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Review article

MicroRNA in kidney disease

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Abstract

Clinical and laboratory findings of kidney disease in an adult may find an explanation in kidney functional and/or structural abnormalities that already existed during infancy and childhood, but that may have been missed or underdiagnosed.

All the cardiovascular abnormalities that occur in adults with chronic kidney disease are also present in children with chronic kidney disease. Complications in childhood chronic kidney disease will have consequences well beyond pediatric age and influence outcomes of affected young adults with disease. Kidney dysfunction appears early in the course of kidney disease and has been observed in children and adults with chronic kidney disease, condition characterised with kidney fibrosis. Transforming growth factor beta is recognized as a major mediator of kidney fibrosis. New evidence illustrates the relationship between transforming growth factor beta signaling and microRNAs expression during kidney diseases development.

MicroRNAs play important roles in kidney development and kidney diseases; they are naturally occurring, 22-nucleotide, noncoding RNAs that mediate posttranscriptional gene regulation. Dysregulation of miRNA expression is an indicator of several diseases including chronic kidney disease. Targeting microRNAs should be a therapeutic potential to ameliorate the disease related to fibrosis. The discovery that circulating miRNAs are detectable in serum and plasma, and that their expression varies as a result of disease, presents great potential to be used as biomarkers in kidney disease prevention and diagnosis.

Keywords: *kidney disease, microRNA*

Introduction

There are five important risk factors for chronic kidney disease (CKD): physical inactivity, high salt intake, smoking, diabetes and hypertension [1]. We have studies on prevention of CKD and its complications at the level of the general population, and at the level of those at high risk for CKD or CKD complications, but we have not enough information about impact of microRNA in CKD patients, both in pediatric and adult age. Some of the typical characteristics of pediatric CKD, such as the etiology or cardiovascular complications, do not only influence on the health of the pediatric patient, but also have an impact on the life of the adult age which is often under-recognized. All the cardiovascular abnormalities that occur in adults with CKD are also present in children with CKD. Despite similarities to the adult, CKD in children presents unique features, mostly preventable if recognized. In this review, we discuss the implications of microRNA in clinical diagnostics of early-onset CKD to prevent kidney fibrosis.

Chronic kidney disease in children

The most common etiologic categories of CKD in children are congenital anomalies of the kidneys and urinary tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis and ciliopathies [2,3]. More than 200 genes are recognized as causative in children with CKD [3]. It is possible to address specific etiologic questions in 20% of children with early-onset CKD by selecting an appropriate panel of genes on the basis of the clinical phenotype of the patient and on a precise diagnostic suspicion [3]. The genetic background of patients with CKD is much more complex than we expected and besides disease-causing genes, a number of other genes are now recognized as playing an important role [3]. MicroRNAs are endogenous small noncoding single-stranded RNAs that regulate gene expression at the post-transcriptional level. MicroRNAs bind to the messenger RNAs of various genes and lead to their degradation. Some specific microRNAs called miR-193a inhibited the transcript for the Wilms tumor protein (WT1) in podocytes and therefore inhibited the expression of a variety of WT1-controlled genes that are important for podocyte function, such as nephrin.

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Premature children and impact on adult chronic kidney disease

Minor reductions in nephron numbers that are seen in low-birth weight and small for gestational age newborns are emerging as important predisposing factors to CKD [4]. It is very important that in humans all of the branches of the ureteric bud (UB) and the nephrons are formed by the 32nd to 36th week of gestation. The metanephros arises from the reciprocal interaction of two structures, UB and the metanephric mesenchyme (MM). These structures are not yet mature and will continue to grow and differentiate even after birth, during the perinatal period, as the generation of Henle's loop occurs [5]. While growing, UB generates the portion of the nephron from the renal papilla to the collecting ducts system of the mature kidneys. The capacity of generating new nephrons is lost at the time of birth so that human kidneys have an estimated number of nephrons of one million per kidney or more [6,7], proportional to body mass [5]. It is an important issue for all nephrologists as the number of premature children continues to grow [4,7]. Secondary sclerosis induced by the adaptive response to nephron loss occurs when there is a reduction in renal mass due to congenital absence or reflux nephropathy and ischemia [2]. Targeting microRNAs should be a therapeutic potential to ameliorate the disease related to fibrosis.

Pediatric obesity and chronic kidney disease in adults

Together with the exploding burden of pediatric obesity both are destined to significantly change the relative distribution of the causes of CKD in the early age [8,9]. An increase in the incidence of chronic kidney disease and hypertension has been parallel with the epidemic of obesity, and obesity and metabolic syndrome were independent predictors of renal injury. The pathophysiology of obesity related hypertension includes activation of sympathetic nervous system, renin angiotensin aldosterone system, hyperinsulinemia and inflammation. The body mass index (BMI) has been used to define obesity based on health risk factors in adult individuals. The National Institute of Health (NIH) determined an adult with a BMI of 25-29.9 as overweight and >30 as obese. The criteria used to define overweight or obese children have varied: based on the Centers for Disease Control and Prevention (CDC) growth charts defined children with >85th percentile BMI to be overweight and BMI >95th percentile to be obese with 10% of infants and <2 years old with a weight-for-height ≥95th percentile, 17% of children aged 2-19 years old ≥95th percentile, and 32% ≥85th percentile of BMI for age [10]. Excess weight gain appears to be a major risk factor for chronic kidney disease and hypertension in children (adults in future). Increased awareness is needed in children for early diagnosis of obesity and implementation of lifestyle modifications. Secondary focal segmental glomerulosclerosis (FSGS) usually results from an adaptive response to glomerular hypertrophy and hyperfiltration. Elevated microRNA-193a expression was found in glomeruli from patients with secondary FSGS, but not in glomeruli from healthy controls or patients with minimal change disease, IgA or membranous nephropathy [11].

MicroRNA and chronic kidney disease

Results from clinical and experimental animal studies demonstrate that miRNAs play essential roles in the pathogenesis of kidney diseases [11,12]. MicroRNAs (miRNAs) are naturally occurring, 22-nucleotide, noncoding RNAs that mediate posttranscriptional gene regulation. MiRNAs play an important role in many biological processes, including differentiation and development, cell signaling, and response to infection by regulating genes involved in these processes [12]. Patients with different types of CKD progressively lose their kidney functions and develop glomerular sclerosis and interstitial fibrosis, characterized by renal fibrosis. Transforming growth factor beta (TGF-β) is recognized as a major mediator of kidney fibrosis (stimulate the accumulation of extracellular matrix (ECM) proteins and impair normal kidney function). Evidence illustrates the relationship between TGF-β signaling and miRNAs expression during kidney diseases development [13]. The expressions of several miRNAs were up-regulated by TGF-β signaling pathway, such as miR-21, miR-29, miR-192, miR-200, and miR-433, in which miR-21, miR-192, and miR-433 are reported to be positively induced by TGF-β signaling, and they play a pathological role in kidney diseases [13]. Members of both miR-29 and miR-200 families that are inhibited by TGF-β signaling protect kidneys from renal fibrosis by suppressing the deposition of ECM and preventing epithelial-to-mesenchymal transition. The abundance of miR-21 is low in normal kidneys, and is greatly increased in both patient samples of kidney diseases and animal models of CKD and acute kidney injury and diabetic nephropathy, and it presents potential to be used as biomarkers in disease prevention and diagnosis [13].

Discussion

All the cardiovascular abnormalities that occur in adults with CKD are also present, to some extent, in children with CKD. As in adults, endothelial dysfunction and fibrosis appear early in the course of kidney disease and have been observed in children with CKD.

The primary causes of chronic kidney disease (CKD) in children differ from those of CKD in adults. In the USA the most common diagnostic groups of kidney disease before the age of 25 years are congenital anomalies of the kidneys and urinary tract, steroid-resistant nephrotic syndrome, chronic glomerulonephritis and renal cystic

ciliopathies, which together encompass >70% of early-onset CKD diagnoses. Findings from the last decade suggest that early-onset CKD is caused by mutations in any one of over 200 different monogenic genes. Use of genetic analyses in patients with early-onset CKD will provide patients a molecular genetic diagnosis, and might have consequences for personalized approaches to the prevention and treatment of CKD [14].

MicroRNAs could be useful as early biomarkers of kidney disease. Targeting miR-21 should be a therapeutic potential to ameliorate the disease related to fibrosis because inhibition of miR-21 is effective in decreasing fibrosis in animal models of heart, lung, and kidney diseases and new data show effect of antifibrotic microRNA in diabetes-related kidney fibrosis [15].

Conclusion

Conditions that alter nephron development or trigger nephron damage during neonatal, juvenile, or adult stages of life are important in development of CKD in early and adult age. Pediatric CKD share the basic pathophysiologic mechanisms with the same disease in the adult population. Kidney health depends on the complete integrity and functionality of the nephrons and their component parts developing in the early phases of life. There are new players like microRNA as biomarkers in diagnosis and prevention of chronic kidney disease in combating kidney fibrosis.

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Conflict of interest statement. None declared.

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