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Multi-Layered Immuno-Epigenetic Regulation of the YY1–SIRT7–H3K18Ac–PD-1/PD-L1 Axis in Renal Allograft Survival: Preliminary Findings

Eda Balkan[1], Necip Altundaş[2], Murat Kızılkaya[3], Elif Demirci[4], Mahmut Aktürk[1]

[1]Atatürk University Faculty of Medicine, Department of Medical Biology, Erzurum, Türkiye; [2]Atatürk University Faculty of Medicine, Department of General Surgery, Erzurum, Türkiye; [3]Ağrı İbrahim Çeçen University Faculty of Medicine, Department of Medical Biology, Ağrı, Türkiye; [4]Atatürk University Faculty of Medicine, Department of Pathology, Erzurum, Türkiye

Abstract

Objective: This study aimed to characterize the immuno-epigenetic role of the YY1–SIRT7–H3K18Ac–PD-L1 axis in renal allograft survival and to identify molecular biomarkers associated with rejection.

Materials and Methods: A total of 65 participants were enrolled: 20 patients with biopsy-confirmed allograft rejection, 25 with stable graft function, and 20 healthy controls. Blood samples were collected into EDTA-containing tubes and stored at –80°C. Total RNA was isolated and complementary DNA (cDNA) synthesized for gene expression analysis by real-time polymerase chain reaction (RT-PCR), using glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and U6 small nuclear RNA (snRNA) as reference genes. Serum concentrations of SIRT7, H3K18Ac, and oxidative stress markers — superoxide dismutase (SOD) and glutathione (GSH) — were quantified by enzyme-linked immunosorbent assay (ELISA). Statistical analyses were performed using SPSS v23.0 ($p < 0.05$).

Results: Messenger RNA levels of STAT3, CD274 (PD-L1), H3F3A, SIRT7, and YY1 were significantly elevated in the rejection group, whereas PDCD1 (PD-1) was higher in the survival group ($p<0.05$). Long non-coding RNAs NEAT1, MALAT1, and GAS5 were upregulated in rejection ($p<0.05$). Significant alterations were detected in miR-21, miR-34a, miR-125, and miR-155 ($p<0.01$). SOD and GSH were decreased, while malondialdehyde (MDA) and catalase were elevated ($p<0.05$). NEAT1 and MALAT1 were predominantly upregulated in humoral rejection, whereas GAS5 was reduced.

Conclusion: The YY1–SIRT7 epigenetic axis, in conjunction with PD-L1 signaling, appears to be implicated in immune evasion and inflammatory amplification following renal transplantation, supporting the potential utility of these molecules as immuno-epigenetic biomarkers of allograft rejection.

Keywords: kidney transplantation; allograft rejection; epigenetics; PD-L1; non-coding RNA; biomarkers

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Correspondence
Eda Balkan

E-mail
eda.diyarbakir@hotmail.com

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Introduction

Kidney transplantation remains the most effective therapeutic strategy for extending survival in patients with end-stage renal disease. Despite considerable advances in immunosuppressive therapy, acute and chronic rejection continue to be the principal barriers to long-term allograft survival. Emerging evidence suggests that epigenetic regulators — including Yin Yang 1 (YY1), Sirtuin 7 (SIRT7), and H3K18 acetylation (H3K18Ac) — may exert significant influence over immune responses, inflammatory signaling, and cellular metabolism (1,2). Nevertheless, the mechanistic interplay of these regulators in the context of solid organ transplantation has yet to be fully elucidated.

The present study aimed to characterize the role of the YY1–SIRT7–H3K18Ac–Programmed Death-Ligand 1 (PD-L1) axis at the immuno-epigenetic level in renal allograft survival, and to contribute to the identification of molecular biomarkers of rejection.

Materials and Methods

This study was approved by the Clinical Research Ethics Committee of Atatürk University Faculty of Medicine (Decision No: B.30.2.ATA.0.01.00/590; Date: 05.05.2025). Written informed consent was obtained from all participants. A total of 65 individuals were enrolled: 20 patients with biopsy-confirmed allograft rejection, 25 patients with stable graft function, and 20 healthy controls. Blood samples were collected from the rejection group prior to or during the early phase of biopsy-confirmed rejection, and from the remaining groups during routine follow-up visits. Samples were collected into ethylenediaminetetraacetic acid (EDTA)-containing tubes, centrifuged at 2,000 × g for 10 minutes, and stored at –80°C until analysis.

Total RNA was isolated using the NucleoGene RNA Extraction Kit, followed by cDNA synthesis. Gene expression was quantified by RT-PCR. GAPDH and U6 snRNA served as reference genes, and relative expression levels were calculated using the ΔCt method. Serum concentrations of SIRT7, H3K18Ac, and oxidative stress markers (SOD and GSH) were measured using commercially available ELISA kits. Statistical analyses were performed using SPSS version 23.0; a p-value of <0.05 was considered statistically significant.

Results and Discussion

At the messenger RNA (mRNA) level, STAT3, CD274 (PD-L1), H3F3A, SIRT7, and YY1 were significantly upregulated in the rejection group, whereas PDCD1 (PD-1) expression was higher in the survival group ($p < 0.05$; Table 1). Long non-coding RNAs (lncRNAs) — NEAT1, MALAT1, and GAS5 — were elevated in the rejection group ($p<0.05$; Table 2). MicroRNA (miRNA) expression profiling revealed significant alterations in hsa-miR-21, miR-34a, miR-125, and miR-155 ($p<0.01$; Table 3). Regarding oxidative stress, SOD and GSH levels were signifi-

Table 1. Comparison of mRNA expression levels of selected genes across rejection, survival, and control groups.

Gene	Rejection Group (Mean±SD / Median [IQR])	Survival Group (Mean±SD / Median [IQR])	Control Group (Mean±SD / Median [IQR])	Test Statistic	*p*
MTOR	28 (22.53–28.18)a	23.29 (20.29–25.48)a	19.32 (18–21.29)b	60.065	<0.001*
PDCD1	20.55 ± 1.97a	25.58 ± 1.18a	24.91 ± 0.7b	23.827	<0.001†
CD274 (PD-L1)	25.18 (22.7–28.1)a	24.33 (20.46–31.77)a	20.6 (19.85–24.33)b	48.506	<0.001*
STAT3	24.79 (22.85–33)a	21.26 (20.19–29.28)a	16.56 (14.52–20.45)b	61.685	<0.001*
H3F3A	29.22 (22.93–29.53)a	27.39 (19.34–32.29)a	14.76 (13.23–16.47)b	60.042	<0.001*
SIRT7	24.73 (22.8–36.82)a	21.49 (21.74–33.73)a	16.74 (17.82–25.39)b	56.369	<0.001*
YY1	25.85 (21.28–29.36)a	21.36 (21.36–28.34)a	16.56 (15.37–19.77)b	60.247	<0.001*

*Values expressed as Mean±SD or Median [IQR]. Superscripts (a,b) indicate statistically homogeneous subgroups by post-hoc analysis. *Kruskal–Wallis test; †One-way ANOVA. IQR: interquartile range; SD: standard deviation; mRNA: messenger RNA.*

cantly decreased, while malondialdehyde (MDA) and catalase were elevated ($p<0.05$). The YY1–SIRT7–H3K18Ac axis was predominantly active in the rejection group, reflecting an immuno-epigenetic regulatory network. Among lncRNAs, NEAT1 and MALAT1 were upregulated in humoral rejection, whereas GAS5 expression was reduced (Table 4). These findings are consistent with previous reports implicating epigenetic dysregulation in immune-mediated allograft injury (3,4,5).

Taken together, these results suggest that the YY1/SIRT7 epigenetic axis, in conjunction with PD-L1 signaling, may be implicated in immune evasion and the amplification of inflammatory activation following renal transplantation (6). These findings contribute to the identification of novel immuno-epigenetic biomarkers in allograft rejection. Further validation in a larger cohort with complementary multi-omics analyses is planned.

Table 2. Comparison of lncRNA expression levels across rejection, survival, and control groups.

Gene	Rejection Group (Mean±SD / Median [IQR])	Survival Group (Mean±SD / Median [IQR])	Control Group (Mean±SD / Median [IQR])	Test Statistic	*p*
GAPDH2	23.53 (21.21–27.01)a	23.33 (20.28–27.01)a	17.81 (15.28–20.92)b	57.262	<0.001
NEAT1	20.06 (18.37–20.76)a	20.7 (18.33–22.57)a	14.54 (13.23–18.51)b	60.221	<0.001
MALAT1	22.31 (20.16–27.28)a	22.28 (20.16–27.28)a	19.38 (18.27–23.64)b	54.589	<0.001
GAS5	19.86 (20.15–23.1)a	22.58 (20.39–25.65)a	15.87 (15.15–17.53)b	59.808	<0.001
PVT1	23.04 ± 1.37a	22.22 ± 1.37a	18.58 ± 0.93b	117.201	<0.001

Values expressed as Mean±SD or Median [IQR]. Superscripts (a,b) indicate statistically homogeneous subgroups. Kruskal–Wallis test applied throughout. lncRNA: long non-coding RNA.

Table 3. Comparison of miRNA expression levels across rejection, survival, and control groups.

Gene	Rejection Group (Mean±SD / Median [IQR])	Survival Group (Mean±SD / Median [IQR])	Control Group (Mean±SD / Median [IQR])	Test Statistic	*p*
U6 snRNA	34.03 (23.73–36.37)a	34.03 (22.73–36.37)a	19.7 (15.47–25.43)b	58.563	<0.001
hsa-miR-21	28.67 (25.92–31.42)a	28.22 (23.42–31.67)a	20.55 (14.25–35.57)b	33.225	<0.001
hsa-miR-34a	29.63 (24.34–32.98)a	27.63 (23.94–33.32)a	19.95 (13.56–35.13)b	46.715	<0.001
hsa-miR-125	33.67 (29.05–36.63)a	32.96 (25.68–36.05)a	19.76 (15.34–33.52)b	51.223	<0.001
hsa-miR-155	34.01 (31.39–35.48)a	32.88 (24.39–36.29)a	20.5 (13.25–33.79)b	54.482	<0.001

Values expressed as Median [IQR]. Superscripts (a,b) indicate statistically homogeneous subgroups. Kruskal–Wallis test applied throughout. miRNA: microRNA.

Table 4. Comparison of ceRNA expression profiles between acute cellular and acute humoral rejection subtypes.

Gene	Acute Cellular Rejection (Mean±SD / Median [IQR])	Acute Humoral Rejection (Mean±SD / Median [IQR])	*p*
PDCD1	20.39 ± 1.94	24.99 ± 1.89	0.025
CD274 (PD-L1)	26.03 ± 1.85	21.33 ± 1.18	0.048
STAT3	26.85 ± 3.45	19.38 ± 1.18	0.014
H3F3A	26.03 ± 2.16	24.75 ± 0.7	0.005
SIRT7	28.49 (22.8–36.82)	21.69 (21.22–30.23)	0.047
YY1	29.96 ± 2.48	25.55 ± 1.98	0.025
NEAT1	25.99 ± 0.82	19.74 ± 0.84	0.050
MALAT1	23.74 ± 2.4	21.92 ± 0.9	0.026
GAS5	18.58 ± 1.16	21.99 ± 0.92	0.046
PVT1	23.15 ± 1.87	22.97 ± 1.04	0.050
hsa-miR-21	29.14 ± 1.18	24.6 ± 1.71	0.047
hsa-miR-34a	31.91 ± 1.74	29.34 ± 2.55	0.025
hsa-miR-125	23.57 ± 1.5	33.69 ± 2.26	0.004
hsa-miR-155	37.82 ± 1.19	33.84 ± 1.24	0.028

Values expressed as Mean±SD or Median [IQR]. Mann–Whitney U or independent samples t-test applied as appropriate. ceRNA: competing endogenous RNA.

Conflict of Interest: The authors declare no conflict of interest. No external funding was received for this study.

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