



MicroRNA and Renal Allograft Monitoring

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Micro RNAs (MiRNAs) are small endogenous, regulatory RNAs comprising of about 19–25 noncoding nucleotides (1-3). Primary miRNAs (pri-miRNA), a capped and polyadenylated transcript are transcribed by RNA polymerase II and processed into precursor miRNAs (pre-miRNAs) in the nucleus by the microprocessor complex (DGCR8/Drosha). Using Exportin-5, pre-miRNAs are exported into the cytoplasm and are cleaved by Dicer to produce mature miRNAs. Mature miRNAs recognize their mRNAs targets and impose their negative regulation of protein synthesis by degradation of corresponding mRNA (1-3). These single-stranded RNAs have essential roles in numerous biological and pathological processes and their aberrant expression is associated with disease initiation and/or progression due to a severe disturbance of downstream gene networks and signaling cascades and protein synthesis. miRNAs have been involved in regulation of inflammation, innate and adaptive immunity, fibrosis and in signaling mechanisms implicated in allograft rejections. miRNAs are detectable in several biologic sources including peripheral blood mononuclear cell (PBMC),

serum, tissue samples, urinary cell pellets and urine supernatant and many other body fluids (4).

Acute rejection is the result of an alloimmune response against the allograft and can be caused by either a cellular or humoral response. An acute cellular rejection normally occurs 5 to 7 days after transplant but can occur in an accelerated fashion or any time after transplantation. Chronic rejection is a progressive deterioration in renal dysfunction characterized clinically by a progressive increase in serum creatinine level, and histologically by tubular atrophy, and interstitial fibrosis. It is an almost universal finding that finally happens in all renal transplant recipients and most commonly have an immunological reason. Previously the terminology of chronic allograft nephropathy (CAN) was used to describe these changes. The Banff classification system for renal allograft injury has recently adopted the term interstitial fibrosis and tubular atrophy (IFTA) to describe these changes (5).

Despite an improvement in renal allograft survival because of advances in immunosuppressive regimens a critical area is the need for sensitive, etiology-specific and

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Renal allograft monitoring is a great challenge of transplantation medicine and different biomarkers have been proposed. MicroRNA is an appealing biomarker because we could trace it from different sources including biopsy samples urine and blood, particularly, miRNA signature of stable and impending to failure allograft in urine would be very important and it opens a new area of precise measurement of allograft function and outcome. Here we reviewed very recent advances in this special area with more emphasis on miRNA patterns in the state of IF/TA.

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noninvasive method for monitoring the function of the renal allograft. Because serum creatinine increment is a very late findings when some irreversible damages has happened on the other hand renal biopsy is an invasive

procedure and it is difficult to implement it as a routine procedure for renal allograft monitoring (6).

Several studies support the idea of earlier diagnosis of acute and chronic rejection by miRNA measurement

Table 1. Different Studies on miRNA in Renal Transplantation

Condition/Monitoring	miRNAs	Sample Size/Source	Control Group	Ref.
Renal allograft status	Up: miR-125a, miR-125a, miR-320, miR-381, miR-602, miR-628, miR-629, miR-658Down: miR-17-3p, miR-197, miR-324-3p, miR-326, miR-330, miR-346, miR-483, miR-516-5p, miR-524, miR-611, miR-654, miR-663	3AR, 3C/Biopsy	Healthy nontransplant recipient volunteers	Sui et al., 2008 (7)
AR^a	Up: miR-142-5p, miR-142-3p, miR-155, miR-223, miR-146b, miR-146a and miR-342down: let-7c, miR-10a, miR-10b, miR-125a, miR-200a, miR-30a-3p, miR-30b, miR30c, miR30e-3p, miR-32	12AR, 21C/Biopsy	Normal allograft biopsies (grafts from living and deceased donors)	Anglicheau et al., 2009 (8)
Acute T-Cell mediated rejection	Up: miR-10aDown: miR-10b, miR-210	62AR, 19C, Urine samples	Transplant patients without rejection	Lorenzen et al., 2011 (9)
AR	Up:miR-223	12 AR, 21 C/PBMC	Normal controls	Liu et al., 2011 (10)
Chronic antibody-mediated rejection	Up: miR-301a, miR-590-5p, miR-142-5p, miR-32, miR-503 down: miR-888, miR-576-5p, miR-548b-5p, miR-125b, miR-194	112 patient (53 STA, 40 CAMR, 10 RF, 9 AR), 11 C/ PBMC and Biopsy	Healthy volunteers	Danger et al., 2013 (11)
ABMR^a, AREJ^a, DGF^a	ABMRUp: miR-146-5p, miR-1228, let-7i, miR-21, miR-182, miR-155, miR-125a, miR-146bAREJ Up: miR-150, miR-155, miR-663, miR-638Down: 18 miRNAs; miR-125b-2, mir-99b, mir-30c-2, mir-424, DGFUp: miR-182, miR-106b, miR-20a, miR-21, miR-18a, miR-17, miR-106a	55 patient [41AR (15 VR, 15 IR, and 11 ABMR), 14 DGF], 10C / Biopsy	Normal protocol biopsies	Wilflingseder et al., 2013 (12)
AR	miR-125b, miR-483, miR-663, miR-326, miR-346, miR-125a, miR-381, miR-602, miR-629, miR-324-3p, miR-658, miR-524	3 AR, 3 C/Biopsy	Normal kidney biopsies	Sui et al., 2013
IF/TA^a	56 miRNAs differentially expressedUp: miR-142-3p, miR-32Down: miR-204, miR-107, miR-211	81 KTR tissue biopsy samples and urinary cell pellets (deceased donor kidneys)	Stable normal allografts	Scian et al., 2011 (13)
IF/TA	33 miRNAsUp: miR-21, 142-3p, and 5p and the cluster comprising miR-506Down: miR-30b and 30c	8 cases (4 IFTA and 4C) Validation set: 18 cases (10 IFTA and 8 C)/ Biopsy	Normal biopsies	Ben-Dov et al., 2012 (14)
IF/TA	50 differentially expressed miRNAs in UUO mouse modeUp: miR-21	42 renal transplanted recipients/serum		Glowacki et al., 2013

^a Abbreviations: AR, acute rejection; ABMR, antibody-mediated rejection; AREJ, acute cellular rejection; CAMR, chronic antibody mediated rejection; DGF, delayed graft function; IF/TA, interstitial fibrosis and tubular atrophy; KTR, kidney transplant recipients; PBMC, peripheral blood mononuclear cell

(Table 1). In an earlier report microarray study of renal allografts biopsy samples disclosed the up regulation of miR-320 and down regulation of, miR-324-3p among the 20 different miRNAs in patient with acute rejection (7). Anglicheau et al. study a panel of 17 different miRNAs in biopsy samples of patients with acute rejection and they found a 100% sensitivity and 95% specificity for miR142-

5p over expression as a diagnosing biomarker of acute rejection (8). The study by Lorenzen et al. offered a new opportunity for earlier diagnosis of cellular rejection and monitoring renal allograft function using urine sample as a source of miRNA measurement. In their study miR-10a were upregulated and miR-10b and miR-210 were down regulated in urine sample of patient with acute

T-cell mediated rejection (9). The results of other studies showed that miR-223 measurement in peripheral blood mononuclear cells (PBMCs) can have a promising potential, with specificity of 90% and sensitivity of 92%, for earlier diagnosing of acute rejection (AR) (10). One recent study indicates that miR-142-5p is a promising biomarker for long-term renal allograft monitoring and with its elevation we could detect chronic antibody mediated rejection (CAMR) in its earlier stages they used PBMC and biopsy samples for their measurements (11). In another very recent publication Wilflingseder et al. revealed the distinct miRNA signatures of biopsy samples in acute cellular and humoral rejection and delayed graft function. In this study up regulation of the following miRNA panel; miR-182, miR-155, miR-125a, miR-146b, was associated with antibody mediated rejection (12).

The major hallmarks of progressive renal allograft dysfunction are interstitial fibrosis and tubular atrophy (IF/TA). It usually starts after the first transplantation year and results in a continuous decrease in renal allograft function. In the preliminary publication of miRNA profiling in CAD with IF/TA, 56 differential regulation of miRNAs were studied in tissue samples and urinary cell pellets. Up regulation of: miR-142-3p, miR-32 and down regulation of: miR-204, miR-107, miR-211 were observed in their studied population with IF/TA (13). All those five miRNAs, were detected from the urinary cell pellets of the histologically diagnosed patients (13). Ben-Dov and colleagues studied a panel of 33 different miRNAs in the biopsy samples of patients with IF/TA and compared it with normal biopsy samples. They found a higher expression of miR-21, 142-3p, and 5p and the cluster comprising miR-506 on chromosome X and lower expression of miR-30a, miR-30d and miR-30e in IF/TA biopsies (14). It has been reported that several miRNAs comprised of miR-21, miR-200 family (miR-200a, miR-200b, miR-200c, miR-429 and miR-141), miR-29 family (miR-29a, miR-29b-1, miR-29b-2 and miR-29c), miR-192, miR-217, miR-377, miR-93, miR-382 and miR-216 all are affected by TGF- β expression, a key fibrogenetic cytokine involved in fibrosis (1, 3). The prominent role of miR-21 (2, 15-18), miR-29 family (19-22) and miR-200 family (23, 24) in kidney transplant fibrosis have been pronounced. Recent study of Glowacki et al. (2013) suggested that miR-21 by itself is a novel, predictive and reliable blood marker of kidney allograft fibrosis (16).

In the context of kidney disease and early noninvasive diagnosis, urine is a specimen of choice. It provides a representative sampling of the entire kidney and an indirect way to visualize intragraft compartment; therefore, it is naturally appealing to nephrologists (25). The role of urinary miRNA as a feasible method is under active research for diagnosis of different disease such as chronic kidney disease (26, 27), diabetic nephropathy (28), adult nephrotic syndrome (29) and severity of fibrosis in Immunoglobulin A nephropathy IgA (22).

The recent discovery of human microRNAs (miRNA) opens a new horizon to biomedical research. Several publications have supported the value of urinary miRNAs for diagnosis renal allograft dysfunction so it could be a useful tool to monitor the status of the kidney allograft function and a feasible biomarker of IF/TA (15).

Authors' Contribution

The authors reviewed recent articles in the field of miRNA implication for renal allograft monitoring.

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