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Recent Advances in miRNA Biomarkers for Diagnosis and Prognosis of Focal Segmental Glomerulosclerosis

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Abstract

Background: Focal segmental glomerulosclerosis (FSGS) is an increasingly prevalent group of refractory glomerular diseases and a significant aetiology of end-stage renal disease. Podocyte injury and depletion significantly contribute to the pathogenesis and progression of FSGS. MicroRNAs (miRNAs) are noncoding RNAs that regulate the expression of specific genes in relevant cells, thereby playing crucial roles in the pathogenesis of FSGS. Many studies have shown that miRNAs can be secreted from cells into body fluids and that these miRNAs in the circulation are highly stable. The gold standard for FSGS diagnosis is kidney biopsy; however, the clinical heterogeneity of FSGS, along with variations in histology and nonspecific morphological features, can impact its diagnostic accuracy. Thus, the discovery of novel and efficacious biomarkers is crucial in facilitating the diagnosis of FSGS. In addition, the degree of kidney damage in patients with FSGS varies at different stages, necessitating individualized diagnosis and treatment approaches. Considering the side effects of glucocorticoids, determining whether a patient is steroid resistant is vital. Thus, ideal biomarkers should not only be specific and sensitive but also have the ability to accurately reflect the stage or prognosis of the disease to improve the treatment for patients. ***Summary:*** To date, numerous studies have shown that both urinary miRNAs and plasma miRNAs are potential biomarkers for FSGS. In addition, the identification of miRNA biomarkers specific for the FSGS disease state may provide new insights into the underlying pathological mechanism of FSGS. ***Key Messages:*** Here we summarize the currently available miRNA biomarkers that could help us better understand the diagnosis, disease activity, prognosis, and clinical features of FSGS.

Introduction

In recent years, the prevalence of focal segmental glomerulosclerosis (FSGS) has been increasing worldwide, making it an increasingly common and refractory glomerulopathy, that is significant contributor to end-stage renal disease (ESRD). Data from the USA indicate that

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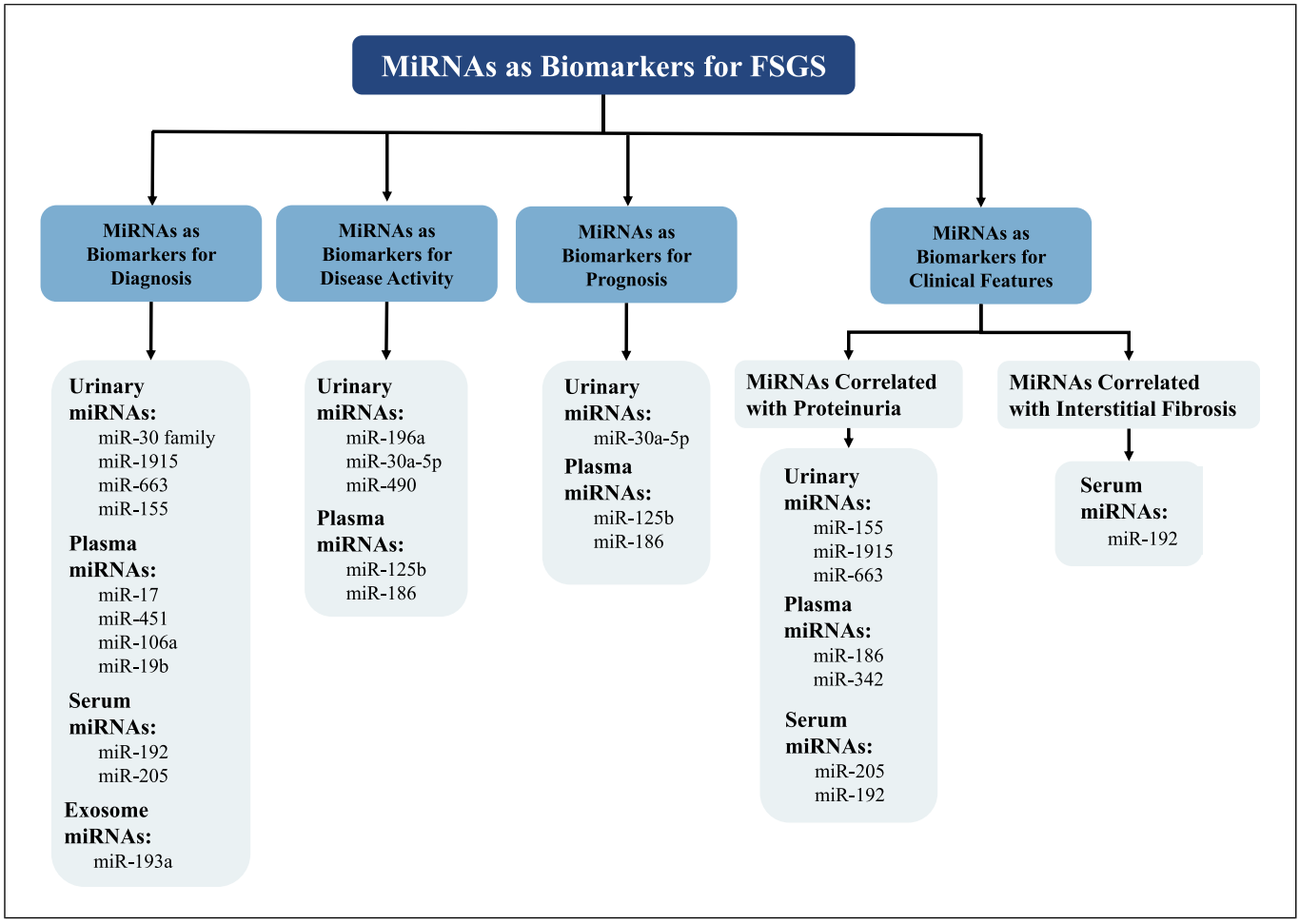

Fig. 1. miRNA as biomarkers for FSGS. FSGS, focal segmental glomerulosclerosis.

approximately 40–60% of ESRD cases are caused by FSGS [1]. Forty percent of adult nephrotic syndrome (NS) cases are caused by FSGS, while 20% of paediatric NS cases are caused by FSGS [2–4]. At present, the gold standard for the diagnosis of FSGS is renal biopsy, but it is a traumatic examination, and the operation technique and puncture site, among others, affect the renal biopsy results; therefore, renal biopsy cannot fully reflect the clinical diversity and different histological and nonspecific morphological features of FSGS. In addition, patients with different stages of FSGS have various degrees of renal injury and receive different medical treatments. The most common pharmacologic therapy for FSGS is still glucocorticoids. It is crucial to determine whether patients are steroid resistant in time to minimize the side effects of glucocorticoids. Repeatable renal biopsies not only cause great physical and psychological harm to patients but also do not fully meet the treatment needs. Therefore, identifying novel biomarkers that can facilitate the diagnosis of FSGS is highly important. The ideal biomarker should not only be specific and sensitive but also reflect the stage or prognosis of FSGS to provide more precise and targeted treatment.

The pathogenesis of FSGS remains poorly understood, but advancements in cellular and molecular biology have substantiated the pivotal role of podocyte injury, and the loss of podocytes is a central process. The pathology is characterized by focal (partial glomeruli) segmental (partial capillary tufts) sclerosis of the glomerulus. In addition, extensive pedicle fusion, subendothelial plasma leakage, and detachment of the pedicle from the glomerular basement membrane can also occur. If left untreated, FSGS undergoes progression, deterioration and eventually leads to ESRD.

FSGS can be divided into primary, secondary, and genetic types according to aetiology. According to the Colombian classification, there are five main types as

follows: collapsing variant, tip lesion variant, perihilar variant, cellular variant, and not otherwise specified [3].

Glomerular podocytes are the primary target of action in most glomerular diseases, including FSGS [5]. The pathogenic mechanisms by which podocytes contribute to glomerular diseases, including FSGS, remain incompletely understood, and numerous causes of podocyte injury exist, with genetic mutations playing a significant role. In studies of podocytes, several crucial genes harbouring mutations that result in alterations within key components of the podocyte structure, such as Nphs1 (renin), Nphs2 (podoplanin), and Actn4 (a-actinin-4), have been identified [6–8]. These gene and component modifications ultimately lead to a broad spectrum of effects resulting in damage and loss. Many studies have shown an inseparable connection between mutations in specific genes and corresponding alterations in certain miRNAs. Moreover, miRNAs are also directly involved in the pathogenesis of chronic kidney diseases (CKDs); however, further research is needed to elucidate the precise underlying mechanisms [9]. In conclusion, miRNAs are closely related to podocyte injury and many glomerular diseases including FSGS.

MicroRNAs (miRNAs) are noncoding RNAs that play important roles in various physiological and pathological processes through posttranscriptional gene silencing [10]. Currently, significant advancements have been made in the investigation of miRNAs in the development of FSGS. miRNAs can regulate the expression of specific genes in relevant cells and thus participate in the development of FSGS [11]. More than a thousand miRNAs have been identified in the mammalian genome [12]. One type of miRNA can regulate 100 different protein-coding genes, whereas multiple miRNAs can collectively target individual protein-coding genes. They perform pivotal functions in various cellular processes, including proliferation, differentiation, apoptosis, tumorigenesis, and fibrosis.

miRNAs have shown remarkable potential as biomarkers across various diseases and systems, particularly in cancer, cardiovascular diseases, and neurological disorders. For example, miR-21 has been identified as a potential biomarker for hepatocellular carcinoma [13, 14], while miR-133a acts as a biomarker for anthracycline-induced cardiotoxicity in women with breast cancer [15]. Additionally, miR-132 is widely expressed in the cardiovascular system and may serve as a potential diagnostic or prognostic biomarker [16]. Similarly, miRNA-146 holds promise as both a biomarker and a potential therapeutic target in Alzheimer's disease [17].

Currently, approximately 700 miRNAs are known to be expressed in normal human kidneys [18]. Recent studies have shown that miRNAs play important roles in the pathogenesis and progression of glomerular diseases, particularly those associated with podocytes. miRNAs can be detected in both serum and plasma [19, 20], and they can passively undergo filtration by the glomeruli and be actively secreted by the renal tubules, resulting in their detection in urine as well [21]. Therefore, miRNAs in serum and urine could be used as potential biomarkers to facilitate the diagnosis and prognosis of FSGS and the therapeutic evaluation. Although many prior studies have demonstrated the critical role of miRNAs in the development of FSGS, to the best of our knowledge, there is a paucity of systematic summaries on this subject topic. This paper provides a concise summary encompassing the diagnosis, prognosis, disease activity, and clinical characteristics associated with FSGS.

miRNAs as Biomarkers for Diagnosis

Renal biopsy, which relies heavily on pathohistological findings, is the gold standard for the diagnosis of FSGS; that is, the pathology identifies the lesion – FSGS – with at least one instance of segmental sclerosis. However, in some cases, the pathological manifestations of FSGS patients are so similar to those of minimal change disease (MCD) that they are difficult to distinguish [22]. In addition, the clinical heterogeneity and diverse histological and nonspecific morphological features of FSGS may influence our judgement of renal biopsy results to some extent [23]. Therefore, there is an urgent need to discover novel diagnostic biomarkers for the diagnosis of FSGS that are easier to perform, less harmful to patients, and have greater sensitivity and specificity. If miRNAs can serve as diagnostic biomarkers, a more accurate diagnosis of FSGS at an early stage will be possible. These miRNAs are categorized according to the source of detection into urine-derived miRNAs, plasma-derived miRNAs, serum-derived miRNAs, and exosome-derived miRNAs.

Urinary miRNAs

Currently, the main urinary miRNAs that have the potential to serve as biomarkers for the diagnosis of FSGS are the miR-30 family, miR-1915, miR-663, and miR-155. Most of the current studies related to the miR-30 family are related to lung diseases such as lung cancer [24], but we believe that the miR-30 family has potential in research on glomerular diseases, especially FSGS. The miR-30 family consists of five members, namely, miR-30a through miR-30e. Members of this family of miRNAs are abundantly expressed in podocytes [25]. A study on the role and potential mechanisms of miR-30 in podocyte injury revealed that members of the miR-30 family are expressed in human

glomerular podocytes and are downregulated in patients with FSGS. The expression of these miRNAs was also downregulated in cultured podocytes treated with TGF-β, PAN, or LPS. Several studies have identified key targets of miR-30c, including Snai1, associated with epithelial mesenchymal transition (EMT); metadherin, linked to p38 MAPK signalling; and Ctgf, a known inducer of extracellular matrix protein production [9]. Overexpression of miR-30e inhibits Glipr2, promoting cell proliferation, and inhibits EMT, potentially attenuating profibrotic pathway [26]. miR-30 is abundantly expressed in normal podocytes and downregulated in the podocytes of FSGS patients, suggesting that the miR-30 family is specific for the diagnosis of FSGS, and has the potential to become a novel marker for the diagnosis of FSGS [27].

Investigators have focused on different miRNA expression profiles between FSGS and MCD patients in studies on the expression profiles of miRNAs in glomerular diseases. The results revealed that urinary miR-1915 and miR-663 levels were downregulated in FSGS patients compared with MCD patients and controls, whereas urinary miR-155 levels were upregulated in FSGS patients compared with MCD patients and controls [28]. Moreover, we reported in another study that the level of miR-155-5p was not increased in the serum but was increased very significantly in the urine of FSGS patients. This study revealed that the HIF-1/miR-155-5p/Nrf2 axis promotes renal oxidative stress and inflammation, which ultimately aggravates renal injury and accelerates the progression of renal fibrosis (RF) in FSGS patients. Another study showed that miR-155 promotes renal inflammation, apoptosis, and fibrosis via the lncRNA CCAT1/miRNA-155/SIRT1 axis [29]. In addition, the increase in urinary miR-155-5p may contribute to the diagnosis of FSGS [30].

Plasma miRNAs and Serum miRNAs

Among the plasma mRNAs, we focused on four miRNAs, namely, miR-17, miR-451, miR-106a, and miR-19b. In a study on miRNAs associated with apoptosis in podocytes [31], researchers identified a set of differentially expressed miRNAs, including 16 upregulated and 18 downregulated miRNAs, in FSGS patients compared with healthy controls. After an initial screening, the investigators chose to further validate four of these plasma miRNAs, namely, miR-17, miR-451, miR-106a, and miR-19b. They reported that all of the above plasma miRNAs were significantly downregulated in FSGS patients compared with healthy controls.

We were surprised to find that the expression of these miRNAs was also correlated with the degree of FSGS progression. When the patients with CKD1 were categorized as patients with mild FSGS and the patients with CKD2-4 as patients with moderate-to-severe FSGS according to the CKD scoring criteria, the study revealed that the expression of miR-17, miR-451, and miR-19b was significantly reduced in patients with moderate-to-severe FSGS compared with patients with mild FSGS.

The expression of these miRNAs also appeared to be significantly different in patients with different types of FSGS according to the histologic classification associated with the Columbia FSGS classification. Patients with the combined variant type of FSGS had significantly lower plasma levels of miR-17, miR-19b, and miR-106a compared with those in the not otherwise specified, tip lesion, or periportal lung groups. Owing to the sample size, the researchers also suggested that this conclusion might require validation in studies with larger sample sizes. However, these findings also suggested that these miRNAs were correlated with different histologic classifications of FSGS.

These miRNAs were equally correlated with whether FSGS patients were in remission. Compared with those in FSGS patients in remission (urinary protein <400 mg/24 h after treatment), miR-17, miR-451, and miR-106a were significantly downregulated in FSGS patients with proteinuria, whereas the expression of miR-19b did not differ between these two groups.

The above findings suggest that these several miRNAs can be used to some extent as biomarkers for FSGS disease diagnosis, disease progression status, therapeutic remission, and even histologic typing. The above review shows that miR-155, miR-1915, and miR-663 can distinguish FSGS from MCD to some extent. Two miRNAs in serum, miR-192 and miR-205, also have the potential to serve as biomarkers for distinguishing between these two diseases. The serum concentrations of miR-192 and miR-205 are higher in FSGS patients than in MCD patients and healthy controls [32].

Exosome miRNAs

Urinary exosomal miRNA was extracted from morning urine samples of children with primary FSGS and MCD by Huang et al. [33]. These authors demonstrated that the level of urinary exosomal miR-193a was significantly greater in patients with FSGS than in those with MCD. Urinary exosomal miR-193a may be a new non-invasive biomarker for the diagnosis of primary FSGS [33]. Similarly, urinary exosomal miR-193a was shown to help differentiate FSGS from microscopic lesions in children in another study examining the role of miR-193a in membranous nephropathy [34]. Conversely, urinary miR-193a can predict the progression of FSGS in children. Elevated levels of urinary miR-193a indicate more rapid progression [35]. miR-193 is involved in disease progression by inducing podocyte dedifferentiation in glomerulonephritis. miR-193a

may play a key role in this process by inhibiting the expression of the nephroblastoma protein (WT1) [36, 37]. In an updated study, miR-193a was hypothesized to be a potentially useful biomarker for the diagnosis of FSGS in children with NS and for the diagnosis of diabetic nephropathy, but this conclusion requires validation in additional studies [18].

miRNAs as Biomarkers for Disease Activity

The disease activity of FSGS plays a crucial role in guiding its treatment. Patients who present with persistent macroproteinuria are prone to rapid progression towards ESRD, whereas those who achieve complete remission exhibit a favourable prognosis, with a 10-year renal survival rate of >80% [38, 39]. Disease activity is very important for improving disease prognosis, and accurately assessing disease activity can facilitate the development of more effective treatment strategies. Urinary protein level is an important and commonly used parameter for FSGS that partially reflects disease activity in FSGS patients. However, its limited specificity and sensitivity hinder its application, so more specific and sensitive biomarkers are needed to evaluate disease activity in FSGS patients. Therefore, we focused on the potential of corresponding miRNAs in blood and urine as novel biomarkers for assessing FSGS disease activity.

Urinary miRNAs

Zhang et al. [40] aimed to characterize the presence in urine of miRNAs that could serve as biomarkers of FSGS disease activity. After they validated the screening of urine samples from patients with active FSGS and remission FSGS, they reported that miR196a, miR-30a-5p, and miR-490 were associated with disease activity.

In another article evaluating the predictive role of urinary miR-196a levels in patients with CKD, researchers selected the FSGS cohort as a representative cohort of CKD patients and ultimately reported that urinary miR-196a was an independent risk factor for FSGS progression. When we combined urinary miR-196a with other indicators such as proteinuria, we were able to significantly improve the accuracy of disease prediction. Urinary miR-196a can be used as a biomarker for the prediction of FSGS and even CKD [41].

Plasma miRNAs

Plasma miRNAs were used as biomarkers to assess disease activity. The plasma levels of miR-125b, miR-186, and miR-193a-3p could be used as predictive biomarkers for FSGS associated with nephropathic proteinuria and to differentiate between patients with FSGS associated with nephropathic proteinuria and healthy control subjects [10]. The investigators also reported that a combination of 3 miRNAs (3-miRNA panel) had better predictive ability than any single miRNA. Notably, renal miR-186-5p was found to be significantly elevated in FSGS patients and in mice with adriamycin-induced kidney injury. Mechanistic studies revealed that miR-186-5p is involved in disease activity by initiating renal tubular cell apoptosis through direct activation of the tubular TLR7/8 signalling axis [42].

miRNAs as Prognostic Biomarkers

Steroid therapy remains the first-line treatment for primary FSGS in adults. However, the effectiveness of treatment and recurrence after treatment remain treatment challenges for physicians [31]. Due to the special characteristics of steroid treatment, we must monitor whether the patient benefits from steroid treatment; for those patients who are steroid resistant, the medication must be adjusted in a timely manner to mitigate harm caused by the side effects of the drug. For patients who benefit from steroid treatment, constant and timely monitoring of the patient's prognosis reduction and discontinuation of drugs to avoid overuse are essential. Therefore, accurate and timely prognostic information of patients are needed, and existing tests have certain insufficiencies. We hope to identify miRNAs that can be used to predict the prognosis of FSGS to provide more appropriate and personalized treatment plans for patients.

Urinary miRNAs

Urinary levels of three miRNAs were analysed before and after steroid treatment in a prospective study [40]. In steroid-responsive patients, the urinary levels of miR-196a, miR-30a-5p, and miR-490 were significantly reduced after steroid treatment. In contrast, the urinary levels of these three miRNAs were essentially unchanged in steroid-resistant patients after treatment.

In particular, only the miR-30a-5p level allowed moderately accurate differentiation between patients with remission FSGS and those without remission FSGS. Interestingly, after 4 weeks of treatment, the miR-30a-5p levels differed significantly between these two groups, whereas the proteinuria levels did not differ. These findings suggest that changes in urinary miR-30a-5p levels can be used to predict treatment response in FSGS patients.

Chen et al. [43] described elevated urinary and serum miR-30a-5p in paediatric NS patients, including FSGS patients, and a decrease in miR-30a-5p levels after achieving

remission on steroid therapy. To the best of our knowledge, only patients with steroid-responsive FSGS exhibit a decrease in urinary miR-30a-5p after treatment [44].

Plasma miRNAs

In a study of plasma miRNAs [10], investigators examined plasma miR-125b and miR-186 levels before and after steroid treatment for 8 weeks in the steroid-treated complete remission and steroid-treated non-responder groups. The results of the investigation revealed that the miR-125b and miR-186 levels were similar in the complete remission and nonresponder groups before steroid treatment. In the group of patients who achieved complete remission after steroid treatment, the levels of both miR-125b and miR-186 were significantly reduced, especially the level of miR-186, which almost returned to the level of healthy controls. In contrast, in the group of patients who did not respond to steroid treatment, the levels of both miRNAs did not change.

miRNAs as Biomarkers for Clinical Features

The primary clinical manifestations of FSGS include massive proteinuria and NS. Current treatment focuses primarily on symptomatic therapy, with steroid therapy still accounting for a large proportion of the present treatment. As previously mentioned, owing to the specificity of steroid therapy, it is crucial to assess patients' response promptly to make timely adjustments to their medication regimens. In addition to the above factors, which are directly related to the prognosis of the disease, the most direct change in the assessment of treatment effects is the improvement of clinical symptoms. There is an urgent need for convenient and efficient biomarkers related to clinical symptoms in the clinical work of physicians. Here, we focused on miRNAs that could reflect the degree of change in proteinuria and the degree of fibrosis to some extent.

miRNAs Correlated with Proteinuria

Proteinuria is the classic clinical manifestation of FSGS and is present in almost all patients to varying degrees. Proteinuria is the continuous and significant loss of plasma proteins in the urine. Although the main component of proteinuria is albumin, other plasma protein components can also be included. FSGS is a disease related to podocytes in which proteinuria is produced in association with damage to the glomerular filtration barrier. The severity of proteinuria has a great impact on the prognosis of patients. It has been shown that remission of proteinuria contributes significantly to the delay of FSGS progression [45]. Among the clinical factors that affect the prognosis of patients, the most important is the degree of proteinuria. Therefore, early diagnosis of the severity of proteinuria is critical to both the diagnosis and prognosis of the disease.

Urinary miRNAs

An advanced study of miRNAs related to FSGS revealed that the level of miR-155 in urine was positively correlated with proteinuria [28]. Furthermore, urinary levels of miR-1915 were negatively correlated with proteinuria, urinary levels of miR-663 were positively correlated with proteinuria, and urinary levels of miR-663 were negatively correlated with the GFR. These findings suggest that each of these urinary miRNAs has potential as a biomarker for determining proteinuria in patients.

Plasma and Serum miRNAs

MiR-186 influences many genes. miR-186 can modulate *PTTG1*, *FOXO1*, the *P2X7* receptor, and *AKAP12*, and it is involved in cell-cycle control, AKT signalling, insulin signalling, and calcium signalling [46–49]. Zhang et al. [10] investigated the relationships between plasma miR-125b and miR-186 concentrations and urinary protein levels in patients with FSGS with nephrotic proteinuria. The results revealed that plasma miR-186 concentrations were significantly correlated with urinary protein levels. There was no significant correlation between the plasma miR-125b concentration and the degree of proteinuria [10]. These results further indicated that miR-186 might be involved in the pathophysiology of FSGS. A recent correlational cohort study on the relationship between T cells and the development of FSGS showed that plasma levels of miR-186-5p correlated with proteinuria in patients with FSGS [42].

Various bioinformatic analyses have shown that miR-342 is a strong candidate regulator of RF. miR-342 is able to negatively regulate Ptch1, which induces autophagy in TGF-β1-stimulated TCMK-1 cells [50]. In a retrospective cohort study, plasma miR-342 levels were positively correlated with proteinuria [28].

Both miR-192 and miR-205 in the serum of FSGS patients were positively correlated with proteinuria. In MCD, serum levels of miR-192 have also been associated with proteinuria [32].

miRNAs Correlated with Interstitial Fibrosis

Serum miRNAs

The process of EMT can contribute to RF [51–54]. Many studies have shown that miR-192 may participate in the EMT [55–58].

The degree of interstitial fibrosis is correlated with the serum level of miR-192 but is not significantly correlated with that of miR-205 [32]. Kato et al. [59] showed that elevated miR-192 levels in mouse mesangial cells increased the expression of collagen, contributing to matrix accumulation and glomerulosclerosis. Kato et al. [60, 61] also reported that increased miR-192 levels could lead to glomerulosclerosis in mesangial cells through TGF-β1 autointroduction and Akt activation. Additionally, Putta et al. [62] reported that the suppression of miR-192 in diabetic mice attenuated proteinuria and ameliorated RF. In-depth investigation of the mechanism revealed that miR-192 played a pivotal role in RF by mediating TGF-β/Smad signalling pathway. Notably, miR-192 is particularly associated with Smad7, which, when overexpressed, inhibits miR-192 expression and alleviates RF. In contrast, the absence of Smad7 promoted miR-192 expression, thereby enhancing TGF-β/Smad signalling and exacerbating fibrosis. Additionally, Smad3 can mediate TGF-β1-induced miR-192 expression by directly binding to the miR-192 promoter [63, 64]. These findings suggest that serum miR-192 is strongly associated with FSGS interstitial fibrosis and has the potential to serve as a biomarker to determine the extent of interstitial fibrosis.

Conclusion

The above summary describes the increasing, annual incidence of FSGS, diagnostic difficulties, clinical symptoms mainly of severe proteinuria and NS, serious consequences of disease development, a prognosis that is not ideal, and the current lack of specialized treatment. Importantly, identifying a new biomarker for FSGS that can help diagnose and judge disease activity and prognosis is highly important. Such a tool is crucial for the precise diagnosis of the disease in patients and the identification of more optimized clinical treatment options. According to many studies, numerous miRNAs in urine and blood have the potential to serve as FSGS biomarkers.

miRNAs are noncoding RNAs that play important roles in various physiological and pathological processes through posttranscriptional gene silencing. miRNAs play important roles in the pathogenesis of glomerular diseases, especially those associated with podocytes. We classified the miRNAs associated with FSGS into four categories according to their roles as biomarkers: diagnosis of FSGS disease, disease activity, disease prognosis, and clinical features (Fig. 1).

Clearly, miRNAs have many advantages as biomarkers for FSGS. First, assessments of miRNAs are less invasive for patients, providing a practical alternative for patients requiring long-term monitoring and follow-up; miRNA levels can be detected in urine, blood, or other bodily fluids, which is relatively non-invasive and less costly compared to kidney biopsy. Second, miRNAs have potential for early diagnosis. As regulators of numerous cellular processes, their levels are more likely to change in the early stages of disease, even before pathological changes occur in the kidneys. Additionally, miRNAs exhibit high specificity and sensitivity. The expression levels of many miRNAs significantly differ across various diseases and even at different stages of the same disease. Finally, miRNAs demonstrate considerable stability in bodily fluids such as blood and urine. The required storage conditions are not stringent, making this detection method highly feasible in practice.

However, there are also some unavoidable drawbacks to using miRNAs as biomarkers for FSGS. The first challenge is interference from external, non-disease factors. miRNA expression levels can be dynamically influenced by various external factors, such as drug interventions and environmental changes. Additionally, there is no established diagnostic standard for miRNA expression levels. Standardized protocols for sample collection, storage, and processing are urgently needed. Finally, clinical research on the application of miRNAs remains limited. More clinical data are needed for in-depth validation and analysis to further identify suitable miRNAs.

Overall, we believe that the advantages of miRNAs as disease biomarkers are highly significant and, to some extent, irreplaceable. However, in practical applications, more clinical experience is needed to refine the selection process and establish more standardized criteria. Addressing this gap remains the greatest challenge for the future.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Yufei Sun: conceptualization; data curation; formal analysis; investigation; and writing – original draft. Shuang Liu: data curation; formal analysis; investigation; and writing – review and editing. Wan Ding: data curation; Chun Zhu: draft revision; Gengru Jiang: project administration and supervision; and Huilin Li: project administration; supervision; and funding acquisition.

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