



## Commentary

## Are microRNA potential biomarkers in children with idiopathic nephrotic syndrome?



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Idiopathic nephrotic syndrome (NS) is the most frequent glomerular disease diagnosed during childhood. NS affects mainly pre-school children with a reported incidence of 15–16.9 per 100,000 children and is characterised by heavy proteinuria ( $>1$  g/m<sup>2</sup>/day or protein/creatinine ratio  $> 200$  mg/mmol), hypoalbuminemia and the presence of oedema. The protein loss is due to an increase permeability of the glomerular membrane barrier (GMB) and more precisely to foot process effacement of the podocytes [1]. Podocytes are highly specialised epithelial cells essential to maintain the physiological properties of the filtration barrier [1]. In NS, the cause leading to the alteration of the GBM is not yet completely understood but the changes in the podocytes structure certainly plays a key role [2].

NS are classified according to the histological findings as minimal change disease (MCD) which is the predominant form, focal segmental glomerulosclerosis (FSGS) and membranous nephropathy. In clinical practice, we habitually distinguish children who respond to corticosteroids treatment (steroids-sensitive) from the non-responder (steroids-resistant) [1]. Steroid-resistant children need adjuvant treatments to get into remission. Close screening for proteinuria is mandatory in NS children, as relapse frequently occurs, to prevent the oedematous state.

More evidence was reported during the last decade, on the importance of miRNAs in many regulatory mechanisms. MiRNAs are negative post-transcriptional regulators of gene expression and have an important physiological role in a variety of biological processes. Their tissue specificity and stability in biological fluid have been proposed to be potential biomarkers in kidney diseases [3,4]. MicroRNAs are small regulatory RNAs composed of 21–25 nucleotides and involved in post-transcriptional gene. MiRNAs have the power to silence a gene to partial binding to its complementary mRNA. Around 3000 human miRNAs have been described and are estimated to regulate 30% of all mRNA transcripts [5]. Increasing evidence suggests a contributing role of miRNAs in kidney disease and development [2]. As previously noted, podocytes are an essential component of the integrity of the glomerular basement membrane. Mice lacking functional miRNAs through podocytes-specific knockout of Dicer results in significant proteinuria, rapid progression of marked glomerular and tubular injury [2].

In *EBioMedicine*, Zhang et al. explored the clinical value of urinary exosomal miRNAs in children with idiopathic nephrotic syndrome [6]. In a previous manuscript, they reported 5 miRNAs increased in the serum and 1 in the urine (miRNA-30a-5p) in children with idiopathic NS compared to controls [7,8]. In the present study, urine samples were collected in 129 children with NS and in 126 age-sex matched healthy controls. 30 exosomal miRNAs were significantly increased in NS children compared to controls, among these, 5 were markedly reduced in remission, including two, miR-194-5p (AUC = 0.8) and miR-23b-3p (AUC = 0.77) with a significant correlation with proteinuria. Therefore, the authors proposed exosomal miR-194-5p and miR-23b-3p as potential biomarkers candidates for diagnosis, monitoring and stratification in idiopathic NS. However, even if these exosomal miRNAs are correlated with proteinuria, the usefulness of these 2 miRNAs for monitoring and stratification of the disease may be taken with caution. Indeed in the first study, miRNAs did not differ between steroids-sensitive and steroid-resistant children [7]. Again, in the present study exosomal miRNAs failed to differentiate between the 3 forms of NS, MCD, mesangial proliferation or FSGS. Even if exosomal miR-194-5p and miR-23b-3p were correlated with the severity of proteinuria, it is questionable if they offer a superiority on usual biomarkers for the diagnosis of NS. For example, in avoiding a kidney biopsy, usually necessary to precise diagnosis in steroid non-responder. Another concern is the certainty of these miRNAs in the diagnosis of NS as they may only indicate significant proteinuria. In addition miR-194-5p and miR-23b-3p may be not specific of the disease but increase secondary to inflammation [5]. Indeed miR-194-5p was also reported to be increased in patients with diabetic nephropathy presenting microalbuminuria. miR 30a-5p was increased in FSGS compared to controls [4].

Interestingly as highlighted by the authors, miRNAs may provide insight in the comprehension of the pathological mechanism of NS. The factor leading to podocytes loss of properties is not clearly understood, but a dysregulation of immune system to inflammatory disease may be the cause. Nevertheless as the triggering factor is unknown, this increase in identified exosomal miRNAs may provide a new approach to explore the pathogenicity of NS. MiR-30a-5p and miR-23b-3p are deficient in podocytes-specific knockout of DICER resulting, inter alia, in foot process effacement of the podocytes as described in NS children [2]. This suggest that miRNAs regulate multiple cellular process in podocytes.

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In conclusion Zhang et al. showed that urine exosomal miR-194-5p and miR-23b-3p miRNAs were correlated with the severity of the proteinuria in children with idiopathic NS. More accuracy in the diagnosis of the different NS types will be necessary to propose miRNAs as biomarkers in clinical practice for diagnosis and stratification. MiRNA knowledge is increasing and may contribute to better explain the causal role inducing changes in permeability of the glomerular basement membrane and offer generation of novel therapeutic approaches. Challenges for the future will be to translate experimental or observational finding as potential biomarkers to discriminate diagnosis and conduct treatment follow up and therapeutic.

#### Disclosure

Nothing to disclose.

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