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Suppressor of cytokine signaling genes in renal transplant receivers: Association with transplant fate

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ABSTRACT

Suppressor of cytokine signaling (SOCS) proteins have acknowledged roles in regulation of immune responses. Moreover, their role in the evolution of allograft rejection is being elucidated. In the current investigation, we measured transcript levels of *SOCS1-4* in the peripheral blood of a group of renal transplant recipients including both rejected and non-rejected allografts. Expression analyses showed that relative expression of *SOCS2* was significantly higher in transplant-rejected male patients compared to non-rejected group. However, such significant difference was not detected between female subjects. Expression of *SOCS2* was significantly higher in T-cell-mediated rejection group compared with non-rejected individuals with creatinine rise (Relative expression difference [95% CrI] =6.74 [0.94, 12.65], $P = 0.043$). Conversely, *SOCS4* expression was significantly lower in T-cell-mediated rejection group compared with non-rejected individuals with creatinine rise (Relative expression difference [95% CrI] = −0.35 [−0.63, −0.1], $P = 0.008$). Patterns of correlations between expression levels of *SOCS* genes were different in non-rejected group. The obtained results indicate the role *SOCS* genes in development of allograft rejection.

1. Introduction

Self-tolerance is a complicated process in which tissues adjust themselves to be shielded from immune-mediated destruction and communicate with immune-regulatory cells to maintain immune-secured microenvironments. However, allograft transplantation can activate identification of graft tissues by the graft recipient as foreign antigens and prompt inflammatory responses. Inhibition of the pro-inflammatory cytokines involved in these responses is crucial for induction of tolerance and maintenance of the allograft [21]. Suppressor of cytokine signaling (SOCS) proteins constitute a framework for regulation of cytokine-mediated routes. These proteins regulate both extent and time of cytokine signaling. SOCS family includes at least eight proteins (SOCS1-SOCS7 and cytokine-induced STAT inhibitor (CIS)) [8]. Cytokine release simultaneously increases transcription of CIS, SOCS1, SOCS2, and SOCS3 coding genes leading to suppression of cytokine-motivated routes by the SOCS proteins [8]. Few studies have assessed the role of SOCS proteins in the process of allograft rejection. For instance, We et al. have measured expressions of SOCS proteins in the peripheral blood mononuclear cells (PBMCs) from renal transplant recipients with or without rejection and detected down-regulation of SOCS1 in rejection group despite up-regulation or normal levels of this protein in transplant recipients without rejection [23]. Lee et al. have reported differential expression of *SOCS1* and *SOCS3* in allogeneic hematopoietic stem cell transplantation (HSCT) recipients in correlation with the occurrence of graft-versus-host disease (GVHD) [10]. The role of SOCS3 in protection against GVHD has also been verified in animal models [6]. In the current projects, we aimed at identification of the contribution of *SOCS* genes in allograft rejection. Thus, we measured transcript levels of *SOCS1-4* in the peripheral blood of a group of renal transplant recipients including both rejected and non-rejected allografts.

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2. Materials and methods

2.1. Patients

A total of 61 renal transplant recipients were included in the current investigation. Twenty-nine transplant recipients (18 males and 11 females) who had experienced transplant rejection were enrolled consecutively during the study period (2016–2018). We considered transplanted patients who had creatinine rise in two consecutive measurements (25% rise compared to baseline) eligible for this study. Blood samples were collected at the day of biopsy from these patients and stored at −80 °C until further analyses. After evaluation of the biopsy samples, we classified patients into 3 groups based on pathology results: Group 1: Patients with antibody mediated rejection (AMR = 22) (based on Banff criteria), Group 2: T-cell mediated rejection (TCR = 7) (based on Banff criteria), Group 3: Creatinine rise but with normal pattern in the pathology ($n = 19$). Groups 1 and 2 were considered as case group (transplant rejected; $n = 29$). We considered patients with creatinine rise and normal pattern in the biopsy (n = 19), patients with normal creatinine and normal pattern in biopsy (who are referred as protocol biopsy, $n = 8$) and patients with stable renal function during past 3 months (who were not assessed by biopsy, $n = 4$) as controls or not-rejected group. So, we included all transplant recipients who were candidate for biopsy (with the condition of 25% creatinine rise) during the certain time limits and categorized them according to the results of pathology. All patients were admitted to Labbafi-Nejad hospital, Tehran, Iran during 2016–2017. Patients with delayed graft function, urinary obstruction and urinary tract infection were excluded. Protocol biopsies of the renal transplants were implemented according to the guidelines of the transplant center. Transplant function was assessed by creatinine clearance, protein excretion, ultrasonography and angiography. Twenty five percent creatinine rises during two successive measurements was regarded as indication of allograft biopsy if drug toxicity and obstructions were ruled out. Rejection was recorded according to the Banff criteria [18]. Non-rejected group had experienced no creatinine rise in the previous 3 months or protocol biopsy ruled out the allograft rejection. These patients were age−/sex-matched to the rejected group.

The study protocol was approved by ethical committee of Shahid Beheshti University of Medical Sciences. Written consent forms were obtained from all study participants.

2.2. Expression assays

Transcript levels of genes were measured in peripheral blood of study participants. Total RNA was extracted from all blood samples using Hybrid-R Blood RNA purification kit (GeneAll Biotech, Seoul, Korea). Then, cDNA was produced from RNA specimens using PrimeScript 1st strand cDNA Synthesis Kit (TaKaRa, Japan). All reactions were prepared in duplicate. Expressions of *SOCS* genes were quantified in Rotor Gene 6000 system (Corbett, Australia) using the *HPRT1* gene as the reference gene. The TaqMan Fast Universal PCR Master Mix (Applied Biosystems, Foster City, USA) was used for preparation of reactions. The sequences of primers and probes and PCR conditions were the same as the previous study [4].

2.3. Statistical methods

Bayesian regression model was used to test difference in relative expression of genes between study groups. The effects of independent variables were adjusted. The t student/Gaussian prior distribution was assumed for parameters with 4000 iteration and 1000 warm-up. *P*-values for regression model were estimated from Quantile and interquartile regression models. Spearman correlation was used to examine the association between expressions of genes. Analyses were carried out in in R 3.5.2 environment using pROC, qreg, and Stan with loo package.

3. Results

3.1. Demographic and clinical data of patients

The mean age (± standard deviation) were 40.4 (± 15.6) and 35.6 (± 16.1) in rejected and non-rejected groups respectively. Transplant rejected group included 22 patients with evidences of T cell mediated rejection and 7 patients with signs of antibody-mediated rejection. In non-rejected group, 19 patients had creatinine rise while others did not. Patients were under immunosuppressive treatment with Tacrolimus, CellCept and Prednisolone. In rejected group, serum levels of creatinine (mean ± standard deviation) were 3.14 ± 1.8 mg/dL and 2.04 ± 1.74 mg/dL before and after transplantation respectively. In this group, one patient expired and nephrectomy was performed for one patient. Live donor kidney transplantation accounted for 10%, 28% and 50% of transplantations in antibody-mediated rejection, T cell-mediated rejection and non-rejected groups respectively. The estimated GFR values based on the MDRD equation are shown in Table 1.

3.2. Expression analyses

Expression analyses showed that relative expression of *SOCS2* was significantly higher in transplant-rejected male patients compared to non-rejected group. However, such significant difference was not detected between female subjects. Expressions of other genes were not different between study groups. The results of expression analysis of *SOCS* genes in study groups are shown in Table 2.

Quantile regression model also confirmed the difference in *SOCS2* expression between rejected and non-rejected patients (Beta [95%CI] = 4.86 [0.22, 9.5], $P = 0.041$) (Table 3).

Expression of *SOCS2* was significantly higher in T-cell-mediated rejection group compared with non-rejected with creatinine rise group (Relative expression difference [95% CrI] = 6.74 [0.94, 12.65], $P = 0.043$). Conversely, *SOCS4* expression was significantly lower in T-cell-mediated rejection group compared with non-rejected with creatinine rise group (Relative expression difference [95% CrI] = −0.35 [−0.63, −0.1], $P = 0.008$). Table 4 shows the results of Bayesian Regression model for comparison of gene expression ratios between subgroups.

Fig. 1 shows relative expression levels of *SOCS* genes in distinct study groups based on the gender of patients.

3.3. Correlations between expression levels of SOCS genes

We assessed correlations between expression levels of *SOCS* genes in distict sex-based and disease-based groups. In female subject (including

Table 1
Mean values (± SD) of estimated GFR (eGFR) values before transplantation and in definite time points after transplantation.

	Before transplantation	1 month after transplantation	2 months after transplantation	3 months after transplantation
Antibody-mediated rejection	8.76 ± 1.4	41.9 ± 3.2	47.195 ± 2.9	40.97 ± 1.95
T cell-mediated rejection	8.98 ± 1.32	43.7 ± 3.4	57.064 ± 3.9	60.29 ± 4.2
Non-rejected	7.96 ± 1.24	55.39 ± 3.8	64.119 ± 4.32	60.935 ± 4.2

Table 2
The results of Bayesian Regression model for comparing *SOCS* genes expression levels between study groups with adjusting the effects of gender (*P* values are estimated from Frequentist method, CrI: Credible Intervals).

Genes	Groups	Rejected	Non-rejected	Relative expression difference	SE	P-value	95% CrI for relative expression
SOCS1	Total	29	32	−0.0063	0.09	0.813	[−0.17, 0.16]
	Male	25	19	−0.0002	0.1	0.551	[−0.2, 0.2]
	Female	7	10	−0.03	0.19	0.994	[−0.41, 0.34]
SOCS2	Total	29	32	3.84	1.69	0.041	[0.5, 7.23]
	Male	25	19	5.467	1.9	0.018	[1.67, 9.15]
	Female	7	10	−0.615	3.77	0.871	[−8.12, 6.75]
SOCS3	Total	29	32	−0.070	0.07	0.5	[−0.2, 0.06]
	Male	25	19	−0.083	0.0837	0.561	[−0.25, 0.08]
	Female	7	10	−0.039	0.1273	0.931	[−0.3, 0.21]
SOCS4	Total	29	32	−0.145	−0.145	0.26	[−0.31, 0.02]
	Male	25	19	−0.2203	−0.2203	0.132	[−0.41, −0.03]
	Female	7	10	0.0624	0.0624	0.927	[−0.31, 0.43]

Table 3
The results of Quantile regression for association between relative expression ratios and independent variables.

Genes	Variables	Beta	SE	t	P-Value	95% CI for Beta
SOCS1	Group	0.08	0.14	0.61	0.544	[−0.19, 0.36]
	Gender	0.01	0.19	0.04	0.971	[−0.38, 0.39]
	Group*Gender	−0.08	0.26	−0.31	0.755	[−0.6, 0.44]
SOCS2	Group	4.86	2.32	2.10	0.041	[0.22, 9.5]
	Gender	3.23	3.26	0.99	0.326	[−3.29, 9.75]
	Group*Gender	−5.49	4.41	−1.24	0.219	[−14.32, 3.35]
SOCS3	Group	−0.05	0.07	−0.68	0.497	[−0.18, 0.09]
	Gender	0.00	0.10	−0.02	0.984	[−0.19, 0.19]
	Group*Gender	0.03	0.13	0.24	0.813	[−0.23, 0.29]
SOCS4	Group	−0.18	0.13	−1.38	0.173	[−0.44, 0.08]
	Gender	−0.03	0.18	−0.19	0.854	[−0.4, 0.33]
	Group*Gender	0.20	0.25	0.81	0.421	[−0.3, 0.7]

both rejected and non-rejected patients), inverse correlations were found between *SOCS1* and *SOCS2*, *SOCS2* and *SOCS3* as well as between *SOCS2* and *SOCS4*. Other pairs of genes were correlated positively (Fig. 2).

In male subjects (including both rejected and non-rejected patients), the pattern of correlations were similar to female subjects (Fig. 3).

However, when dividing patients into rejected and non-rejected groups, no significant correlations were found between *SOCS2* and *SOCS3* or between *SOCS1* and *SOCS4* in non-rejected patients (Fig. 4). In rejected patients, the patterns of correlations were similar to when dividing patients based on their sex (Fig. 5).

4. Discussion

Rejection and tolerance as different consequences of the allograft response are mainly determined by immunological factors. Cytokine release by T helper cells can stimulate, increase, and induce other effector cells of the immune system [22]. Cytokines can affect several aspects of immune response against the allograft including maturation of antigen processing cells, increase in number of T helper cells and their differentiation, survival of effector cells and regulatory T cell expansion [22]. Based on the crucial roles of cytokines in determination of allograft fate, SOCS proteins as the main regulatory mechanism of cytokine-associated signaling pathways are expected to participate in the process of transplant rejection. In the current study, we detected higher levels of *SOCS2* in transplant-rejected male patients compared to non-rejected male group. Lack of difference between female subgroups might imply a sex-specific role for SOCS2 in the process of allograft rejection. Previous studies have reported the role sex of both donor and recipient in the fate of transplant. However, the underlying mechanism is not clear [17]. The sex-based differences in expression of SOCS genes have been also noted before when Lee et al. reported SOCS3 as an appropriate marker for differentiation of only male normal individuals from latent tuberculosis infection ones [9]. Such difference might be due to effects of sex hormones on the expression of SOCS genes. Supporting evidences have come from an animal study which reported that estrogen increases expression of SOCS2 and SOCS3 in hepatocytes through estrogen receptor alpha [11]. This receptor also mediates the effects of estrogen on SOCS3 expression in breast cancer cells [14]. So it is possible that the presence of estrogen in female subjects alters

Table 4
The results of Bayesian Regression model for comparison of gene expression ratios between subgroups with adjusting the effects of gender (*P* values are estimated from Frequentist method, CrI: Credible Intervals, Reference group: Non-rejected with creatinine rise ($n = 19$)).

	Group	Number of patients	Relative expression difference	SE	P-value	95% CrI for relative expression
SOCS1	Antibody-Mediated Rejection	7	−0.0626	0.1	0.996	[−0.27, 0.14]
	T-Cell Mediated Rejection	22	0.0152	0.15	0.695	[−0.27, 0.3]
	Stable GFR	4	−0.1867	0.18	0.941	[−0.53, 0.15]
	Protocol Biopsy	8	−0.0358	0.14	0.958	[−0.3, 0.22]
SOCS2	Antibody-Mediated Rejection	7	3.3789	2.0361	0.162	[−0.53, 7.35]
	T-Cell Mediated Rejection	22	6.742	2.954	0.043	[0.94, 12.65]
	Stable GFR	4	3.2146	3.2146	0.376	[−3.77, 10.23]
	Protocol Biopsy	8	0.1682	0.1682	0.815	[−5.26, 5.65]
SOCS3	Antibody-Mediated Rejection	7	−0.057	−0.057	0.813	[−0.21, 0.1]
	T-Cell Mediated Rejection	22	−0.0917	0.11	0.821	[−0.31, 0.13]
	Stable GFR	4	−0.2229	0.14	0.09	[−0.5, 0.04]
	Protocol Biopsy	8	0.1431	0.11	0.292	[−0.06, 0.35]
SOCS4	Antibody-Mediated Rejection	7	−0.1025	0.1	0.689	[−0.3, 0.1]
	T-Cell Mediated Rejection	22	−0.3566	0.1351	0.008	[−0.63, −0.1]
	Stable GFR	4	−0.073	0.1711	0.387	[−0.42, 0.27]
	Protocol Biopsy	8	−0.0401	−0.0401	0.879	[−0.3, 0.22]

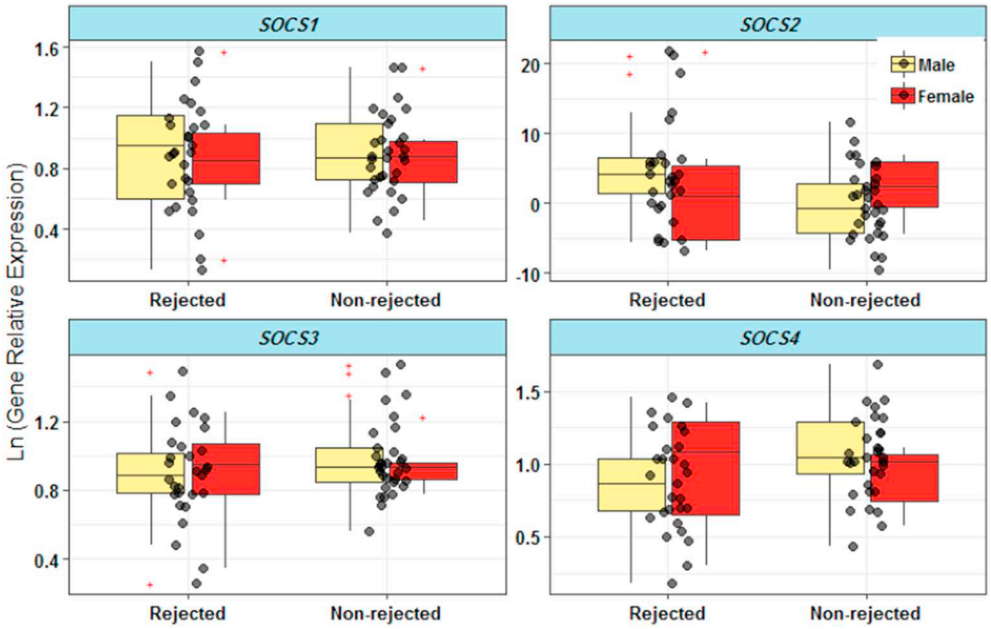

Fig. 1. Relative expression levels of *SOCS* genes in distinct study groups based on the gender of patients.

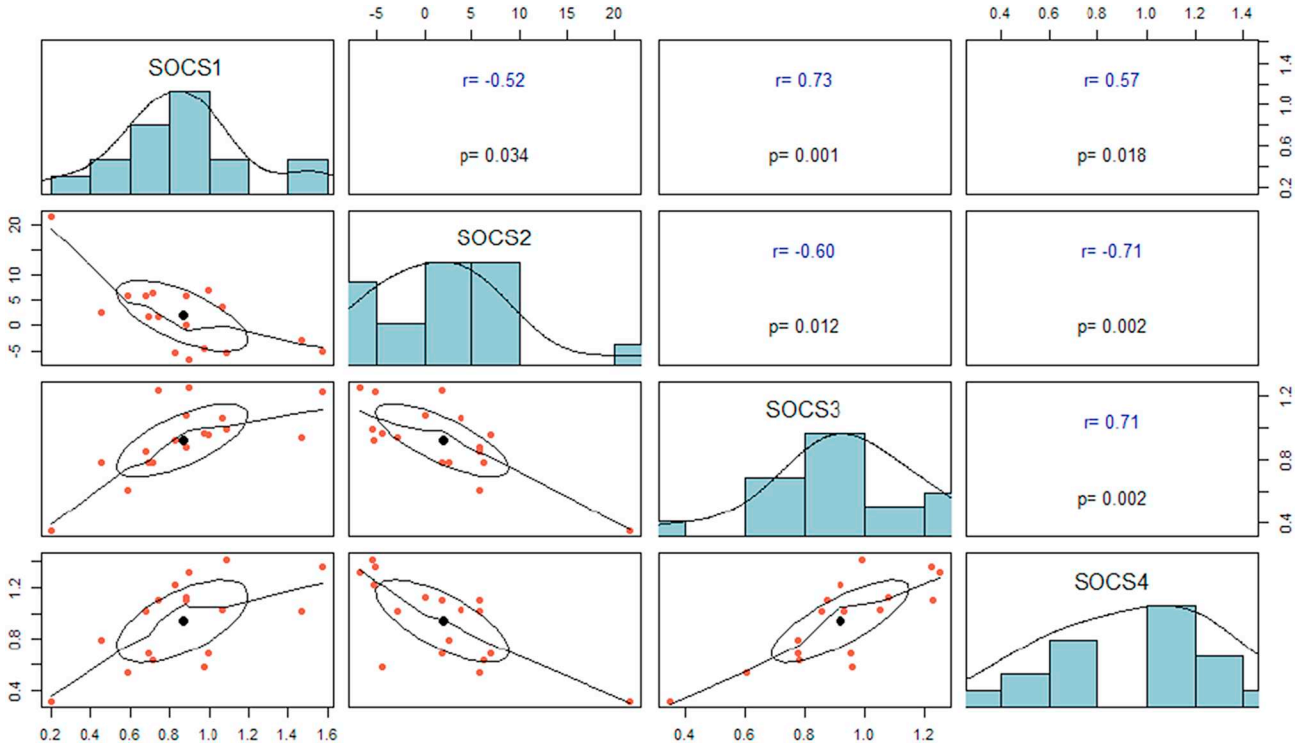

Fig. 2. Correlations between expression levels of *SOCS* genes in female subjects (both rejected and non-rejected groups).

the observed dysregulation of SOCS2 in association with transplant rejection.

We also reported higher expression levels of *SOCS2* gene in T-cell-mediated rejection group compared with non-rejected individuals with creatinine rise. In a previous study in allogeneic HSCT recipients, Pidala et al. have reported lower levels of this gene in tolerant patients [15] which is consistent with our results. Totally, they detected lower expression of anti-apoptotic (including SOCS2) and higher expression of pro-apoptotic genes in tolerant patients [15]. Consequently, such observations imply that SOCS2 might be involved in the induction of apoptosis in immune cells leading to improvement of allograft fate. In addition, SOCS2 participates in the control of dendritic cell (DC) function. Human and animal studies have shown that expression of this gene is regulated by Toll like receptors (TLR). *SOCS2* knock-down in DCs has led to hyperphosphorylation of STAT3 and over-production of IL-1β and IL-10 [16]. The acknowledged role of IL-10 in suppression of T-cell and antigen-presenting cell activities [1] provides a possible explanation for the observed higher levels of *SOCS2* gene in T-cell-mediated rejection group compared with non-rejected persons. Others have also reported that controlled expression of IL-10 prevents cardiac allograft vasculopathy through decreasing mononuclear cell calling and modification of cytokine release from these cells [3]. Although IL-1 is

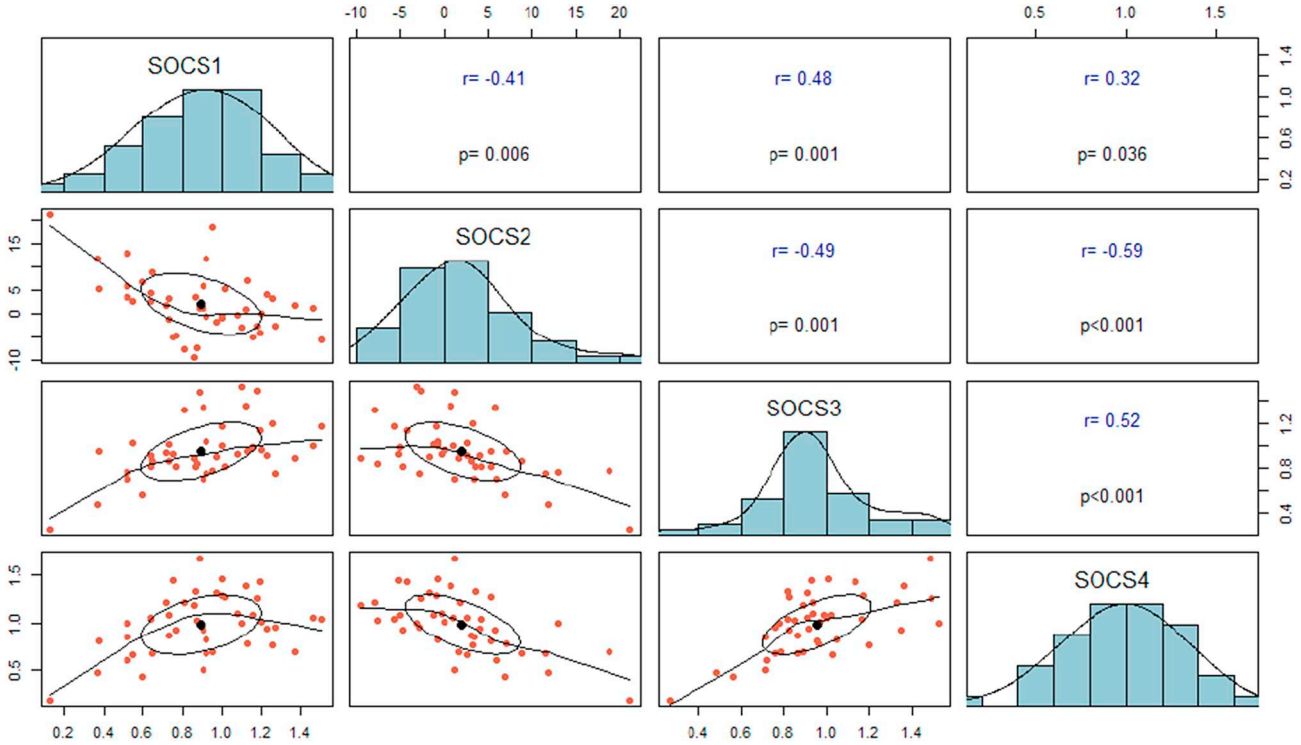

Fig. 3. Correlations between expression levels of *SOCS* genes in male subjects (both rejected and non-rejected groups).

regarded as a pro-inflammatory cytokine, it functions as a costimulator for the proliferation of Th2 but not for Th1 cells [12]. So, the anticipated higher levels of this cytokine following *SOCS2* down-regulation do not contradict our observation in T-cell-mediated rejection group.

Contrary to Wu et al. study [23], we could not detect any difference in expression of *SOCS1* between study groups. However, we detected lower levels of *SOCS4* expression in T-cell-mediated rejection group compared with non-rejected individuals with creatinine rise. A previous animal study has shown that absence of functional SOCS4 protein leads to boosted cytokine/chemokine release among them were IL-6, IFNγ and Monocyte chemoattractant protein-1 (MCP-1) [7]. IL-6 and MCP-1 have been among cytokines whose expression levels could predict transplant fate with the former being the most accurate one [2]. Moreover, IFNγ has a crucial role in induction of T cell mediated rejection in allografts [5]. Taken together, *SOCS4* down-regulation is expected to stimulate this kind of immune-mediated response through

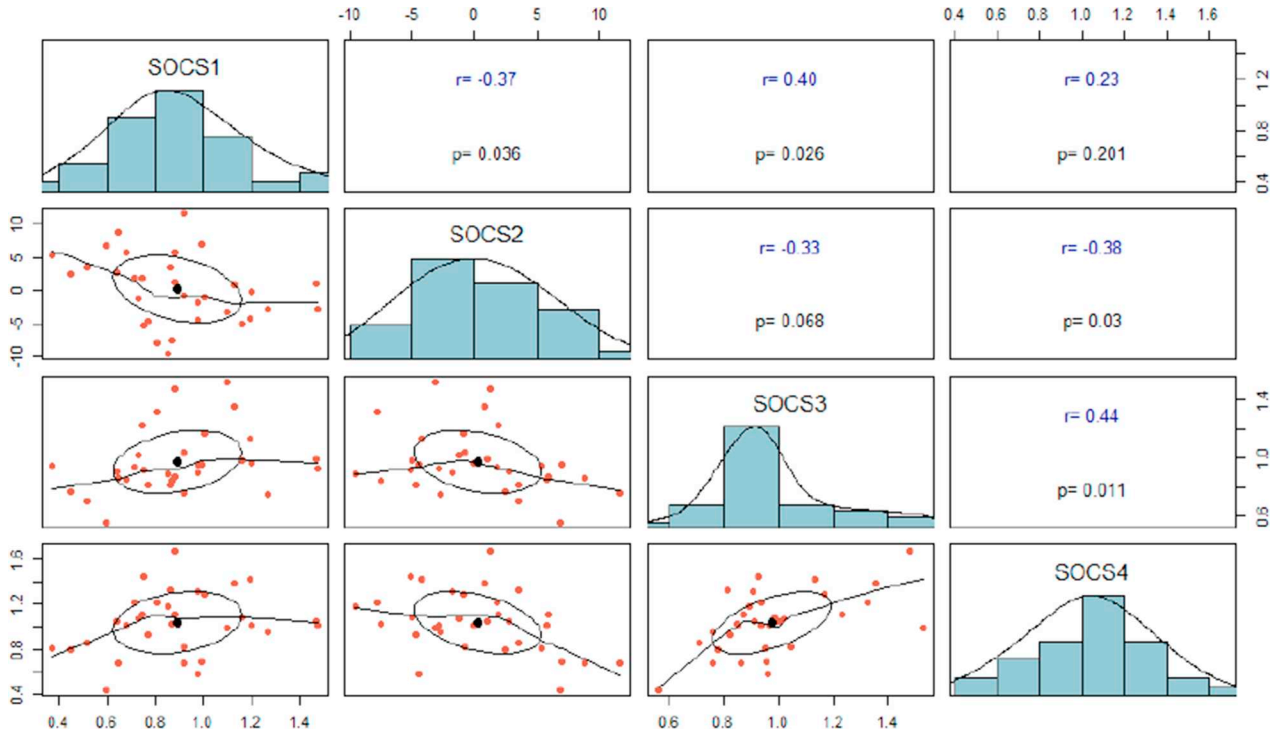

Fig. 4. Correlations between expression levels of *SOCS* genes in rejected patients (both males and females).

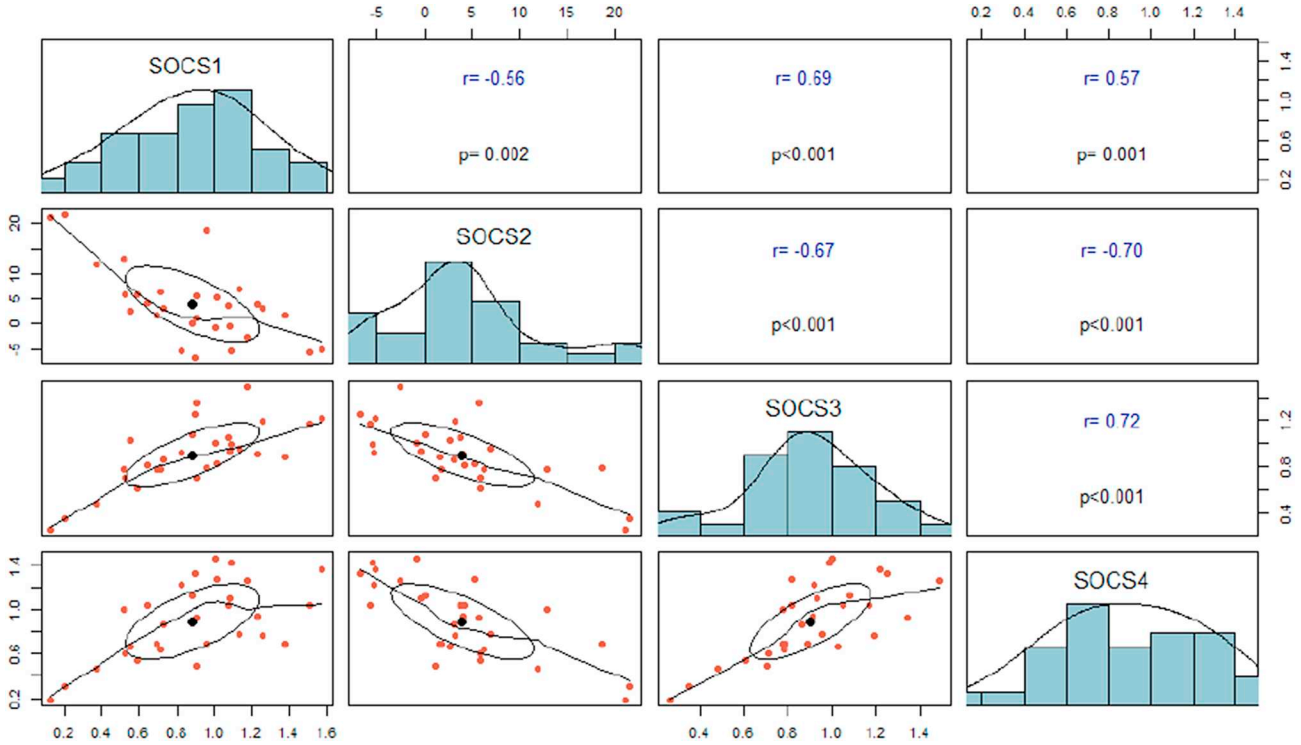

Fig. 5. Correlations between expression levels of *SOCS* genes in non-rejected patients (both males and females).

increase in the levels of IL-6, IFNγ and MCP-1. Further assessment of cytokines levels in Socs4 knock-out mice is needed to unravel the underlying mechanism of our observation. Our results are also in line with Luckey et al. study which reported that up-regulation of SOCS4 in T lineage has led to compromised T cell expansion in the thymus [13].

Finally, we assessed correlations between pairs of *SOCS* genes in different subgroups of study and found inverse correlations between *SOCS1* and *SOCS2*, *SOCS2* and *SOCS3* as well as between *SOCS2* and *SOCS4* in total participants of both sexes. Other pairs of genes were correlated positively. Such correlations patterns imply the distinct trend for *SOCS2* versus other *SOCS* genes. This result also is in line with the previously reported role of SOCS2 in promoting proteasome-mediated degradation of SOCS3 and SOCS1 proteins [20]. However, when dividing patients into rejected and non-rejected groups, no significant correlations were found between *SOCS2* and *SOCS3* or between *SOCS1* and *SOCS4* in non-rejected patients. Taken together, it is possible to speculate the presence of disease-specific pattern of expression in *SOCS* genes. Consistent with this speculation, Lee et al. have shown decreased expression of SOCS1 in HSCT recipients with grade II to IV acute GVHD and chronic GVHD when compared to healthy persons and non-GVHD ones. However, SOCS3 expressions had a similar pattern in all transplant recipients [10].

A previous study in chronic renal failure has demonstrated that higher levels of SOCS3 in monocytes and SOCS1 in lymphocytes are associated with gradual loss of kidney function [19]. However, we could not detect any difference in expression of these genes between four study groups. Such discrepancy might be explained by the effects of renal transplantation on expression of genes.

Taken together, the obtained results imply the role *SOCS* genes in development of allograft rejection and warrants further studies in animal models to find therapeutic options for amelioration of *SOCS* genes dysregulation and possible improvement in allograft fate. Certainly, more experiments are needed to deduce causal relationship between dysregulation of *SOCS* genes expression and transplant rejection.

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