Review Article

Trends of non-coding RNAs research in acute rejection after kidney transplantation

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Abstract: The success of kidney transplantation as the treatment of choice for patients with end-stage kidney diseases (ESKD) is hindered by eventual failure of grafts mainly due to immune mediated rejection. Early detection of acute rejection (AR) for early initiation of proper anti-rejection therapy is very important in preventing allograft damage or loss. Understanding of non-coding RNAs' (ncRNAs) function and the existence of a highly regulated interplay between mRNA/miRNAs/lncRNAs in allograft rejection has gained the attention of research groups to explore different expression patterns of ncRNAs in the field of organ transplantation. Finding a specific pattern of ncRNAs as biomarker will be extremely important for monitoring the kidney allograft function, diagnosis, treatment and even preventing of AR occurrence. In this review list of miRNAs and lncRNAs have been linked to AR following kidney transplantation until now is presented.

Keywords: Non-coding RNAs; kidney transplantation, acute rejection (AR)

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Introduction

Kidney transplantation is the treatment of choice for patients with end-stage kidney diseases (ESKD) that increases patients' survival and improve quality of life (1,2). During the past decades by introduction of new and potent immunosuppressive drugs and improvements in surgical techniques, the incidence of acute rejection (AR) has decreased from 50% to about 10%. Early detection of AR and early initiation of proper anti-rejection therapy remains as a frequent and serious challenge in preventing allograft damage or loss (3-5). Currently, acute allograft rejection is diagnosed by rising serum creatinine level or by performing multiple and repeated kidney allograft biopsies. Allograft biopsy is invasive, costly and may be associated with poor interpretation, sampling error or even very rarely with graft loss (6-8). Unfortunately, rise in serum creatinine level or histological abnormalities in biopsy is seen when approximately 40–50% of reversible or irreversible graft parenchyma damage has been already occurred (9,10). The etiology of AR is related to the infiltrating cells of the recipient's immune system that affects kidney hemodynamics and molecular regulatory factors and in turn leads to T-cell mediated or adaptive antibody-mediated graft rejection (11-13).

By understanding of non-coding RNAs' (ncRNAs) function, cellular biology has revolutionized and a totally novel level of gene transcription regulation mechanism has been introduced which gain the attention of research groups to explore different expression patterns of ncRNAs in the field of organ transplantation (14,15). To date myriad efforts have been done to find out more about molecular mechanisms underlying AR to identify patients at high risk and early detection of affected patients (16,17). It is evident that the pathologic processes at molecular level occur long before histological abnormalities and clinical manifestations. Unfortunately we are still far away from understanding ncRNAs' related molecular signaling networks which occur in AR.

Molecular mechanisms of AR at a glance

Innate and adaptive immune systems both play key roles in rejection mechanism. Being a result of genetic differences between organ donor and recipient, transplanted graft consists of many foreign antigens that can trigger the recipient's immune response and lead to activation of T and B cells of recipient's adaptive immune system following recognition of non-self antigens (alloimmune response) (18). Allorecognition mainly depends on the cell-surface proteins called major histocompatibility complex (MHC) molecules. There are two classes of MHCs: class I, that are constitutively expressed on all nucleated cells; and class II, that are constitutively expressed only on antigen presenting cells (APCs) such as dendritic cells (DCs), macrophages (MQs) and the B cells. After vascularization of a transplanted organ, depending on the source of the APCs, recipient's T cells recognize donor-derived antigens through two distinct pathways: direct pathway, in which intact non-self MHC molecules on the surface of donor cells is recognized and a potent anti-graft immune response is elicited; and indirect pathway, in which donor fragmented MHC molecules on the surface of recipient's MHC molecules is recognized that induce a less intense immune response (18,19). In direct pathway, CD8 positive cytotoxic T cells recognize peptides within class I MHC molecules while CD4 positive helper T cells recognize peptides within class II MHC molecules. It is believed that alloreactive T cells have the ability to recognize polymorphic residues on allogenic MHC regardless of processed peptide bound to it (20). After T cell receptor CD3 (TCR-CD3) associated allorecognition-specific signal (signal 1) and accessory (CD4 or CD8) and costimulatory (ex: CD40/CD40L or CD28/B7 pathway) signal (signal 2), a chain of signaling protein phosphorylation is induced for genes transcription and T cells become activated (18,19,21-23). Tissue destruction happens following T cell mediated lysis of graft cells, activation of accessory T cells and their byproducts such as granzyme B and perforin, B cells mediated anti-transplant antibody production, cytokines production and complement activation (18,19,24,25). Regulatory T cells (T_{reg}) can suppress immune responses through suppressor cytokines production, modulating of DCs' maturation/function and suppression of effector cells; such as MQs and natural killer (NK) cells (18,19,26-28) providing tolerance and graft survival in transplant recipients. Activated T and B cells also can differentiate into memory cells that can respond more quickly and strongly to an antigen years after its first presentation (19).

Definition of ncRNAs

In humans, genome consists of the intron sequences, 3' or 5' untranslated regions, the protein—coding sequences (~28%) and other transcripts that are referred to as ncRNAs (29). Since they play important roles in regulatory pathways engaged in biological functions and human diseases, in recent years this field has gained international attention by investigators as a new discipline in biological research. However except for miRNAs, still intense efforts are needed to focus on elucidating detailed function and mechanisms of action underlying other types of ncRNAs. Non-coding RNAs are divided into three groups according their length: (I) small ncRNAs such as: endogenous small interfering RNAs (endo-siRNAs), microRNAs (miRNAs), Piwi-interacting RNAs (piRNAs), transcription initiation RNAs (tiRNAs); (II) mid-size ncRNAs such as: transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs); and (III) long ncRNAs such as: XIST, HOTAIR, AIR, very long intergenic RNAs (vlincRNAs), macro lncRNAs. Many of ncRNAs may fall into more than one group such as: promoter associated RNAs (PATs), enhancer associated RNAs (eRNAs) and circular RNAs (circRNAs) (30-34). Part of currently identified nc-RNAs and their characteristics are highlighted in (*Table 1*). Some other nc-RNAs which are not described in *H. sapiens* are not mentioned here.

MiRNAs, lncRNAs and circRNAs have been detected in tissue samples and easily accessible body fluids such as peripheral blood mononuclear cells (PBMCs), serum, plasma, urine cell pellets and urine supernatant (58-62). They even are found in packed forms into macrovesicles, exosomes or HDL and can be picked up by neighboring cells functioning as secondary messenger molecules and growing evidence shows that their dysregulation is implicated in kidney diseases and AR (63-67). Taking the aforementioned kidney biopsy substantial risks and the existence of an urgent need to discover early noninvasive biomarkers, ncRNAs seems to be as promising candidates to tackle these problems by better stratification of rejection risks, diagnosis, monitoring the progression of AR and evaluation of treatment strategies which in turn may lead to improvement in allograft survival and patient outcome.

Biogenesis and function of MicroRNA

MicroRNAs (miRNAs) are short (~22 nt in length) single stranded endogenous non-coding RNAs that are able to

Table 1 Part of currently identified nc-RNAs and their characteristics

RNA species	Full name	Function	Length	References
Housekeeping/infra-structural ncRNAs				
tRNA	Transfer RNA	Amino acids carriers	73–93	(35)
snRNA	Small nuclear RNA	RNA splicing	90–216	(36)
snoRNA	Small nucleolar RNAs	RNA modifications	60–90	(37)
rRNA	Ribosomal RNA	Translation machinery	5SrRNA =~120, 5.8SrRNA =~160, 28SrRNA =~4,200, 18SrRNA =~1,900	(38)
Small sized ncRNAs mainly with regulatory roles				
miRNA	MicroRNA	RNA stability and translation control	20–25	(39)
piRNA	Piwi-interacting RNA	Silencing transposon and mRNA decay	26–31	(40)
endo-siRNA	Endogenous small interfering RNA	RNA degradation	18–30	(41)
tiRNA	Transcription initiation RNA	Marking or regulating the epigenetic landscape around transcription start sites	13–28	(42)
eRNA	Enhancer associated RNA	Regulation of gene expression	<2,000 (50–2,000)	(43)
PASR	Promoter associated RNA	Correlate with the expression state of protein-coding genes	19–70	(44-46)
TTSa RNA	Transcription termination site associated RNA	Epigenetic control of gene expression	22–24	(47)
TASR	Termini-associated short RNA	These sRNAs antisense to the 3' ends of the annotated transcripts could increase the RNA copy numbers	20–70	(45,46)
nro-RNA	Nuclear run-on assay derived RNAs	Probably play role in promoter activation and transcription orientation	Short RNAs mapping 20 to 50 downstream to transcriptions starting sites of mRNAs	(48)
Long sized ncRNAs mainly with regulatory roles				
HOTAIR	HOX transcript antisense RNA	Promoting epigenetic repression of Homeobox D gene cluster	2.2 Kb	(49)
XIST	X-inactive specific transcript	X chromosome inactivation mediated by xist RNA stabilization	Full length sequences have not been determined	(50)
AIR	The autoimmune regulator	Silencing autosomal imprinted genes	Full length transcripts have yet to be characterized	(51)
PROMPT	Promoter upstream transcripts	Unknown since they are rapidly degraded by the RNA exosome enzymes	Hundreds of nt	(52)
PALR	Promoter-associated long RNAs	May regulate gene expression and function as a recognition motif to direct epigenetic silencing complexes to the corresponding targeted promoters to mediate transcriptional silencing in human cells	Hundreds nt long RNAs spanning regions on proximal promoters to the first exon	(45,53)
TALR	Terminus-associated long RNAs	May be primary transcripts for the production of short RNAs or correlate with the expression state of protein-coding genes	~3,100 nt	(45,54)
T-UCR	Transcribed ultraconserved regions	Regulation of alternative splicing and gene expression, and altered in some of human cancers	>200 nt	(55)
circRNA	Circular RNA	Regulation of gene transcription acting as miRNA sponges, or binding to RNA-associated proteins	100 bp to 4 kb	(56,57)

regulate gene expression by repressing mRNA translation or enhancing of mRNA decay (68,69). Several studies has shown that miRNA play pivotal roles in wide range of biological processes, such as cell differentiation, organ development, apoptosis, innate and adaptive immunity, cell death, stress responses and diseases (70-74). MiRNAs exhibit temporal and tissue-specific expression patterns. The miRNA biogenesis starts from long primary transcripts of relative genes (pri-miRNA) generated from RNA polymerase II (RNA Pol II). Following cleavage by microprocessor complex DROSHA and Di-George syndrome critical region gene 8 (DGCR8), a stem-loop structural precursor (pre-miRNA) of about 70 nt long is generated and then exported to the cytoplasm by Exportine5 through the nuclear pores where they are further processed by the Dicer into ~22 nt duplexes of mature miRNAs. After unwinding of dsRNA and loading of guide-strand onto the RNA-Induced Silencing Complex (RISC), the final complex recognizes target mRNAs via complementary binding of seed sequences (6–8 nt) to them and in turn degrade them or inhibit their translations (75-77). Intriguing fact about microRNAs is that a single type miRNA is able to bind to many different mRNA targets and regulates their expression. On the other hand, a single mRNA can be targeted by variety of miRNAs (78,79). Some evidences showed that miRNAs can play roles as transcriptional activators or co-activators of several genes (80). It is believed that AR, as frequent complication of kidney transplant, is associated with alterations in interplay relationship between mRNAs and miRNAs that are highly regulated molecular mechanisms (81). Thank to solid base technologies studying and monitoring of antibody mediated immunity has been remarkably progressed, but T-cell mediated immunity is still mainly depends on invasive tissue biopsies (67,82,83).

Biogenesis and function of lncRNA

Noticeable portion of human genome is actively transcribed into lncRNAs that recently has been shown some of them harbor short open reading frames (sORF) which minority of them translated to stable and functional peptides with even enhancer role (84-87). Most of lncRNAs but not all of them resemble mRNAs with respect to synthesizing by RNA Pol II or rarely by RNA Pol III (88), 5'capped (except for the intronic RNAs and circRNAs) and 3'-end polyadenylated, non polyadenylated or as both forms (bimorphic transcripts) (89-92). Aside RNA Pol machinery, for their transcription, they need assisting factors such as pre-initiation complex, mediators, transcription elongation complex and transcription factors (93). Their promoters are more conserved than the promoter of protein coding genes (94) and enriched in A/T mono-, di- and trinucleotide stretches while the levels of histone H3K4 trimethylation (H3K4me3) are reduced in them leading lower transcription rate (95). Just like as protein coding genes, lncRNA genes comprise multi-exonic regions with identical splicing signals that leads to production of many different isoforms with specific functions (96-98).

lncRNAs may localize either in nucleus or in cytosol (99) but under special conditions such as environmental changes or infection they can be delocalized from one cellular compartment to another (100). Nuclear lncRNAs mainly are related to chromatin architecture of genes in cis or in trans (101) while cytoplasmic ones are believed to be competing endogenous RNAs that can regulate miRNAs (101). lncRNAs exhibit highly specific tissue- and cell-type expression patterns compared with protein coding genes (93,102). On the basis of their genomic location they are categorized into six following groups: (I) intergenic; (II) intronic; (III) bidirectional protein associated; (IV) sense; (V) antisense and (VI) enhancer associated (93,101,103).

Regarding the role of lncRNAs in gene expression regulation, they can be classified as: (I) scaffold lncRNAs that recruit multiple partners in order to form chromatin modifying complex (104); (II) guide lncRNAs that sequester ribonucleoprotein complexes and direct them to target genes (101,105); (III) elncRNs that are transcribed from enhancer elements and link the enhancer to the promoter to increase transcription (106,107); (IV) signal lncRNAs that are transcribed in response to different developmental and environmental stimuli (101,104); (V) decoy lncRNAs that can tittering away transcription factors, induce RNA degradation, functioning as sponges and tittering the miRNAs' concentrations and compete with them for binding to target mRNA (108,109). Although in some cases it has been shown that lncRNAs-protein interactions are sequence independent and even exon deletions or sequence replacement does not affect neighboring genes' expression (110-113), it has been demonstrated that some single nucleotide polymorphisms (SNPs) within lncRNAs or their promoters contribute to some disease- associated pathologies (114).

MicroRNAs in acute kidney transplant rejection

Increasing number of studies suggest that miRNAs have critical regulatory roles in innate and adaptive immune responses and thus in organ status after transplantation.

The relationship between hematopoietic cells' differentiation stages and miRNA profiling status was first described by Monticelli *et al.* in the murine hematopoietic system in which increased levels of miR-142-3p in naïve T cells compared with differentiated Th1 and Th2 cells has been reported (115). According to genomic studies the molecular injury in chronic allograft nephropathy (CAN) and AR resembles. This likely reflects the threshold effect for AR at which the same molecular injuries occurs at higher and sever levels in AR compared with CAN (17). Surprisingly, increased levels of forkhead box protein 3 (FOXP3) transcription factor's mRNA was observed in urine samples of patients with AR (90% sensitivity and 73% specificity) compared with patients with CAN and recipients with normal biopsy results (116). This finding was confirmed by other studies (117,118). FOXP3 is known as miR-142-3p transcription repression mediator and it is expected to decrease the expression level of it (119). Further studies revealed that normally the expression of two opposite arms of miR-142 in hematopoietic cell lineage are different and the expression level of miR-142-3p (3' arm of miR-142) is approximately 10 times more than that of miR-142-5p (5' arm of miR-142) (120). In 2011, performing an investigation of miRNA, mRNA and protein expression on activated T lymphocytes, Grigoryev *et al.* introduced the concept of miR-142-3p being associated with tolerant kidney allograft recipients while decreased levels of miR-155 and miR-221 are associated with T-cell proliferation (121). The results of subsequent studies revealed that miR-142-3p, miR-204 and miR-211 can be used to distinguish patients with CAN from those without (122-124). Also the overexpression of miR-142-3p in PBMCs of operationally tolerant kidney transplant recipients has been shown (125). Soltaninejad *et al.* identified 4 miRNAs (miR-142-3p, miR-142-5p, miR-155 and miR-223) that were abundantly expressed in 17 biopsy samples as well as two miRNAs (miR-142-3p and miR-223) in their paired PBMC samples of patients with confirmed TMAR compared with patients with stable graft function (SGF) (126). Previously Anglicheau *et al.* found that miR-142-5p, miR-155, and miR-223 that are highly expressed in AR biopsies are overexpressed in normal PBMCs too (127). Liu and Xu have found that miR-223 was increased 2 folds in PBMCs of patients with AR within 1 month after kidney transplantation (128).

A recent study conducted by Domenico *et al.*, showed that miR-142-3p is significantly increases in peripheral blood and urine of kidney transplant recipients with acute tubular necrosis (ATN) but not in those with SGF and AR (129). The authors supported another study's findings and suggested that this provide strong evidence for necrosis processes and inflammatory injuries such as interstitial fibrosis and tubular atrophy (IF/TA) (124,129). MiR-142-5p overexpression in non-invasive samples was found in patients with chronic antibody mediated rejection but not in those with AR or SGF (130).

In a study using sera from 42 kidney transplant recipients the association of circulating miR-21 levels with renal fibrosis severity was assessed. The fibrosis grades were evaluated by allograft biopsy result interpretations and authors concluded that levels of circulating miR-21 are significantly increased in cases with sever IF/TA but not in other renal histological lesions (131).

In one study the circulating miRNAs in urinary samples of patients with AR, patients before and after rejection, patients with urinary tract infection (UTI) and patients with SGF were performed. Deregulation of miR-10a, miR-10b and miR-210 in urine samples of patients with AR, from which miR-10b and miR-210 were down-regulated while miR-10a was up-regulated in Acute TCMR patients compared with those with SGF were determined. It was also shown that decreased levels of miR-210 were associated with higher glomerular filtration rate (GFR) during first year after transplantation. Among aforementioned deregulated miRNAs, it was determined that only expression level of miR-210 was corrected after successful rejection treatment (132). Conversely Betts *et al.* examined the sera of patients with AR and found that miR-223 and miR-10a to be significantly down-regulated during AR compared with patients with SGF and without a history of rejection (133). Liu *et al.* performed miRNA next generation sequencing in normal and acutely rejected kidney allografts. The main finding was that miR-10b was significantly down-regulated in AR inducing glomerular endothelial cell apoptosis by derepressing of its pro-apoptotic target, B-cell lymphoma2-like-11protein (BCL2L11), and releasing of pro-inflammatory cytokines and MQs chemotaxis. All of these are key features of AR and the authors suggested that restoring of miR-10b expression in glomerular endothelial cells can be used as therapeutic approach in order to ameliorate acute kidney allograft loss (134).

Lv *et al.* showed that miR-29-c in urinary exosomes correlated with GFR and could be used for distinguishing mild from moderate to severe fibrosis with 68.8% sensitivity and 81.3% specificity (135).

Sui *et al.* integrated array-based proteomics and

microarray-based genomics data to find transcription factors (TF), miRNAs and ncRNAs of biopsy specimens from patients with AR in order to further understand the mechanism underlying AR. They reported the expression of 5 TFs (AP-1, AP-4, STATX, c-Myc and P53), 12 miRNAs and 32 ncRNAs with critical roles in molecular signaling pathways related to AR. For example, down-regulation of has-miR-324-3p and up-regulation of has-miR-381 had been correlated with poor prognosis or key proteins with regulatory effects on apoptosis, innate immunity, inflammation and hematopoietic differentiation are repressed by miR-125b at translation level (136). Also they investigated the expression levels of miR-181a, miR-483-5p and miR-557 in sera samples of 15 kidney transplant recipients before transplantation, on the first, third and seventh days after transplantation by RT-PCR. Based on receiver operating characteristic (ROC) analysis results, they concluded that these three miRNAs could serve as predictive biomarkers for rejection (137). This same research group in a study conducted in 2008, have indicated an AR profile of 20 miRNAs in biopsy samples of 3 patients with AR and compared them with 3 patients with SGF, out of which 2 (miR-320 and miR-324-3p) were confirmed by QRT-PCR (118).

A research group led by Wilflingseder, has also done a number of studies regarding miRNAs expression patterns according to rejection type or injury in renal transplantation. In 2013, they reported miRNA signatures that discriminate acute TCMR (up-regulation: miR-150, miR-155, miR-663 and miR-638; down-regulation: 18 miRNAs; miR-125b-2, miR-99b, miR-30-c-2 and miR-424), acute ABMR (up-regulation: miR-146-5p, miR-1228, let-7i, miR-21, miR-182, miR-155, miR-125a and miR-146b) and delayed graft function (DGF) (138). Following year, they showed a molecular acute kidney injury (AKI) signature consisting 20 mRNAs and 2 miRNAs (miR-182-5p and miR-21-3p) from which miR-182-5p was identified as biomarker in addressing AKI (139).

Tao *et al.*, found 6 deregulated miRNAs in serum samples of patients with AR compared with kidney recipients with SGF and patients with DGF. Out of 6, up-regulation of only 2 (miR-99a and miR-100) were confirmed by QRT-PCR in AR patients and according to ROC analysis, only miR-99a had a potent diagnostic value for discriminating patients with AR from those with SGF or with DGF. Thus they concluded that serum level of miR-99a could serve as a biomarker for detection of AR (140).

Rejection associated events such as production of cytokines and growth factors can result in microvascular endothelial cells damage and promotion of dysregulated angiogenesis within the graft (141). Bijkerk *et al.* selected 48 miRNAs to assess the AR and microvascular injury associated circulating miRNAs in plasma samples of 13 patient with AR on the first, sixth and twelve months after AR and 25 transplant recipients with SGF using QRT-PCR. The investigators identified 8 miRNAs (up: miR-17, miR-140-3p, miR-130b, miR-122 and miR-192; down: miR-135a, miR-199a-3p, miR-15a) as being able to discriminate AR and SGF. Furthermore, the authors showed miR-130b, miR-199a and miR-192 were associated with markers of vascular injury. MiR-140-3p, miR-130b, miR-122 and miR-192 were normalized within 1 year after AR (142). Cheng *et al.* investigated the role of miRNA-181b in peripheral blood of renal allograft recipients whit acute vascular rejection (n=14) and non-acute vascular rejection (n=20) using QRT-PCR. They found that the expression level of peripheral blood miR-181b in patients with acute vascular rejection was remarkably lower at different time points of 1, 2, 3 and 4 weeks post transplantation compared with that of the non-acute vascular rejection. Furthermore the authors suggested that miR-181b might be one of the markers for monitoring of acute vascular rejection after kidney transplantation (143).

Recently in a study Matz *et al.* from France aimed to identify miRNAs signature in ABMR and IF/TA using high-throughput sequencing and validated results in 53 patients with SGF, 17 with UTI, 19 with borderline rejection (BL), 40 with TCMR, 22 with ABMR and 30 with IF/TA by QRT-PCR. miR-142, miR-223-3p, miR-424-3p and miR-145-5p could discriminate acute TCMR and acute ABMR only from SGF, but not from others. Also miR-145-5p was identified as IF/TA specific biomarker from SGF only and others combined with highly diagnostic accuracies (AUC =0.891 and AUC =0.835 respectively) (144).

Finally, Misra *et al.* from India investigated the impact of 4 SNPs namely MIR146A C>G (rs2910164), MIR149 T>C (rs2292832), MIR196A2 T>C (rs11614913), and MIR499A A>G (rs3746444) among patients with end-stage renal disease (ESRD) and those with AR. They observed an increased risk of approximately two-fold in ESRD and three-fold in AR for mutant genotypes of rs2910164, rs11614913, and rs3746444. They concluded that these SNPs might have roles in susceptibility to ESRD and AR (145).

lncRNAs in acute kidney transplant rejection

As mentioned before, since TFs, miRNAs and lncRNAs are

the most important gene regulators, Sui *et al.* for the first time investigated and constructed the regulation network of the target genes by 5 TFs, 12 miRNAs and 32 lncRNAs which were differentially expressed in biopsy specimens from patients with AR integrating high throughput screening data and different algorithms' data (136).

Using lncRNAs microarray Chen *et al.* studied the differentially expressed lncRNAs in biopsy tissue samples of 3 patients with AR and compared them with those with SGF. Then based on their expression fold changes five lncRNAs (uc001fty, uc003wbj, AK129917, uc010ftb and AF113674) have been chosen to be validated by QRT-PCR (146). Taking the notion that depending on their genomic location lncRNAs have divers regulatory functions such as negatively/positively regulating the target gene, protein-coding mRNA stabilization, regulation of alternative splicing of mRNAs and etc. (147); they have done KEGG pathway enrichment analysis for these five lncRNAs to gain new insights into the pathogenesis of AR. The authors concluded that AR is associated with immune activation and inflammation (146).

Lorenzen *et al.* analyzed the lncRNAs expression profiles in tissue biopsies and urine of kidney transplant recipients with acute TCMR and identified three intergenic lncRNAs: LNC-MYH13-3:1, RP11-395P13.3-001 and RP11-354P17.15-001. They demonstrated that urinary RP11-354P17.15-001 can predict AR and loss of graft function at 1 year post transplantation. Also they showed that exposure of cultured tubular epithelial cells to the IL-6 as an inflammatory cytokine increased the expression levels of all lncRNAs, however, in the cell culture supernatant the expression levels of only RP11-395P13.3-001 and RP11-354P17.15-001were increased. The authors suggested that these lncRNAs might be secreted under inflammatory conditions (148).

In a study on a cohort of 72 patients with allograft rejection and 36 patients with SGF, lncRNA activated by transforming growth factor β (TGF-β) (lncRNA-ATB) was found to be significantly increased in biopsies of patients with AR compared with those with SGF. The authors stated that lncRNA-ATB could serve as a novel biomarker for AR, nephrotoxicity of immunosuppressive drugs and predict loss of graft function (149).

Evaluation of lncRNAs profile in peripheral blood of kidney transplant recipients was done by Ge *et al.* for the first time in cohorts of 150 pediatric and adult recipients. Among differentially expressed lncRNAs in pediatric and adult patients, 32 lncRNAs could distinguish both groups with AR from those without AR. Also, they showed that the two most significant lncRNAs, AF264622 and AB209021 had remarkable diagnostic values (AUC =0.829 and AUC =0.889, respectively) in both recipients groups for discriminating AR episodes from SGF (150).

Nagarajah *et al.* measured lncRNA, β-1, 4-mannosylglycoprotein 4-β-N-acetylglucosaminyltransferase antisense RNA1 (MGAT3-AS1) levels in mononuclear cells using QRT-PCR and showed that MGAT3-AS1 decreased significantly at first postoperative day after kidney transplantation. In addition, they observed an association between decreased level of MGAT3-AS1 and decreasing of plasma creatinine level within first day post transplantation and concluded that lncRNAs-MGAT3-AS1 assessment could be used for determining immediate allograft function (151).

Huang *et al.* showed that the serum concentration of interferon-induced protein 10 (IP-10) in acute TCMR episode was significantly higher compared with patients with SGF (152). There are numerous reports of fundamental role of IP-10 and its receptor CXCR3 in amplifying intragraft inflammation, enhancing inflammatory reactions via stimulating resident and alloreactive memory T-cells during rejection and ischemia induced tubular damage in human recipients as well as mouse and rat transplant models (152-157). On the other hand, increased levels of NF-κB resulted by reactive oxygen species and renal inflammation were seen (157,158). It was also documented that Arid2-IR lncRNA functions to promote NF-κB-dependent renal inflammatory cytokine expression (159). In a recent study, the regulatory effect of chemokine IP-10 on expression of Psoriasis susceptibility related RNA gene induced by stress (PRINS) lncRNAs was investigated (157). The increased levels of IP-10, NF-κB as well as up-regulation of PRINS lncRNAs were detected. Furthermore expression level of PRINS lncRNA was decreased following IP-10 antibody treatment was reported in the same study. The authors suggested that antibody treatment reduced T-cell recruitment and concluded that this might become indicative for PRINS lncRNA involvement in AR (157).

Conclusions

The success of organ transplantation as a preferred therapy is hindered by eventual failure of grafts mainly due to immune mediated rejection responses. Growing variety of human ncRNAs are emerged and their discoveries has opened a new window to biomedical research and

toward pathogenesis of AR after transplantation. In AR the pathologic process can be detectable at molecular level before histological or clinical manifestations occur. Several investigations were done for profiling of miRNAs in biopsy, serum, plasma and urine samples of transplant recipients with AR to develop insights into pathways responsible for the rejection process and to find novel targets for therapy. However, till now involvement of only minority of lncRNAs in the pathogenesis of AR has been documented and other kinds of ncRNAs have not been identified yet in this aspect.

In this review list of miRNAs and lncRNAs have been linked to AR following kidney transplantation was presented and the usefulness of them as non-invasive biomarkers in early detection of AR was examined. The existence of a highly regulated interplay between mRNA/miRNAs/lncRNAs in allograft rejection mentioned in above studies lead to the notion that these ncRNAs might promote the identification of feasible biomarkers for monitoring the kidney allograft function, diagnosis, treatment and even preventing of AR occurrence. These could be achieved by further investigation of association between AR and ncRNAs to illuminate the mechanisms underlying the organ rejection.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2019.03.04). The author has no conflicts of interest to declare.

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