Expression Levels of lncRNAs in the Patients with the Renal Transplant Rejection

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Purpose: Long non-coding RNAs (lncRNAs) include a vast portion of human transcripts. They exert regulatory roles in immune responses and participate in diverse biological functions. Recent studies indicated dysregulation of lncRNAs in the process of transplant rejection. In the current study, we aimed at identification of the expression of five lncRNAs (OIP5-AS1, FAS-AS1, TUG1, NEAT1 and PANDAR) in association with the process of transplant rejection.

Material and Methods: We assessed expression of these lncRNAs in the peripheral blood of 61 kidney transplant receivers including 29 transplant rejected patients and 32 transplant non-rejected patients using real time PCR technique.

Results: Expression of FAS-AS1 was significantly higher in rejected group compared to non-rejected group in males, however, differences between case and control groups were insignificant among females. For other lncRNAs no significant differences were detected between two study groups. Quantile regression model showed that patients' gender was an important parameter in determination of FAS-AS1 expression (Beta = - 9.46, t =- 2.82, P = 0.007) but not for other lncRNAs expressions. Significant pairwise correlations were detected between expression levels of lncRNAs in a disease related manner.

Conclusion: Based on the higher expression of FAS-AS1 in patients with transplant rejection, this lncRNA might be associated with the pathogenesis of renal transplant rejection.

Keywords: kidney transplant; rejection; lncRNA; OIP5-AS1; FAS-AS1; TUG1; NEAT1; PANDAR

INTRODUCTION

End stage renal disease (ESRD) is a catastrophic condition which has limited therapeutic options including renal transplantation[1]. The fate of renal transplants is endangered by acute rejection which might happen in spite of application of immunosuppressive treatment and sophisticated surgical techniques[2]. The dependence of diagnosis of acute rejection on the invasive method of renal biopsy has encouraged researchers to find suitable non-invasive methods for this purpose[3]. Long non-coding RNAs (lncRNAs) as main regulators of immune response have been suggested to exert functional roles in the process of immune-mediated tissue rejection[3]. These transcripts regulate expression of target genes through different mechanisms and at different genomic, transcriptomic and post-transcriptomic levels. They have interaction domains for almost all fundamental biological molecules including DNA, mRNAs, miRNAs, and proteins[4]. Consequently, they participate in regulation of nearly all aspects of life. Their interactions with Toll-like receptors result in modulation of expression of immune response genes[5]. A previous study in patients with acute rejection and control subjects revealed that tens of lncRNAs are differentially expressed between groups[6]. Besides, lncRNA microarrays have shown distinctive expression profiles of acute rejection in renal transplant biopsies[7]. Another study in animal models has shown the role of PRINS lncRNA in allograft rejection linking between persistent ischemia and transplant rejection[8]. In the present study, we selected five lncRNAs to assess their expression profile in the peripheral blood of renal transplant receivers including patients with acute rejection and those with normal glomerular filtration rate (GFR) and no sign of rejection. LncRNAs were selected based on their involvement in regulation of immune response or cell apoptosis. The lncRNA OPA-interacting protein 5 antisense transcript 1 (OIP5-AS1) participates in regu-

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Table 1. Demographic and clinical data of study participants.

Groups Parameters		Antibody-mediated rejected	T cell-mediated rejected	Non-rejected
Age (mean ± standard error of mean)		40.7 (±15.2)	39.33 (±15.1)	35.6 (±16.1)
Sex ratio (Female/ male)		9/ 13	1/ 6	8/ 24
Estimated GFR (eGFR)	Before transplantation	8.76 ± 1.4	8.98 ± 1.32	7.96 ± 1.24
	1 month after transplantation	41.9 ± 3.2	43.7 ± 3.4	55.39 ± 3.8
	2 months after transplantation	47.195 ± 2.9	57.064 ± 3.9	64.119 ± 4.32
	3 months after transplantation	40.97 ± 1.95	60.29 ± 4.2	60.935 ± 4.2

lation of cell proliferation and apoptosis through interaction with PTEN/PI3K/AKT pathway[9]. This pathway has crucial roles in regulation of chemokine-induced recruitment of immune cells and their function. Moreover, a certain isoform of PI3K controls development and activity of B and T cells. Notably, suppression of this pathway has decreased the strength of inflammatory responses in animal models[10]. Fas –antisense 1 (FAS-AS1) is transcribed from antisense stand of Fas. Defects in Fas or Fas ligand (FasL) leads to systemic autoimmune responses in both human subjects and animals[11]. Moreover, excessive release of autoantibodies have been reported following Fas defects in T and B lymphocytes or dendritic cells[12]. Taurine up-regulated gene 1 (TUG1) participates in regulation of cell apoptosis and inflammatory responses in diverse pathological conditions. Such functions are possibly exerted through modulation of activation of immune-related signaling pathways namely NF-κB and JAK/STAT [13]. Nuclear paraspeckle assembly transcript 1 (NEAT1) binds to Splicing Factor Proline And Glutamine Rich and participates in modulation of the innate immune system and production of IL-8[14]. The lncRNA Promoter Of CDKN1A Antisense DNA Damage Activated RNA (PANDAR) recruits polycomb repressive complexes and inhibits expression of senescence-enhancing genes (15). A recent study has reported up-regulation of this lncRNA in peripheral blood of multiple sclerosis (MS) patients[16]. Consequently, the selected lncRNAs in the current project are possibly associated with immune response regulation and are hypothesized to participate in acute transplant rejection.

PATIENTS AND METHODS

Patients

The current retrospective study was conducted on 29 transplant rejected patients (18 males and 11 females) and 32 transplant non-rejected patients (24 males and 8 females). Patients were admitted to Labbafi-Nejad hospital, Tehran, Iran during 2016-2018. Patients who received renal transplant during the mentioned period entered the study. Exclusion criteria were delayed graft function, urinary obstruction and urinary tract infection. Protocol biopsies of the renal allografts were performed based on the guidelines of the transplant center. Renal function was evaluated by creatinine clearance, protein excretion and renal ultrasound and angiography. Biopsy was performed in cases with at least 25% creatinine rise during two consecutive measurements after rule out of drug toxicity and obstructions. Acute rejection was scored based on Banff criteria[17]. Control subjects (non-rejected group) were matched to rejected group regarding sex and age parameters. These individuals either had no creatinine rise in the prior 3 months or protocol biopsy ruled out the transplant rejection. Patients were under treatment with Tacrolimus, CellCept and Prednisolone with no significant inter/intra-group differences in treatment regimens. In antibody-mediated rejection, T cell-mediated rejection and non-rejected groups, 10%, 28% and 50% of patients received transplants from live donors, respectively.

The study protocol was approved by ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1398.193). Written consent forms were obtained from all study participants.

Expression analysis

Peripheral blood was obtained from the enrolled patients at the day of biopsy in the same time and stored at -80 °C until additional investigations. Total RNA was isolated from all specimens using Hybrid-R Blood RNA (GeneAll Biotech, Korea). All steps were performed based on the protocol provided by the company. Subsequently, cDNA was produced from all samples using PrimeScript 1st strand cDNA Synthesis Kit (Clontech, Japan). Expressions of five lncRNAs were measured in real-time PCR system (Rotor Gene 6000, Corbett, Australia) using the HPRT1 gene as the reference gene. The RealQ Plus Master Mix (Ampliqon, Denmark) was used for amplification of lncRNAs. Primers and PCR conditions were the same as our recently published study[18].

Statistical methods

Mean values (± standard error of mean) of lncRNAs ex-

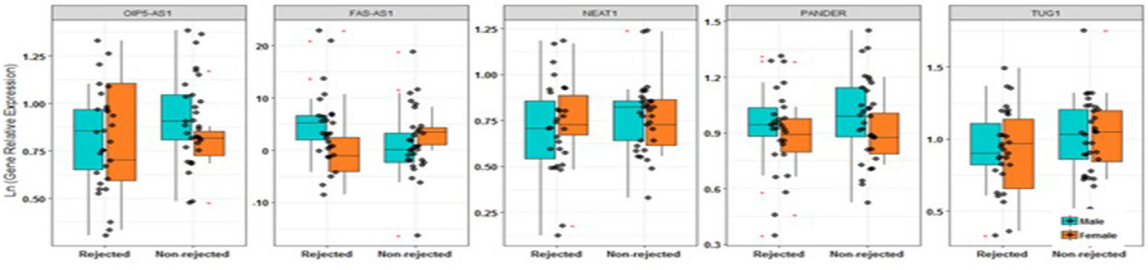

Figure 1. Relative expression of lncRNAs in study groups based on the gender of subjects (Black dots show the expression level in each patient, Red crosses show outlier values).

Table 2. The results of Bayesian Regression model to compare gene expression ratios between study groups with adjusting the effects of gender (a Expression difference: Rejected - Non-Rejected, [b] *P*-Value estimated from Frequentist method).

LncRNAs	Groups	Rejected	Non-Rejected	Relative Expression difference a	SE	*P*-value [b]	95% CrI
OIP5-AS1	Total	29	32	-0.0936	0.07	0.623	[-0.22, 0.04]
	Male	25	19	-0.1268	0.07	0.581	[-0.27, 0.02]
	Female	7	10	-0.0102	0.17	0.765	[-0.35, 0.33]
FAS-AS1	Total	29	32	4.0647	2.07	0.005	[0.01, 8.18]
	Male	25	19	4.0609	2	0.005	[0.19, 8]
	Female	7	10	-1.822	3.88	0.347	[-9.42, 5.95]
TUG1	Total	29	32	-0.0964	0.08	0.310	[-0.24, 0.05]
	Male	25	19	-0.0664	0.08	0.282	[-0.22, 0.1]
	Female	7	10	-0.1718	0.19	0.744	[-0.55, 0.21]
NEAT1	Total	29	32	-0.057	0.06	0.210	[-0.18, 0.07]
	Male	25	19	-0.0647	0.07	0.194	[-0.2, 0.07]
	Female	7	10	-0.0406	0.15	0.949	[-0.33, 0.26]
PANDAR	Total	29	32	-0.0462	0.06	0.527	[-0.17, 0.07]
	Male	25	19	-0.0496	0.08	0.572	[-0.2, 0.1]
	Female	7	10	-0.0344	0.11	0.917	[-0.26, 0.19]

pressions were compared between study groups using Bayesian Regression model. The observation effects were regarded as random in the analysis model. The t student/Gaussian prior distribution was assumed for parameters with 8000 iteration and 1000 warm-up. The effects of possible confounding parameters were judged by Quantile regression model. The Box-Cox transformation was used for normalization of the data. P-values were estimated from Frequentist method. Stan package in R 3.5.1 environment was used for statistical analysis. $P < 0.05$ was regarded as significant.

RESULTS

General data of patients

Table 1 shows demographic and clinical data of patients. In transplant rejected patients, graft biopsy revealed T cell mediated rejection and antibody-mediated rejection in 22 and 7 patients respectively. In non-rejected patients, 12 patients had no creatinine rise whereas others had creatinine rise. In rejected group, mean (± standard error of mean) values of serum levels of creatinine were 3.14 ± 1.8 mg/dL and 2.04 ±1.74 mg/dL prior and post-transplantation, respectively. In this group, one patient died and nephrectomy was done for one patient[19].

Expression assays

The results of expression analysis of lncRNAs in rejected and non-rejected groups are shown in **Figure 1**. Expression of FAS-AS1 was significantly higher in rejected group compared to non-rejected group in males, however, differences between case and control groups were insignificant among females. For other lncRNAs no significant differences were detected between two study groups. As shown in **Table 2**, expression of FAS-AS1 was different between rejected and non-rejected groups (relative expression difference = 4.0647, P value = 0.005). However, gender-based analysis showed that the difference was due to the dissimilar expression levels in males, as females did not show any significant difference in this regard.

Quantile regression model showed that patients' gender was an important parameter in determination of FAS-AS1 expression (Beta = -9.46, t = -2.82, $P = 0.007$) but not for other lncRNAs expressions. Table 3 shows the results of Quantile regression for assessment of association between expression ratio and independent variables.

Subsequently, we assessed expression of lncRNAs between four subgroups (T cell mediated rejection, antibody-mediated rejection, stable GFR, non-rejected with creatinine rise). The results of Bayesian Regression model after adjustment of the effects of gender showed no significant difference in lncRNA expressions between four study subgroups (**Table 4**).

Correlations between expression levels of lncRNAs

Finally, we assessed correlations between expression

Table 3. The results of Quantile regression for assessment of association between expression ratio and independent variables (Group: Rejected/ Non-rejected; Gender: Male/Female).

LncRNA	Variable	Beta	SE	*t*	*P*-Value	95 % CI for Beta
OIP5-AS1	Group	-0.05	0.10	-0.49	0.623	[-0.26, 0.16]
	Gender	-0.09	0.15	-0.61	0.542	[-0.38, 0.2]
	Group*Gender	-0.03	0.20	-0.15	0.884	[-0.42, 0.37]
FAS-AS1	Group	5.14	1.76	2.91	0.005	[1.61, 8.68]
	Gender	3.36	2.48	1.35	0.181	[-1.61, 8.32]
	Group*Gender	-9.46	3.36	-2.82	0.007	[-16.19, -2.74]
TUG1	Group	-0.13	0.13	-1.03	0.310	[-0.38, 0.12]
	Gender	0.02	0.18	0.11	0.909	[-0.33, 0.37]
	Group*Gender	0.04	0.24	0.18	0.859	[-0.44, 0.52]
NEAT1	Group	-0.11	0.09	-1.27	0.210	[-0.3, 0.07]
	Gender	-0.09	0.13	-0.74	0.460	[-0.35, 0.16]
	Group*Gender	0.13	0.17	0.74	0.460	[-0.22, 0.47]
PANDAR	Group	-0.05	0.07	-0.64	0.527	[-0.19, 0.1]
	Gender	-0.12	0.10	-1.15	0.257	[-0.32, 0.09]
	Group*Gender	0.03	0.14	0.23	0.818	[-0.25, 0.31]

Table 4. The results of Bayesian Regression model for comparison of gene expression ratios between subgroups with adjusting the effects of gender (Reference category: Antibody-Mediated Rejection).

LncRNA	Group	Relative Expression difference	SE	*P*-value	95% CrI
OIP5-AS1	T-Cell Mediated Rejection	-0.15	0.11	0.259	[-0.37, 0.07]
	Stable GFR	0.02	0.1	0.836	[-0.17, 0.21]
	Non-rejected with Creatinine Rise	0.08	0.08	0.750	[-0.08, 0.23]
FAS-AS1	T-Cell Mediated Rejection	-0.09	0.12	0.220	[-0.33, 0.16]
	Stable GFR	0.07	0.1	0.327	[-0.13, 0.28]
	Non-rejected with Creatinine Rise	0.08	0.09	0.283	[-0.11, 0.25]
TUG1	T-Cell Mediated Rejection	5	2.94	0.540	[-0.83, 10.88]
	Stable GFR	0.34	2.53	0.602	[-4.56, 5.24]
	Non-rejected with Creatinine Rise	-1.99	2.11	0.430	[-6.05, 2.17]
NEAT1	T-Cell Mediated Rejection	-0.14	0.1	0.159	[-0.33, 0.06]
	Stable GFR	-0.03	0.08	0.989	[-0.19, 0.14]
	Non-rejected with Creatinine Rise	0.05	0.07	0.537	[-0.09, 0.18]
PANDAR	T-Cell Mediated Rejection	-0.17	0.1	0.835	[-0.36, 0.03]
	Stable GFR	0.02	0.08	0.557	[-0.15, 0.19]
	Non-rejected with Creatinine Rise	0	0.07	0.760	[-0.14, 0.14]

levels of lncRNAs in rejected and non-rejected groups (**Figures 2 and 3**). Significant inverse correlations were found between expression levels of OIP5-AS1 and FAS-AS1 as well as FAS-AS1 and NEAT1 in both study groups. Expression levels of FAS-AS1 and TUG1 were inversely correlated in transplant-rejected group. However, no significant correlation was found between expressions of them in the other group. Expression levels of FAS-AS1 and PANDAR were inversely correlated in non-rejected group but not the other group. Expression levels of OIP5-AS1 and PANDAR were positively correlated in transplant-rejected patients but not the other group. Expressions of other pairs of lncRNAs were correlated in both groups.

DISCUSSION

In the current study, we assessed expression of five lncRNAs in the peripheral blood of transplant receivers with and without transplant rejection. The role of lncRNAs in the process of transplant rejection has been assessed previously though high throughput or single gene expression analysis in biopsied samples[7,20]. Moreover, genome-wide assessment of lncRNA signatures in peripheral blood samples has shown that expression profile of two lncRNAs can be used as non-invasive diagnostic biomarker for transplant rejection[3]. Although the selected lncRNAs in the current study were previously shown to be associated with regulation of immune response, our expression analysis showed dysregulation of only one of them in patients with transplant rejection. Expression of FAS-AS1 was significantly higher in rejected group compared to non-rejected group in males, however, differences between case and control groups were insignificant among females. FAS-AS1 is transcribed from the antisense direction of intron 1

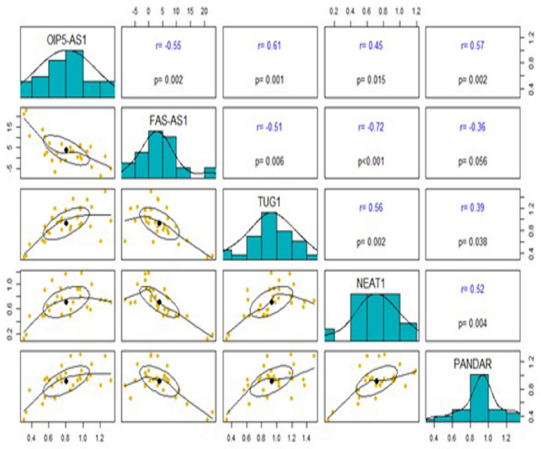

Figure 2. Correlation between expression levels of lncRNAs in transplant rejected individuals (Bivariate scatter plots with confidence ellipses below the diagonal, histograms on the diagonal, and Pearson correlations above the diagonal; Expression levels of lncRNAs are shown in X- and Y- axes; The expression value of an lncRNA (designated by points) determines the relative position of the symbol along the X-axis and the expression value of a second lncRNA determines the relative position of the symbol along the Y-axis.).

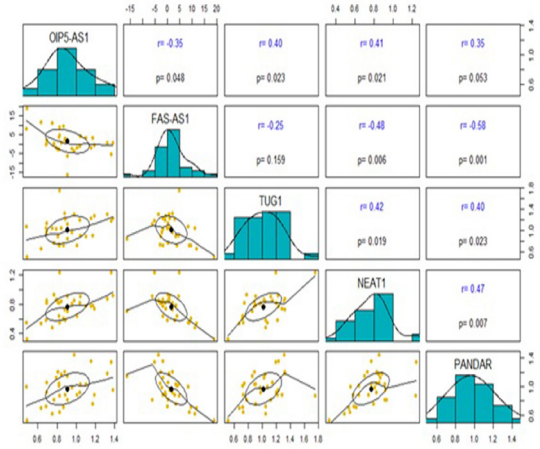

Figure 3. Correlation between expression levels of lncRNAs in transplant non-rejected individuals (Bivariate scatter plots with confidence ellipses below the diagonal, histograms on the diagonal, and Pearson correlations above the diagonal; Expression levels of lncRNAs are shown in X- and Y- axes; The expression value of an lncRNA (designated by points) determines the relative position of the symbol along the X-axis and the expression value of a second lncRNA determines the relative position of the symbol along the Y-axis.).

of the FAS gene[21]. This lncRNA has a putative role in preservation of T lymphocytes from Fas-induced apoptosis[21]. Consequently, higher expression of this lncRNA in peripheral blood of transplant-rejected patients reflects higher activity of lymphocytes in these patients and is in accordance with pathogenic process of graft rejection. Previous studies have shown inverse correlation between levels of FAS-AS1 and soluble Fas (sFas)[22]. sFas is regarded as an endogenous apoptosis suppressor that hinders the binding of Fas to Fas-L, precludes monocyte-induced and T cell–induced endothelial cell apoptosis which participate in the process of rejection[23]. The observed effect of gender on expression of FAS-AS1 has also been reported previously. For instance, FAS-AS1 expression has been associated with schizophrenia in a subgroup of male subjects but not in female subjects[24]. Moreover, a previous study has demonstrated an association between female sex hormones and the Fas/FasL system in reproductive tissues [25].

When dividing patients into four subgroups, we could not detect any significant difference between expressions of mentioned lncRNAs between them. Such lack of difference might be due to the small sample size in each subgroup. So we recommend design of similar studies with larger sample sizes to appraise whether expressions of these lncRNAs are involved in the pathogenesis of T cell mediated or antibody mediated transplant rejection.

Finally, we appraised correlations between expression levels of lncRNAs in the study groups and found distinct patterns of correlation in each group. From this data, it is possible to speculate that immune-related mechanisms during allograft rejection influence/ are influenced by the interactive network between lncRNAs. Future studies are required to unravel the underlying mechanisms and clarify the cause-effect relationship.

In brief, in the current study we have shown dysregulation of FAS-AS1 in male transplant receivers who experienced acute rejection. Future studies in larger sample sizes are needed to evaluate the potential of this lncRNA as peripheral biomarker for allograft rejection. The difference in expression level of this lncRNA between rejected and non-rejected groups might be applied as biomarker for stratifying patients if future studies in larger sample sizes verify the results of the current study. Our study has limitations regarding sample size and lack of functional assessment of underlying molecular mechanisms for participation of FAS-AS1 in transplant rejection. When dividing patients into subgroups, the size of sample in each subgroup was small, so the relation between FAS-AS1 expression and rejection should be interpreted with caution. Another limitation of our study was lack of assessment of other lncRNAs with putative function in transplant rejection. Moreover, the retrospective nature of the study limits its potential to be translated into clinical application.

CONCLUSIONS

Based on the higher expression of FAS-AS1 in patients with transplant rejection, this lncRNA might be associated with the pathogenesis of renal transplant rejection.

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CONFLICT of INTERESET

The authors declare they have no conflict of interest.

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