genes controlling cellular growth and proliferation, including caveolin-1 (*Cav-1*), inhibitor of DNA binding 3 (*Id3*), Ras-dexometasone-induced-1 (*Rasd1*) and the human antigen D/embryonic lethal abnormal vision-like 4 (*HuD/Elavl4*)[46]. HuD/Elavl4 is an RNA-binding protein that regulates preproinsulin (*Ins2*) translation and insulin production[47]. This finding suggests that the reduced insulin secretion observed in the pancreatic β-cells from the miR-375 null mice may be due to increased HuD expression in pancreatic β-cells. Moreover, miR-375 targets myotrophin (*Mtpn*), a gene involved in actin depolymerization and vesicular trafficking, thereby reducing insulin exocitosis[46].

Other miRNAs that regulates insulin secretion

In addition to miR-375, other miRNAs have been shown to regulate insulin release including miR-124a, miR-9, miR-96a and miR-33[48–51]. miR-124a regulates insulin secretion by controlling the expression of *Rab27a* which is involved together with its effector, granuphilin/Slp4, in the exocytosis of insulin-containing secretory granules in pancreatic β-cells[48]. Granuphilin/Slp4, a Rab effector known to negatively modulate insulin exocytosis, is also regulated by miR-9, which directly targets Onecut-2 (*Oc2*)[49, 50]. OC2 binds to the granuphilin promoter and represses its transcriptional activity. Therefore, over-expression of miR-9 in insulin-secreting cells results in a reduction of insulin exocytosis elicited by glucose or potassium[49, 50]. Similarly to miR-9, miR-96 also up-regulates the expression of granuphilin, but independently of OC2[48]. miR-96 and miR-124a over-

expression also inhibits Noc2, a Rab effector involved in exocytosis, in an insulin-secreting mouse cell line (MIN6B1)[48]. Lastly, miR-29 also controls insulin secretion by regulating the monocarboxylate transporter 1 (*Mct1*) expression[52]. In summary, these reports demonstrate that miR-9, mi-96 and miR-124 control the expression of multiple genes regulating the exocytotic machinery to fine-tune insulin release.

Changes in cellular cholesterol content affect insulin secretion. In this regard, the ABCA1 transporter plays an important role in regulating cholesterol homeostasis in pancreatic β-cells. Indeed, β-cell specific deletion or loss-of function mutations in ABCA1 result in impaired glucose tolerance, insulin secretion and β-cell dysfunction[53]. Very interestingly, it has been recently shown that miR-33 also modulates the expression of ABC transporters in human and mouse pancreatic islets[51]. Overexpresion of miR-33 reduces the expression of ABCA1 and insulin secretion in primary islets and MIN6, a mouse insulinoma cell line. Conversely, endogenous inhibition of miR-33 increases ABCA1 expression and insulin secretion in wild-type mouse islets but not in islets isolated from ABCA1-deficient mice[51]. Altogether, these results suggest that miR-33 also plays an important role in regulating insulin secretion and glucose homeostasis. Further studies are important to elucidate the role of miR-33 in regulating glucose metabolism *in vivo*.

Regulation of insulin signaling by miRNAs

Other miRNAs regulate insulin sensitivity in the liver and peripheral tissues by controlling the expression of many components of the insulin signaling pathway, including insulin-like growth factor receptor 1 (IGF1R), insulin receptor (INSR), IRS2, phosphatidylinositol 3-kinase regulatory subunit-α (PIK3IP1), AKT2, tuberous sclerosis protein 1 (TSC1), CAV1 and rapamycin-insensitive companion of mTOR (RICTOR).

Two independent groups have recently shown that the Let-7 family of miRNAs regulates glucose homeostasis and insulin sensitivity[54, 55]. Global and pancreas specific over-expression of *Let-7* in mice results in impaired glucose tolerance and reduced glucose-induced pancreatic insulin secretion[54, 55]. Specific knockdown of Let-7 in *Let-7* transgenic mice reverses the phenotype by improving insulin sensitivity in the muscle and adipose tissues. Let-7 directly targets many components of the insulin-signaling pathway such as *Igf1r*, *Insr*, *Irs2*, *Pik3ip1*, *Akt2*, *Tsc1*, and *Rictor*, thereby reducing insulin sensitivity[54, 55]. LIN28 tightly controls the expression of Let-7. This RNA-binding protein represses the biogenesis of Let-7 miRNAs and is highly expressed during normal embriogenesis and is up-regulated in some cancers[56, 57]. Interestingly, *Lin28* transgenic mice reduce the expression of Let-7 and improve glucose clearance and insulin sensitivity[55]. By contrast, skeletal muscle-specific *Lin28* knockout mice show impaired glucose tolerance[55]. Altogether these studies strongly suggest that the *Lin28/Let-7* axis regulates glucose metabolism[54, 55].

In addition to Let-7, other miRNAs, including miR-33, miR-103, miR-107 and miR-29a/b, also regulate the insulin-signaling pathway[6, 52, 58, 59]. As described before, miR-33 targets *Irs2* and regulates insulin sensitivity in human hepatic cell lines. Moreover, miR-33 also regulates the expression of *Ampkα* and *Sirt6*, which are involved in regulating lipid and

glucose metabolism[6]. *miR-103* and *miR-107* were recently shown to be up-regulated in obese mice[59]. Moreover the expression of both miRNAs is increased in subjects with NAFLD, a condition often associated with diabetes. *miR-103* and *miR-107* have similar mature sequences and are thought to target similar genes. Over-expression of miR-107 results in an increase in fasting glucose and insulin levels[59]. Conversely, silencing of miR-103/miR-107 enhances insulin sensitivity in the liver and in the adipose tissue. Mechanistically, miR-103/107 inhibition increases the expression of CAV-1, a scaffold protein required for caveolae formation, and enhances insulin signaling by increasing insulin receptor stability in the cell membrane[59]. Indeed, miR-103/107 antagomirs are not able to enhance insulin sensitivity in *Cav-1* null mice. miR-29a and miR-29b are also up-regulated in white adipose tissue and in the liver of diabetic rats. In addition, to targeting *Cav-2*, another caveolae structural component[52, 58], the miR-29 family members also regulate phophatidylinositol 3-kinase regulatory subunit alpha (PIK3R1), which regulates insulin signaling.

Other miRNAs that regulates glucose homeostasis

The complexity of miRNAs in regulating physiological processes is exemplified by *miR-208a*, a heart-specific miRNA that also regulates glucose metabolism and energy homeostasis[60]. miR-208 regulates the expression of the mediator complex 13 (MED13) which controls the transcription of the thyroid hormone (TH) and other nuclear hormone receptors. TH enhances energy expenditure and regulates body weight. Interestingly, mice administrated with anti-miR-208 oligonucleotides are resistant to obesity and glucose intolerant[60]. In contrast, *Med13* cardiac-specific transgenic mice are resistant to diet-induced obesity with improved glucose tolerance[60]. This remarkable finding demonstrates how a cardiac-specific miRNA is able to regulate systemic energy homeostasis.

Besides the role of miR-208 in the heart, another interesting possibility that could be explored is that this miRNA maybe secreted in microvesicles by the heart and regulate insulin signaling and glucose metabolism in other peripheral tissues. However, several studies have not be able detect miR-208 in the plasma of subjects with type 2 diabetes (D2M) or dyslipidemia[61].

In summary, multiple miRNAs are able to control glucose metabolism by regulating a network of genes in the liver and peripheral tissues. The contribution of specific miRNAs will be determined by the tissue and metabolic state.

Circulating miRNAs

Recently, several studies have highlighted the presence of miRNAs in the plasma. Plasma miRNAs are packaged in microvesicles (including exosomes) that protect them from degradation[62]. Moreover, recent reports have also identified these small RNAs associated with proteins including the RNA-binding protein Argonaute 2 (AGO2)[63]. The role of circulating miRNAs is under intense investigation and some studies suggest that they might play important roles in regulating atherogenesis and endothelial cell functions. Some miRNAs are enriched in the plasma under pathological conditions, including myocardial infarction (miR-208, miR-1, miR-133a and miR-21)[64], hepatic steatosis and hepatic injury

(miR-122)[65] and hypertension (Let-7e)[66] or reduced such as miR-126 in D2M[61]; therefore they can be used as disease biomarkers. Finally, Vickers and colleagues have also recently found miRNAs associated with lipoproteins. Interestingly, the HDL-miRNA profile of normal subjects is significantly different from that of familial hypercholesterolemia subjects[67]. HDL-miRNAs can be delivered to hepatic cells via the scavenger receptor class B type I (SR-BI), however the physiological relevance of this process in regulating gene expression in the liver and peripheral tissues, including atherosclerotic plaque macrophages, remains unknown and warrants further investigation.

Concluding remarks

miRNAs have emerged as key regulators of many physiological processes including lipid and glucose metabolism. Several preclinical studies have pointed out that targeting specific miRNAs, such as miR-33, miR-122, miR-103/107 and let-7 may be a promising strategy to ameliorate cardiometabolic disorders. However, the complexity of gene networks that a single miRNA may control and the potential adverse effects of the total inhibition of a specific miRNA remains to be deeply explored. For example, a global deficiency of miR-122 results in reduced plasma cholesterol levels but increased hepatic steatosis and hepatic cancer[23, 25]. Contrastingly, miR-122 pharmacological inhibition for few a months leads to a significant reduction of plasma lipid levels and reverses hepatic steatosis in mice. These paradoxical results strongly suggest that much work is necessary to fully understand the role of a single miRNA in regulating animal physiology. New approaches that integrate RNA-sequencing, proteomics and system biology methodologies will help us to elucidate how the modulation of gene networks by miRNAs contribute to the regulation of metabolic processes.

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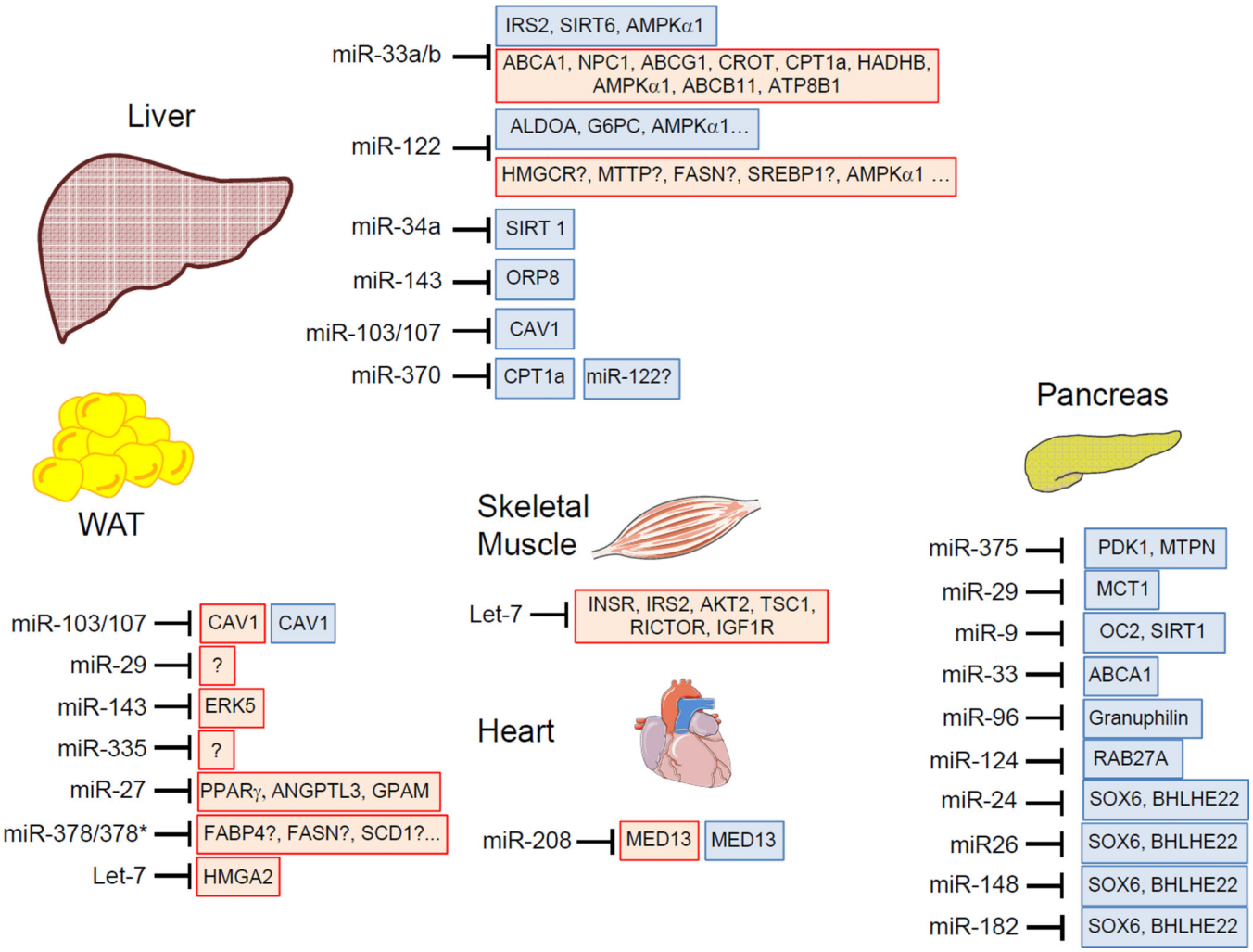

Figure 1. miRNA regulation of lipid metabolism, insulin signaling and glucose homeostasis

Schematic overview of miRNAs involved in the regulation of glucose and lipid metabolism. Red boxes highlight genes involved in lipid metabolism and blue boxes highlight those genes related to insulin signaling and glucose homeostasis. Unknown direct target genes or molecular mechanisms that regulate the highlighted genes are marked with a question mark. **Note that the target genes showed in the figure are those validated experimentally but these genes can be also modulated by other miRNAs and the miRNAs highlighted can regulate other genes that do not appear in the figure.**

Table

MicroRNA involved in lipid and glucose

Regulator	Tissue/Cell Type	Target genes	Function	Reference
Let-7	Mouse adipose and skeletal muscle	*INSR, IGF1R, IR2, TSC1, RICTOR*	↑Insulin Sensitivity,↑ Glucose metabolism	54,55
	3T3-L1 cells	*HMGA2*	↓Adipogenesis, Adipose differentiation	20
miR-9	NS-1E cells, Mouse pancreatic β islets	*OCT, SIRT1*	↓Insulin secretion	49,50
miR-24	Mouse pancreatic β cells	*SOX6, BHLHE22*	↑Insulin biosynthesis	44
miR-26	Mouse pancreatic β cells	*SOX6, BHLHE23*	↑Insulin biosynthesis	45
miR-27	3T3-L1 cels	*PPARG, ANGTPL3, GPAM*	↓Adipogenesis, Adipose differentiation	13,14
miR-29	MIN6 cells, Mouse pancreatic β islets 3T3-L1 cels	*MCT1* ?	↓Insulin secretion	52 58
miR-33a/b	Huh-7, HepG2, Mouse liver	*ABCA1, ABCG1, ABCB11, ATP8B1*	↓ Cholesterol Transport/Export	15, 16, 19, 33
	Huh-7, HepG2, Mouse liver	*NPC1, CROT, CPT1A, HADHB, AMPKα1*	↓ β-Oxidation	10,19,6
	Huh-7, HepG2, Mouse liver	*IRS2, SIRT6*	↓Insulin signaling	6
	MIN6 cells, Mouse and human pancreatic β islets	*ABCA1*	↓Insulin secretion	51
miR-34a	HepG2, Mouse liver	*SIRT1*	↑Insulin secretion	37
miR-96	INS-1E cells, MIN6 cells	*Granuphilin*	↓Insulin secretion	48
miR-103/107	3T3-L1 cels, Mouse Liver	*CAV-1*	↓Adipose differentiation, ↓Insulin sensitivity	59
miR-122	Mouse liver	*HMGCR*	↑Cholesterol Synthesis	22
	HepG2	*ALDO, G6PC*	Glucose homeostasis	7
		AMPKα1	↑ β-Oxidation	7
miR-124	MIN6 cells	*RAB27A*	↓Insulin secretion	48
miR-143	Human adipocytes	*ERK5*	↑Adipose differentiation	8
miR-148	MI N6 cells	*SOX6, BHLHE22*	↑Insulin biosynthesis	44
miR-182	MI N6 cells	*SOX6, BHLHE23*	↑Insulin biosynthesis	45
miR-208	Mouse heart	*MED13*	↑Insulin sensitivity, ↑glucose tolerance	60
miR-370	HepG2	*CPT1A*	↓ β-Oxidation	11
miR-375	Mouse pancreas	*PDK, MTPN*	Pancreas homeostasis	46
miR-378/378*	3T3-L1 cels	*FABP4, FASN, SCD1*	↑Adipose differentiation	9