MicroRNAs in Nephrotic Syndrome

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Contributor: Kenji Tsuji

Nephrotic syndrome represents the clinical situation characterized by presence of massive proteinuria and low serum protein caused by a variety of diseases, including minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS) and membranous glomerulonephropathy. Differentiating between diagnoses requires invasive renal biopsies in general. Even with the biopsy, we encounter difficulties to differentiate MCNS and FSGS in some cases. There is no other better option currently available for the diagnosis other than renal biopsy. MicroRNAs (miRNAs) are no-coding RNAs of approximately 20 nucleotides in length, which regulate target genes in the post-transcriptional processes and have essential roles in many diseases. MiRNAs in serum and urine have been shown as non-invasive biomarkers in multiple diseases, including renal diseases.

Keywords: Nephrotic Syndrome,MicroRNAs,Biomarkers

1. Introduction

Nephrotic syndrome (NS) is defined as massive proteinuria and low serum total protein due to the disrupted function of glomerular filtration barrier [1][2]. It may cause multiple metabolic effects and complications, including hypercoagulability, bacterial infection and acute kidney injury [2]. The underlying pathological etiologies of NS are diverse. For younger ages, the etiology of NS is more likely to be from minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS), while there are varieties of etiologies for older ages, including MCNS, FSGS, membranous glomerulonephropathy (MGN) and others [3][4]. Accumulating evidence suggests that MCNS and FSGS may be due to the circulating factors [5][6]. For example, Sharma et al. reported that a single injection of plasma obtained from FSGS patients into rats caused transient proteinuria, suggesting that circulating factors might be involved in the pathogenesis in FSGS [7]. Wei et al. reported that soluble form of the urokinase receptor (suPAR), which was shown to activate podocyte integrin β3, might be the cause of FSGS [8]. However, it is still controversial whether suPAR is the pathogenetic of FSGS, and exact pathophysiology of FSGS and MCNS are still uncertain. In the point of prognosis of NS, patients with MCNS are generally steroid sensitive, while patients with FSGS are more likely to be steroid resistant. Although renal biopsy is the standard method to differentiate these diseases especially in adult patients, it is an invasive examination with possible complications. In addition, it is difficult to make the accurate diagnosis in some cases, especially because the glomerular segmental sclerosis in FSGS patients is focal and sometimes patients need repeated biopsies for the accurate diagnosis. Therefore, non-invasive biomarkers may be used to differentiate between different etiologies of NS. In addition, ideal biomarkers also reflect disease activity for monitoring response to treatment, progression and determining disease prognosis.

MicroRNAs (miRNAs) are single-stranded non-coding RNAs, which are an average of 22 nucleotides in length, and which regulate target genes in the post-transcriptional processes [9][10]. In mammals, more than a thousand different miRNAs have been identified [9][10] and these miRNAs are reported to be involved in multiple biological cellular and molecular processes, including cell proliferation, apoptosis and differentiation [11]. In most cases, miRNAs interact with three prime untranslated regions (3′-UTR) in the target genes, which results in the degradation of mRNAs or translational inhibition [12]. Aberrant expression of miRNAs has been reported to be associated with human diseases [12][13]. miRNAs have been reported to be secreted into biological fluid, including serum and urine. miRNAs are also carried in the extracellular vesicles, including exosomes and microvesicles, which are transferred into recipient cells, in which gene translations are regulated as the cell–cell communication. miRNAs have been widely reported as promising biomarkers for many diseases. In fact, they have been shown as non-invasive biomarkers in multiple diseases including cancers and renal diseases [14][15][16][17]. Because miRNAs may directly be associated with pathogenesis of some types of NS, to analyze miRNA profiles in NS patients is not only for the diagnosis for the specific diseases, but also for understanding and elucidating the disease pathogenesis and even for establishing novel therapies. There is accumulating evidence for novel and non-invasive biomarkers of miRNAs as liquid biopsy in NS.

2. miRNAs in Nephrotic Syndrome

There are several reports that have analyzed miRNAs in NS patients (Table 1). Luo et al. analyzed serum and urine miRNAs in child idiopathic NS patients and indicated increased levels in serum miR-30a-5p, miR-151-3p, miR-150, miR-191 and miR-19b as well as urine miR-30a-5p in NS patients compared to healthy controls [18]. Zhang et al. also analyzed child NS patients and reported the increased levels of peripheral blood miR-17-5p in child NS patients compared to healthy controls [19]. Chen et al. analyzed urine samples from child NS patients by high-throughput illumina sequencing via synthesis technology and reported that levels of urine miR-194-5p, miR-146b-5p, miR-378a-3p, miR-23b-3p and miR-30a-5p were higher compared to age and sex-matched healthy controls, and these miRNAs were decreased during the clinical remission period [20]. They also indicated that levels of urine miR-194-5p and miR-23b-3p were positively correlated with levels of urine protein, and proposed that urine miR-194-5p and miR-23b-3p can be the potential biomarkers for diagnosis and monitoring in NS patients. Wang el al. reported that levels of serum miR-503 in child NS patients measured by qPCR were lower than in healthy controls [21]. They used rat mesangial cells to explore the effect of miR-503, and indicated that miR-503 may contribute to the aberrant proliferation by targeting cyclin E, which was found to be the target of miR-503 by luciferase reporter assay. In addition to the analysis of biological fluid, kidney tissues have also been applied for the analysis of miRNAs. Lu et al. analyzed kidney tissues from child NS patients in different subtypes, and indicated that miR-191 levels were higher and miR-151-3p levels were lower in all NS subtypes compared to the controls [22]; that is the different trend as increased levels in both miR-191 and miR-151-3p under the analysis of serum [18]. These differences might be because of the different regulatory mechanism between expression in tissue and secretion into blood or urine. Further exploration might uncover the pathophysiology of podocyte injury and disease mechanism of NS.

Table 1. MiRNAs in nephrotic syndrome.

miRNA	Analyte	Disease	Comparison	Levels	Feature	Reference
miR-30a-5p miR-151-3p miR-150 miR-191 miR-19b	**serum**	**Child NS**	**healthy control**	↑		[18]
miR-30a-5p	**urine**	**Child NS**	**healthy control**	↑		[18]
miR-17-5p	**peripheral blood**	**Child NS**	**healthy control**	↑		[19]
miR-194-5p miR-146b-5p miR-378a-3p miR-23b-3p miR-30a-5p	**urine**	**Child NS**	**healthy control**	↑	• All decrease in clinical remission period • miR194-5p and miR-23b-3p positively correlate with urine protein	[20]
miR-503	**serum**	**Child NS**	**healthy control**	↓		[21]
miR-191	**kidney**	**Child NS**	**healthy control**	↑		[22]
miR-151-3p	**kidney**	**Child NS**	**healthy control**	↓		[22]
miR-638	**urine**	**NS**	**non-NS control**	↓		[23]
miR-16-1	**serum**	**NS**	**healthy control**	↓		[24]

miRNA	Analyte	Disease	Comparison	Levels	Feature	Reference
miR-181a miR-210 miR-30a miR-942 miR-192 miR-586	**serum**	**NS**	**healthy control**	↑	• miR-30a: higher in steroid resistant patients	[25]
miR-181a	**serum**	**NS**	**healthy control**	↑		[26]

NS: nephrotic syndrome; ↑: increase; ↓: decrease.

In the adult study, Wang et al. analyzed the urine sediment from patients with NS caused by diabetes nephropathy (DN), MCNS, FSGS and MGN, and reported that the levels of urine miR-638 in NS patients were lower than non-nephrotic controls, and that urine miR-29a, miR-192 and miR-200c levels were significantly different between diagnostic groups [23]. Specifically, urine miR-200c levels in MCNS and FSGS patients were higher than patients with other diagnosis, while urine miR-192 levels were lower in DN patients compared to patients with other diagnosis. Zapata-Benavides et al. reported that serum miR-16-1 levels in NS patients analyzed by qPCR were lower than healthy controls [24]. Teng et al. also investigated the miRNA profile using serum samples with qPCR verification and reported that serum miR-181a, miR-210, miR-30a, miR-942, miR-192 and miR-586 levels were upregulated in NS patients [25]. In addition, serum miR-30a levels in treatment-resistant NS patients were higher than treatment-sensitive NS patients, indicating the use of miR-30a levels to differentiate between pathological subtypes or predict prognosis. Another report using qPCR indicated the increase in serum miR-181a levels in NS patients compared to healthy controls [26].

This increase and/or decrease in miRNAs might be the reflection of podocyte injury or associated with pathophysiology of the diseases. It is reported that podocyte cytoskeleton is regulated by several miRNAs, including miR-30, miR-132, miR-134 and miR-29a [27]. The increase in serum and urine miR-30a-5p levels in child NS might be associated with the disorder of podocyte cytoskeleton [18][20]. Although the changes in the expression of these miRNAs in NS patients have been shown, further reports are required to differentiate the causes of NS, such as MCNS, FSGS and MGN.

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