Chronic transplant failure, which is associated with early acute rejection, has become one of the major challenges in the care of kidney transplant patients. Several novel techniques have been used to identify biological markers for acute transplant rejection as well as chronic allograft failure. These approaches include mRNA quantification from allograft biopsies as well as from urine or blood samples [1,2]. Although a number of studies have reported potential candidate biomarkers, to date none of these have been introduced into routine diagnostics. In addition to the technical challenges in applying this information, it may also be in part due to the complexity of the underlying biology of gene regulation.

The human genome is more than a library of discrete genes, and gene regulation goes beyond switching on or off the transcription of protein-encoding messenger ribonucleic acid (mRNA). A majority of genes can undergo alternative splicing yielding unique transcripts, which may also be regulated by different promoters [3]. An additional level of regulation at the level of microRNAs (miRNAs) has been recently added to this scheme. miRNAs are single-stranded RNAs of ~22 nucleotides in length, which are not translated into a peptide but have regulatory properties. Since their initial description in 1993, hundreds of miRNAs have been identified [4]. miRNAs are transcribed as longer primary transcripts (pri-miRNAs), which are cleaved by the nuclear enzyme Drosha to precursor miRNAs (pre-miRNAs) (Figure 1). The pre-miRNA then exits the nucleus and is further processed to a mature miRNA by the RNase Dicer. After entering the RNA-induced silencing complex (RISC), the specific miRNA binds to its target mRNA leading to suppression of translation. The dimension of the potential effects of this class of biological regulators becomes more obvious when one considers that up to two-thirds of protein-coding mRNAs may be regulated by miRNAs [5]. Our current understanding of the multifaceted nature of miRNA biology has been recently extensively reviewed elsewhere [6]. Changes in specific miRNA levels have been reported for various physiological processes as well as disease states including kidney diseases as discussed below.

In a recent study, the group of Manikkam Suthanthiran, who had already pioneered transcriptomic profiling in renal transplantation [7], set out to characterize potential associations of intrarenal miRNA levels with the clinical and histological status of renal allografts [8]. They conducted a global miRNA expression study on four renal protocol biopsies with a normal histology and three biopsies with acute rejection (AR) and graft dysfunction. A subset of 17 miRNAs (out of an initial group of 365 miRNAs on the analysis platform) were found showing differential expression in both cohorts. A subset of these miRNAs was then quantified in an additional group of biopsies (17 protocol biopsies and 9 AR). The altered expression of 6 of the 17 miRNAs was again observed in this confirmatory analysis. The authors went on to study if miRNA levels could predict AR and graft function. They reported impressive sensitivity and specificity values for two to three miRNAs in this cohort and association of some of the miRNAs with estimated glomerular filtration rate for these biopsies. To gain further insight into the underlying biology, miRNA levels were correlated with cell type-specific mRNA templates (e.g. CD3 and CD20). In addition, miRNA levels were studied in isolated peripheral blood mononuclear cells (PBMCs) and human renal tubular epithelial cells. Some miRNAs found to be increased in AR were also found to be expressed in PBMCs. This indicates that cell infiltration and immunological processes may help explain the changes in miRNA levels. Indeed, regulatory potentials in immune-competent cells were previously reported for some of the miRNAs. The report by Anglicheau et al. follows a second paper on miRNA quantification on a smaller number of allograft biopsies [9]. Both studies should help to fuel further research on miRNA and allograft damage as well as in native kidney disorders. The important questions that remain include which changes in miRNA expression are due to AR alone, and which may be triggered by other factors such as renal function, time since transplantation and other parameters.

The study adds to the accumulating data on the general importance of miRNAs for the proper function of the
miRNAs in mesangial cells can lead to a pro-fibrotic milieu. Additional reports demonstrating that alterations of specific miRNAs but also that cell-specific interruption has detrimental effects on the function of the entire biological unit, which in the kidney is the nephron. This is further supported by two studies of the glomerulus. Three recent publications all reported that podocyte-specific deletion of Dicer, the central RNAse for miRNA maturation, leads to proteinuria accompanied by foot-process effacement and alterations of the glomerular basement membrane in mice. All three models showed a progressive decline of renal function with high proteinuria and tubular injury with protein cast formation [14]. These data elegantly demonstrate that miRNAs are not only essential for intracellular regulation of target mRNAs but also that cell-specific interruption has detrimental effects on the function of the entire biological unit, which in the kidney is the nephron. This is further supported by two additional reports demonstrating that alterations of specific miRNAs in mesangial cells can lead to a pro-fibrotic milieu in the glomerulus [16,17].

Our understanding of miRNA biology is still incomplete, so the interpretation of all these studies is only preliminary. With our current knowledge, it is very difficult to accurately predict the target genes of a specific miRNA [18]. Therefore, the effects downstream of miRNA changes are still vague. In addition, the effects of miRNAs may go beyond the inhibition of target mRNA translation and may also include activation of translation [19].

miRNAs have proven to be of key relevance in the regulation of gene expression, and by this, for organ function. Specific alterations in miRNA levels are clearly involved in disease processes such as nephropathies. However, the qualification of miRNA levels as biomarkers in nephrology, including in renal transplants, remains elusive. Future efforts should be combined to help identify reliable biomarkers for diagnosis, outcome and response to therapy in transplant nephrology as well as in primary renal diseases.

Take home message

miRNAs are a central mechanism for gene regulation and specific miRNAs may prove to function as biological markers for acute allograft rejection.

Conflict of interest statement

None declared.

References

Will non-coding RNAs help to decipher renal allograft failure?


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