Role of microRNAs in Obesity-Related Kidney Disease

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1. Introduction

Obesity is a burgeoning global epidemic and represents an important risk factor for the development and progression of chronic kidney disease (CKD). Indeed, the incidence of obesity-associated nephropathies, as one of the complications of obesity, has risen 10-fold over the last years [1]. Increased fat deposition can lead to a systemic and chronic inflammation, alterations in renin–angiotensin–aldosterone system (RAAS), generation of reactive oxygen species (ROS), as well as hemodynamic and morphological changes in the kidney [2][3][4][5]. All these mutually interdependent processes may subsequently lead to a deterioration of kidney function and its progression to end-stage renal disease (ESRD). Regardless of numerous reports associating fat accumulation and lipotoxicity to renal damage, the underlying pathways responsible for the development of obesity-associated renal impairment is not fully understood.

miRNAs are short non-coding, single stranded RNA molecules who have a critical role in the regulation of gene expression. miRNAs have been reported to be involved in fundamental biological processes, thus playing an essential role in normal organ development and homeostasis [6][7]. Moreover, miRNAs have been identified as important players in a variety of pathophysiological conditions such as cancer, autoimmune diseases, cardiovascular and renal disorders [8][9][10]. Owing to their unique characteristics such as highly conserved nucleotide sequence of small length and known composition, miRNAs represent a potential basis for the development of novel therapies for miRNA-associated diseases.

2. miRNAs and Their Functional Role in Obesity-Related Kidney Disease

Numerous studies have supported the role of miRNAs in diverse renal diseases, yet the knowledge of their role in obesity-associated nephropathy is scarce. Here we describe the contribution of miRNAs to different aspects of obesity-associated renal disease. We depict how miRNAs influence initiation and progression of obesity-related kidney injury. In addition, wherever possible, we describe signaling pathways involved in miRNAs-mediated responses in the kidney (**Table 1**).

Table 1. miRNAs involved in obesity-associated nephropathy.

miRNA	Experimental Model	Expression Pattern	Target Gene	Signaling Pathway	Reference
miR-155	C57BL/6J HFD MECs	Increase	SHIP1/INPP5D	SHIP1/NF-kB	[11]
	T2DN patients HFD/STZ	Increase	n/i	NF-kB	[12]
miR-146a	HFD/STZ	Increase	n/i	NF-kB	[12]
miR-802	C57BL/6J HFD Obese patients	Increase	NRF	NF-kB/NRF	[13]
miR-451	db/db PBMCs GMCs	Decrease	LMP7	LMP7/NF-kB	[14]
	TallyHo/Jng HFD		YWHAZ, CAB39	mTOR	[15]

miRNA	Experimental Model	Expression Pattern	Target Gene	Signaling Pathway	Reference
miR-18a-5p	db/db Podocytes	Decrease	ATM	n/i	[16]
miR-130b	adipoKO HFD	Increase	n/i	n/i	[17]
miR-21	HuCRP HFD	Increase	n/i	PPAR-y	[18]
miR-365	HFD/STZ HK2	Increase	BDNF	BDNF/TrkB	[19]
miR-34a-5p	HFD/STZ HK2	Increase	SIRT1	SIRT/TGF-b1	[20]
miR-26a-5p	HFD/STZ HK2 T2DN patients	Decrease	CHAC1	CHAC1/NF-kB	[21][22]
miR-10a	HFD/STZ	Decrease	CREB1	HDAC3/CREB1	[23]
miR-133b	HFD/STZ	Increase	RB1CC1	AMPK/PI3K	[24]
miR-342	HFD/STZ	Increase	MAP1LC3B	AMPK/PI3K	[24]
miR-30a	HFD/STZ	Increase	ATG-12	AMPK/PI3K	[24]
miR-214-3p	HFD/STH	Increase	n/i	PTEN/Akt	[25]

HFD, high fat diet; MECs, microvascular endothelial cells; T2DN, diabetic nephropathy in type 2 diabetes; STZ, streptozotocin; PBMCs, peripheral blood mononuclear cells; GMCs, glomerular mesangial cells; HK2, human proximal tubular epithelial cells; STH, sodium taurocholic injection.

miR-155 is expressed in diverse cells of the kidney such as tubular cells, endothelial and stromal cells, and its elevated levels have been reported to be associated with different types of CKD. Zheng et al. (2019) demonstrated an important role for miR-155 in obesity-associated nephropathy [11]. Namely, the authors revealed that mice fed a high fat diet (HFD) exhibited a marked increase of renal miR-155 which positively correlated with structural and functional damage of the kidney. Moreover, treatment of renal microvascular endothelial cells with palmitic acid led to an increase of miR-155 expression followed by lipotoxic cell damage, inflammation, and oxidative stress. The authors demonstrate that miR-155 directly targets the 3´-UTR of SHIP1/INPP5D and suppresses its expression in vitro and in vivo inducing renal inflammatory response through the NF-kB pathway [11]. Interestingly, specific inhibition of miR-155 led to a suppression of SHIP1/NF-kB signaling in the kidney and significantly ameliorated diet-induced inflammation, oxidative stress, and renal dysfunction [11]. Similar results were obtained in T2DN, a renal disorder characterized by obesity and renal lipid accumulation. Namely, the authors showed a marked increase of miR-155 expression in human and rat kidneys affected by T2DN [12]. The same group described a similar pattern of expression for miR-146a in T2DN [12].

Another piece of evidence on the role of miRNAs in obesity-associated nephropathy is the recent work of Sun et al. (2019) [13]. Namely, the authors demonstrated a marked increase of miR-802 expression in the kidneys of C57BL/6J mice fed a HFD, which positively correlated with renal functional parameters of obese mice, such as serum BUN and creatinine [13]. Consistently, obese patients demonstrated higher circulating levels of miR-802 than lean subjects, which correlated positively with creatinine levels but negatively with creatinine clearance. Interestingly, using ultrasound-based microbubble carrying lentivirus delivery method to silence renal miR-802, the authors confirmed that the inhibition of miR-802 protected against HFD-induced inflammation, macrophage infiltration, fibrosis, and functional kidney damage. Mechanistically, Sun et al. provide the evidence of direct binding of miR-802 to 3′UTR of NF-kB repressing factor (NRF) and confirmed that miR-802/NF-kB/NRF signaling could be one of the molecular mechanisms governing the progression of obesity-related nephropathy. The authors proposed therapeutic benefits of using miR-802 inhibitor and suggest miR-802 as a potential biomarker of renal dysfunction in obese subjects [13].

Sun et al. (2016) [14] proposed a protective role for miR-451 in kidney injury associated with obesity. Namely, the authors showed a significant downregulation of miR-451 in the kidneys of obese db/db DN mice and peripheral blood mononuclear cells (PBMCs) of patients with DN. Consistently, mesangial cells treated with high glucose showed a dose dependent downregulation of miR-451 [14]. Sun et al. confirmed that miR-451 directly targets 3′-UTR of LMP7 and suppresses LMP7/NF-kB pathway regulating downstream proinflammatory molecules in mesangial cells. Importantly, overexpression of miR-451 significantly ameliorated glomerular injury, albuminuria and expression of proinflammatory and

profibrotic factors in the renal cortex of db/db obese mice. Another piece of evidence on the role of miR-451 in the obesity-induced kidney damage is the study of Fluitt et al. (2020) [15]. The authors used an insulin resistant TallyHo/Jng (TH) mouse model shown to be unsusceptible to the development of renal inflammation, injury and fibrosis and they assessed the role of miR-451 in the initiation of nephropathy induced by HFD feeding. Of interest, prolonged systemic inhibition of miR-451 led to a significant renal hypertrophy, albuminuria, kidney injury, fibrosis, and glycogen deposition, as well as dysregulation of autophagy in TallyHo/Jng (TH) obese mice. Moreover, in vitro experiments confirmed the YWHAZ and CAB39 as direct targets for miR-451 and supported the role for miR-451 in reducing renal tubular damage by enhancing autophagy in obese mice via the mTOR signaling pathway [15].

miR-18a-5p was found to be markedly downregulated in kidneys of obese db/db mice with an evident renal glomerular dysfunction and injury [16]. Upregulation of miR-18a-5p by resveratrol treatment in mice led to an increase of autophagy and a decrease of apoptosis in the affected kidney, alleviating kidney damage in obese mice. Consistently, overexpression of miR-18a-5p in podocytes confirmed the in vivo results, proposing this miRNA as a negative regulator of apoptosis via modulation of autophagy. The authors identified the Atactic telangiectasis mutation (ATM) gene as a direct target of miR-18a-5p and proposed that the effect of this miRNA on autophagy and apoptosis might be governed via targeting ATM.

miR-130b has also been investigated in the context of obesity-associated renal disease. Particularly, the authors found a marked increase of miR-130b levels and an accelerated kidney dysfunction in adiponectin KO (adipoKO) mice fed a HFD [17]. AdipoKO mice fed an HFD showed signs of renal hypertrophy, albuminuria, lipid accumulation, and decreased nephrin expression. The authors propose that increased expression of miR-130b in adipoKO mice fed an HFD may contribute to renal lipid accumulation, and subsequently to the progression of renal disease in the absence of renoprotective effect of adiponectin.

miR-21 has been one of the widely investigated pathogenic miRNAs in renal disease, mostly due to its profibrotic characteristics and involvement in the TGF-β1 signaling pathway [26]. Of interest, Morrison et al. (2017) [18] investigated the involvement of miR-21 in obesity-associated renal dysfunction. In vivo, HuCRP transgenic mice fed a lard-based HFD developed obesity accompanied by albuminuria, renal inflammation, injury, and fibrosis. The authors demonstrated that obese mice showed an increased expression of miR-21 in the kidney compared with mice fed a regular chow, which correlated significantly with the expression of renal tubular injury marker Kim-1 and the grade of renal fibrosis. The authors propose PPAR-γ pathway as a possible link in regulating miR-21 levels in obesity-induced nephropathy [18].

As stated above, T2DN has also been considered an obesity-associated kidney disease [27], while the renal lipid accumulation and metabolic changes related to obesity have been shown to be essential for the onset and progression of T2DN. One of the animal models frequently used to study the pathological progression of type 2 diabetes and its consequences to other organs, is the high fat diet-streptozotocin (HFD/STZ) rodent model. Thus, Zhao et al. (2021) [19] described the role of miR-365 in nephropathy induced by the HFD/STZ treatment in rats. miR-365 was significantly expressed in diseased renal tissue alongside an elevated serum BUN and creatinine, urinary albumin, and inflammatory markers. The authors proposed that miR-365 had a potential binding site for BDNF and that the increase of miR-365 repressed the protein expression of BDNF and p-TrkB, thereby promoting the kidney damage through BDNF/TrkB signaling axis. Downregulation of miR-365 led to a reduced secretion of inflammatory cytokines and profibrotic markers in high glucose-treated human proximal tubular epithelial (HK2) cells, while increased BDNF expression allowed for alleviation of renal cell damage and dysfunction [19].

Xue et al. (2018) [20] demonstrated an involvement of miR-34a-5p in T2DN induced by HFD/STZ in mice and proposed this miRNA as a promising candidate for the development of a novel therapeutic tool to prevent/treat DN. Namely, miR-34a-5p showed a significant upregulation in the renal tissue of HFD/STZ-induced diabetic mice and high glucose treated HK2 cells, alongside a dramatical increase of profibrotic markers such as collagen, fibronectin, and TGF-β1. The authors provide evidence that miR-34a-5p directly targets 3′UTR of SIRT1 as its genuine target and propose miR-34a-5p/SIRT/TGF-β1 signaling as a crucial in tubulointerstitial damage during T2DN [20].

Li et al. (2019) [21] proposed a protective role for miR-26a-5p in kidney dysfunction induced by HFD/STZ treatment. The authors demonstrated that inhibition of miR-26a-5p in HK2 cells promoted inflammatory response in these cells, while its overexpression ameliorated cell dysfunction. Using TargetScan and luciferase reporter assay, the authors confirmed that miR-26a-5p directly targeted the 3′-UTR of CHAC1 in HK2 cells, while subsequent gain- and loss-of-function experiments revealed that miR-26a-5p ameliorated the inflammatory response in renal cells through the CHAC1/NF-kB pathway. Interestingly, the same group showed that miR-26a-5p was significantly decreased in urinary exosomes of T2DN patients [21][22].

Shan and colleagues (2016) [23] assessed the role of miR-10a in extracellular matrix accumulation in the kidney of diabetes mellitus induced by combined treatment of HFD/STZ. They observed that both HFD and HFD/STZ administration decreased levels of miR-10a expression in the mouse kidney. Moreover, tail intravenous injection of miR-10a mimics attenuated the higher urine albumin-to-creatinine (ACR) ratio and reversed the kidney damage induced by HFD/STZ, while silencing of miR-10a elevated the kidney ACR ratio in naive mice. Of interest, Shan et al. demonstrated that miR-10a directly targeted the 3′UTR of CREB1, thus regulating the production and accumulation of extracellular matrix and kidney function in obesity-induced nephropathy. Altogether, the authors propose the HDAC3/miR-10a/CREB1 pathway as a new possible signaling mechanism governing kidney injury in type 2 diabetes.

Matboli et al. (2017) [24] described the role of miR-133b, miR-342, and miR-30a in nephropathy induced by HFD/STZ treatment in rats. Analyzed miRNAs were significantly upregulated in diseased renal tissue alongside an elevated serum lipids and BUN, creatinine clearance, and urinary albumin. Furthermore, the authors identified autophagy genes RB1CC1, MAP1LC3B, ATG-12 as direct targets of miR-133b, miR-342, and miR-30a, respectively. The authors hypothesized that HFD/STZ upregulated miR-133b, miR-342, and miR-30a with subsequent downregulation of autophagy in the kidney leading to renal dysfunction possibly via the AMPK/PI3K pathway [24].

miR-214 has been shown to be highly expressed in human renal disease and animal models of kidney disease [28]. Thus, Yan et al. (2019) found miR-214-3p to be upregulated in the kidney and serum of rats treated with a combined treatment of long-term HFD and short-term sodium taurocholic injection [25]. Rats developed renal damage and pancreatitis followed by an inhibition of PTEN expression and an increase of pAkt levels in kidneys. Treatment of rats with anti-miR-214-3p reversed the renal inflammation and fibrosis, as well as expressions of PTEN and pAkt. The authors propose the miR-214-3p/PTEN/Akt pathway as responsible for tissue damage and fibrosis in HFD/sodium taurocholic rat model.

Li et al. [29] showed strong dysregulation of miRNA expression profile in both porcine model and human subjects with obesity and metabolic syndrome (MetS). Namely, delivery of extracellular vesicles produced by adipose tissue mesenchymal stem cells from obese MetS pigs to animals with renovascular disease aggravated senescence and renal fibrosis in injured kidneys [29].

3. miRNAs as a New Therapeutic Approach in CKD: Advantages and Perspectives

Given the ample evidence of the involvement of miRNAs in the pathogenesis of various diseases, it is plausible to think that modulation of miRNAs and their function could be used as a therapeutic approach in different renal diseases, including obesity-associated nephropathies. miRNAs play essential roles in the gene regulation and have the ability to inflect numerous gene pathways [10]. Owing to their specific features, such as highly conserved short sequence of known nucleotide composition, miRNAs represent a new attractive class of targets for potential therapeutic mediation [30].

Principally, we can distinguish two approaches in the development of miRNA-based therapeutics: (a) inhibition and (b) restoration of miRNA activity/function. The specific miRNA activity can be silenced by using several methods that comprise chemically modified antisense oligonucleotide (ASO) inhibitors or the transgenic introduction of tandem miRNA-binding site repeats (known as Decoy or Sponge technologies) [31][32][33]. Modified antisense oligonucleotides (hereafter called anti-miRs) are composed of full or partially complementary reverse sequence of a mature miRNA and are capable of reducing indigenous levels of specific miRNA. Anti-miR works as a competitive inhibitor of miRNAs and elicits its effects following the annealing to the mature miRNA guide strand after the RNA-induced silencing complex has removed the passenger strand [34]. According to Rooij et al. [35], the essential requirements for a successful and effective anti-miR are (a) cell permeable chemistry; (b) slow excretion; (c) an in vivo stability; (d) high specificity binding to the miRNA of interest [35]. Therefore, several modifications were done in this context so far, such as chemical modifications for stability and cholesterol conjugation for better cellular uptake [32]. Thus, some examples of these approaches are the inhibition of miR-122 by 2′-O-methoxyethyl phosphorothioate antisense oligos [36], cholesterol-tagged 2′-O-Me antisense oligo (antagomir-122) [32], or antisense locked nucleic acid modified oligos (LNA–anti-miR) [37] that ameliorated hypercholesterolemia in mouse models [32][36][37]. Moreover, systemic delivery of LNA–anti-miR-122 led to a long-lasting decrease of total plasma cholesterol in a nonhuman primate model without any evidence for LNA-associated toxicity, thus confirming the potential of modified oligonucleotides as a novel class of therapeutics for disease-associated miRNAs [31].

Another described approach for the inhibition of specific miRNA action is the expression of tandem repeats of miRNA-binding sites (Decoy or Sponge) [33][38]. Namely, miRNA sponges contain complementary binding sites to a miRNA of interest, specifically to its seed region. Therefore, according to Ebert et al. miRNA sponges should be able to block a whole family of related miRNAs [33]. Zheng et al. (2019) demonstrated that suppression of renal miR-155 by miR-155

sponge treatment efficiently attenuated HFD-induced renal inflammation, lipotoxicity, macrophage infiltration, as well as structural and functional damage of the kidney induced by obesity in mice [11].

In renal pathologies in which miRNAs are downregulated, a potential therapeutic approach would be the reestablishment of miRNA's function by the administration of miRNA mimic. miRNA mimics are double-stranded RNA molecules which can separate intracellularly to a single-stranded RNA. Subsequently, one strand loads into the RISC and functions as a miRNA [30]. Restoration of expression of several miRNAs such as miR-146, miR-155, miR-451, miR-10a, miR-18a-5p using RNA mimic technology ameliorated significantly renal injury and dysfunction in different in vitro and in vivo models of renal disease [12][14][16][23]. In spite of significant progress of miRNA mimic technology, there are still issues that need to be addressed before using miRNA mimics in clinical practice. Such issues would be an in vivo delivery, dosage, immune response, cellular uptake, and in vivo stability [28].

Targeting miRNAs to the kidney continues to be an important challenge especially if we wish to bypass possible undesirable consequences in other tissues and organs, as well as target-off effects [26]. Despite many examples of successful delivery of mimics and inhibitors to the kidney via intravenous and subcutaneous injections [39], the aspect of targeting miRNAs to the kidney or specific kidney cells, while at the same time avoiding toxicity and adverse effects in other tissues and/or activation of adaptive immune response, still stays an important issue to be considered. Apart from delivery of miRNAs and safety concerns, another aspect that should be taken into consideration while designing miRNA therapies for the kidney disease would be the clearance of these molecules. Currently, there are scarce data from animal studies dealing with this matter.

Stability of miRNAs is an essential requirement for the miRNA-based therapies. Significant progress has been made to increase RNA stability in vivo by different molecular modifications of the backbone [30]. In this context, development of locked nucleic acid (LNA) technology holds a great promise as LNA-modified oligonucleotides (LNA-anti-miRs) exhibit high binding affinity to complementary RNA target and high stability in vivo and in vitro [31][37]. Furthermore, to augment the affinity for complementary nucleotides, 2′-O-methoxyethyl (2′-MOE) and 2′-oxy-methyl (2′-OMe) modifications have been successfully designed and applied [32][36].

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