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Original Article

Altered expression of micro-RNA 199a and increased levels of cardiac SIRT1 protein are associated with the occurrence of atrial fibrillation after coronary artery bypass graft surgery

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ABSTRACT

Background: Postoperative atrial fibrillation (POAF) is a potentially life-threatening complication after coronary artery bypass graft (CABG) surgery. The expression of the cardioprotective SIRT1 protein with its antioxidant activity is increased in cardiac tissue of patients suffering from POAF. So far, information is lacking about the relationship between SIRT1 regulating micro RNAs (miRs), SIRT1 protein and the occurrence of POAF.
Methods: A total of 63 patients undergoing CABG were recruited, and biopsies were obtained from the right atrial appendage during cannulation. Postoperative, all patients were rhythm-monitored until discharge and randomized to POAF ($n=20$) or sinus rhythm ($n=43$). The expression of the micro RNAs miR-199a and miR-195 was quantified by real-time PCR. SIRT1 protein was detected by western blot analysis.
Results: The relative expression of miR-199a in the POAF group was significantly decreased compared to the control group (0.77 ± 0.27 vs. 1.11 ± 0.69, $P=.022$) Accordingly, SIRT 1 protein was significantly induced in tissue probes of patients with POAF ($P<.001$).
Conclusion: Altered expression of the SIRT1 protein regulating miR-199a in human atrial tissue was found to be related to the occurrence of POAF, indicating its usefulness as a biomarker for cardiac surgery management.

1. Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia, affecting 5% of the population older than 65 years and 7.1% of those older than 85 years [1]. Approximately 70% to 80% of patients with AF have structural heart disease, including coronary artery disease and valvular heart disease [2].

It is associated with significant morbidity and mortality, including a quadrupled risk of heart failure and a nearly doubled risk of death [3].

Postoperative atrial fibrillation (POAF) is a common complication after coronary artery bypass surgery (CABG); a third of all patients suffer from POAF during the early postoperative period [4,5]. The mechanism POAF is not well defined and is probably multifactorial. There are several risk factors, which are associated with POAF, such as advanced age, male gender; gene polymorphism; history of chronic heart failure (CHF) or AF, chronic obstructive pulmonary disease, chronic renal insufficiency, diabetes mellitus, rheumatic heart disease; previous cardiac surgery, metabolic syndrome, obesity; severe proximal right coronary artery stenosis; increased left atrial size; preoperative increase in P wave duration on surface (>116 ms) or on signal averaged (>140 ms) EKG [16,17] and blood transfusion before surgery [6]. Prolonged mechanical ventilation, atrial ischemia, hypokalemia and hypomagnesemia are other known risk factors for POAF. There is conflicting data whether increased aortic cross-clamp and cardiopulmonary bypass time increase POAF [6].

Ulkan Kilic and Aylin Hatice Yamac take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Despite several basic and clinical studies, the precise underlying mechanism of onset and persistence of AF has not been completely elucidated. The following pathophysiological factors might play an important role: atrial factors like atrial dilatation, hypertrophy and fibrosis; postoperative inflammation; electrical remodeling (shortening of the effective refractory period); autonomic imbalance and alterations in atrial oxidative stress [6].

It is of great importance to understand the early and causative changes in AF pathogenesis to avoid persistence and recurrence and initiate targeted prophylaxis [3].

The expression of the cardio-protective protein SIRT1 is induced in cardiac disease such as AF and CAD, indicating a compensatory mechanism to overcome the disease-related pathologies such as oxidative stress [7,8].

SIRT1, known as a *longevity gene*, protects cells against oxidative stress and promotes DNA stability by binding and deacetylating several substrates. In the cardiovascular system, SIRT1 activation exerts multiple protective effects through distinct metabolic and stress-response pathways. Importantly, SIRT1 has been recognized as a key regulator of vascular endothelial homeostasis and also regulates angiogenesis, endothelial senescence and dysfunction [9,10]. It prevents atherosclerosis by improving endothelium relaxation through up-regulating eNOS expression and production of nitric oxide [11].

In cardiomyocytes, due to its antioxidant activity, nuclear SIRT1 increases the resistance of myoblast to oxidative stress by enhancing the MnSOD expression through p53 deacetylation [12]. Protection of cardiomyocytes from oxidative stress is also regulated by overexpression of SIRT1 protein and activation of FoxO1-dependent pathway [13]. The activation of this pathway also reduces cardiac infarct volume and improves functional recovery after ischemia/reperfusion in mice [14].

The expression of SIRT1 protein in the cardiac and vascular tissue is inter alia regulated by the micro RNAs 195 and 199a [15].

MicroRNAs are small noncoding RNAs composed of 21–25 ribonucleotides, which control the expression of complementary target messenger RNAs [16–18]. These small nonprotein-coding RNAs began to compose an important role in the cardiovascular system, and recent research indicates the potential of miRNAs as a novel mechanism for AF [16–19]. However, published studies that focused on miRNAs and AF are sparse, and most investigated chronic AF, partially using animal models. As a result, information regarding the relationship between miRNA expression in human atrial tissue and new onset of AF is not available.

In cardiomyocytes, SIRT1 is controlled by miR-195 and -199a. The free fatty acid palmitate up-regulates miR-195 expression, which inhibits SIRT1 and promotes apoptosis [20]. MiR-199a inhibits the expression of both SIRT1 and HIF-1α [21]. Hypoxia or cardiac ischemia decreases miR-199a, permitting an increase in SIRT1 in cardiocmyocytes. SIRT1 in turn down-regulates prolylhydroxylase2 (PHD2), which stabilizes HIF-1α and induces HIF-related signaling. Thus, miR-199a increases HIF-1α in two ways: first by regulating HIF-1α directly, second by a SIRT1–PHD2–HIF-1 pathway [21]. As enhanced SIRT1 expression is associated with the occurrence of AF [7], we investigated whether SIRT1 regulating miR-195 and -199a are involved in the pathogenesis of AF.

2. Materials and methods

Sixty-three patients referred for isolated coronary artery bypass graft (CABG) surgery at the Bezmialem Vakif University Hospital and at the Mehmet Akif Ersoy Heart Hospital were included in this two-center, prospective study. Patients with severe hepatic, renal or pulmonary disease were excluded. The study was performed in compliance with the Declaration of Helsinki and was approved by the Committee for Medical Research Ethics of the Bezmialem Vakif University. All patients gave written informed consent before inclusion. Presurgical preparations, surgical techniques, anesthetics and drug administration and postoperative care were performed according to standard routines of the department.

Cardiopulmonary bypass (CPB) was performed at mild hypothermia (34 °C) using a membrane oxygenator. Standard crystalloid or blood cardioplegia was administered for cardiac protection every 30 min. Coronary anastomoses were constructed under aortic cross-clamping (ACC). All patients were monitored with telemetric assessment of heart rhythm by electrocardiography intraoperatively until discharge.

2.1. Atrial biopsies

Myocardial tissue samples were excised from the right atrial appendage during atrial cannulation. After opening the chest/heart, a purse string was placed in the aorta and in the right atrial appendage, which was subsequently tightened. After heparinization and an ACT (activated clotting time) > 400 s, the cannulas were inserted, and the biopsies were taken during the insertion of the cannulas but before starting the cardiopulmonary bypass circulation.

The samples were immediately snap-frozen in liquid nitrogen and kept at − 80 °C until further analyses.

2.2. miRNA expression

After homogenization of 50-mg tissue per sample, the entire process involving miRNA analyses, including RNA isolation, miRNA analysis and quantitative reverse transcription polymerase chain reaction, was performed. RNA quality was controlled by use of the Implen NanoPhotometer (Implen), and the RNA samples were equalized to a concentration of 2 ng/μl. For miRNA isolation, samples were processed using mirVana miRNA Isolation Kit (Life Technologies, AM1560). For miRNA reverse transcription polymerase chain reaction the TaqMan MicroRNA Reverse Transcription Kit (Life Technologies, 4,366,596) was used. Real-time PCR was conducted with the system from Applied Biosystems (Applied Biosystems, 7500).

Level of miRNA expression is presented as normalized crossing point, which was calculated by subtracting the crossing point of the investigated miRNA from the average crossing point of normalization miRNAs.

Relative expression levels were calculated using the CT (cycle number) method after normalization to the endogeneous control RNU43.

2.3. Western blot analysis of SIRT1 protein expression

Western blot analysis for anti-sirt1 was performed using myocardial tissue samples excised from the right atrial appendage (POAF $n = 8$ and NON-POAF $n = 8$). Each sample separately was homogenized with Lysis buffer (RIPA Lysis Buffer, Thermo Fisher Scintific, CatNo:89,900) and treated with protease inhibitor cocktail and phosphatase inhibitor cocktail. The protein concentration was measured using Quibit® Fluoremeter according to the manufacturer's protocol (Invitrogen, Life Technologies Corporation, Carlsbad, CA, USA). Equal amounts of protein (40 μg) were size-fractionated by 4–12% NuPAGE electrophoresis then transferred to polyvinylidene fluoride membrane (PVDF) using iBlot® Dry Blotting System (Invitrogen, Life Technologies Corporation). Membrane was blocked in 5% nonfat milk in 50-mm Tris-buffered saline containing 0.1% Tween (blocking solution) for 1 h at room temperature, washed in Tris buffered saline containing 0.1% Tween (TBS-T) and incubated overnight with rabbit polyclonal anti-sirt1 (rabbit polyclonal, 07–131, Milipore). The following day, the membrane was first washed in TBS-T and incubated with peroxidase-conjugated goat anti-rabbit (Amersham, GE Health Care UK Limited, Buckinghamshire, England) antibody, diluted 1:5000 in blocking solution for 1 h at room temperature. Blots were performed at least three times. Protein loading was controlled by stripping and reprobing the blots with rabbit monoclonal GAPDH (rabbit monoclonal antibody, 14C10, Cell Signaling). The blots

Table 1
General characteristics of the study groups

	POAF ($N=20$)	Non-POAF ($N=43$)	P
Age	60.3 ± 9.1	59.4 ± 9.1	n.s
Male gender (%)	15 (75)	35 (81.4)	n.s
History of smoking (%)	15 (75)	33 (76.8)	n.s
Positive family history for CAD (%)	16 (80)	37 (86)	n.s
Arterial hypertension (%)	10 (50)	21 (48.8)	n.s
Diabetes mellitus (%)	12 (60)	24 (55.8)	n.s
Dyslipidemia (%)	5 (25)	21 (48.8)	n.s
BMI (kg/m^2)	28.96 ± 4.9	29.28 ± 4.9	n.s
History of MI (%)	4 (20)	18 (41.9)	n.s
History of stroke (%)	0 (0)	4 (9.3)	n.s
Carotid artery disease (%)	2 (10)	1 (2.3)	n.s
Peripheric artery disease (%)	0 (0)	1 (2.3)	n.s
Chronic heart failure (%)	0 (0)	4 (9.3)	n.s
COLD (%)	1 (5)	5 (11.6)	n.s
CKD (%)	1 (5)	4 (9.3)	n.s
Preop. LA diameter (mm)	40.5 ± 5.7	41.4 ± 4.6	n.s
Preop LA volume (ml)	51.04 ± 24.05	57.88 ± 23.09	n.s
Preop LA volume index (ml/m^2)	27. 34 ± 14.89	30.60 ± 11.80	n.s
Preop. LVEF (%)	59.25 ± 8.79	54.25 ± 13.23	n.s
NYHA functional class ≥ II (%)	0 (0)	4 (9.3)	n.s
Glucose (mg/dl)	154.05 ± 89.07	164.97 ± 79.73	n.s
TSH (mmol/l)	2.28 ± 1.5	1.77 ± 1.36	n.s
Hematocrit (%)	42.01 ± 5.14	41.33 ± 6.21	n.s
WBC (×10^3/ml)	8.99 ± 2.4	9.33 ± 2.77	n.s
Serum potassium (mmol/l)	4.33 ± 0.4	5.26 ± 0.56	n.s
Creatinine (mg/dl)	0.93 ± 0.51	1.01 ± 0.81	n.s
CRP (mg/dl)	4.86 ± 2.80	6.83 ± 3.90	n.s

n, number of individuals. Differences in continuous variables were tested using Student's *t* test. Categorical variables were compared by chi-square test. The results are shown as mean±standard deviation (SD).
*$P<.05$.

were developed using ECL-Advanced Western Blotting Detection kit (Amersham, GE Health Care UK Limited) and visualized by the Bio-Rad ChemiDoc XRS (Bio-Rad Laboratories, Inc). Protein levels were analyzed densitometrically using the ImageJ program and corrected with values determined on GAPDH blots and expressed as relative values compared with NON-POAF group. Statistics were evaluated by Student's *t* test. The results are shown as mean±standard deviation (SD). *$P<.05$.

2.4. Statistical analysis

Statistical analyses were conducted using a standard software package (SPSS 18 for Windows; SPSS Inc., Chicago, IL, USA). Differences in proportions were tested with chi-square test, and differences in continuous variables were tested with Student's *t* test. Relative risk at 95% confidence intervals (CI) was calculated as the odds ratio (OR).

Table 2
Procedural characteristics of the study groups

	POAF ($N=20$)	Non-POAF ($N=43$)	P
Total operation time, min	91.90 ± 31.26	87.83 ± 24.74	n.s.
Aortic cross clamp time, min	49.10 ± 20.25	46.06 ± 15.88	n.s.
Pump temperature, °C	31.0 ± 0.87	29.46 ± 2.44	.085
Total graft number, *n* (%)	3.43 ± 1.31	3.42 ± 0.82	n.s.
LIMA use, *n* (%)	19 (95)	43 (100)	n.s.
RCA graft use, *n* (%)	11 (55)	30 (69.8)	n.s.

n, number of individuals. Differences in continuous variables were tested using Student's *t* test. Categorical variables were compared by chi-square test. The results are shown as mean±standard deviation (SD).
*$P<.05$.

Table 3
Postoperative characteristics of the study groups

	POAF ($N=20$)	Non-POAF ($N=43$)	P
Duration of postop. Mechanic ventilation, h	7.0 ± 3.1	7.27 ± 3.6	n.s.
Use of inotropic agents, *n* (%)	2 (10)	4 (9.3)	n.s.
Use of IABP, *n* (%)	2 (10)	0	.097
Re-intubation, *n* (%)	1 (5)	0	n.s.
Mediastinitis, *n* (%)	0	2 (4.7)	n.s.
Stroke, *n* (%)	1 (5)	0	n.s.
MI, *n* (%)	0	0	n.s.
Wound infection, *n* (%)	0	2 (4.7)	n.s.
Duration of ICU stay, h	34.85 ± 22.70	31.63 ± 24.45	n.s.
Hospital stay until discharge, d	7.70 ± 7.71	6.72 ± 3.26	n.s.
Renal failure, *n* (%)	0	1 (2.3)	n.s.
Mortality, *n* (%)	0	0	n.s.

n, number of individuals. Differences in continuous were tested using Student's *t* test. Categorical variables were compared by chi-square test. The results are shown as mean±standard deviation (SD).
*$P<.05$.

3. Results

3.1. Demographic and clinical analysis

Demographic and clinical characteristics of the subjects are summarized in Table 1. Both groups were predominantly male (POAF 75% vs. non-POAF 81.4%, n.s.) with an average age of 60 years (POAF 60.3 ± 9.1 vs. non-POAF 59.4 ± 9.1, n.s.). Cardiovascular risk factors like history of smoking, positive family history for CAD, arterial hypertension, diabetes mellitus and dyslipidemia were equally distributed between the study groups. There was no significant difference in the preoperative determined left atrial (LA) — diameter (POAF 40.5 ± 5.7 mm vs. non-POAF 41.4 ± 4.6 mm, n.s.) — volume (POAF 51.04 ± 24.05 ml vs. non-POAF 57.88 ± 23.09 ml, n.s.) and — index (POAF 27. 34 ± 14.89 ml/m^2 vs. non-POAF 30.60 ± 11.80 ml/m^2, n.s.). The left ventricular ejection fraction (LVEF) was slightly decreased in both groups without a marked difference (POAF 59.25 ± 8.79 vs. non-POAF 54.25 ± 13.23, n.s.).

The concentration of fasting blood glucose, potassium, TSH, creatinine and CRP was comparably high in both groups.

The intraoperative characteristics of the study groups are given in Table 2. The total operation, aortic cross-clamp time and pump temperature were similar in both groups. There was no significant difference in total graft number, LIMA and RCA graft use between both groups.

The postoperative variables are shown in Table 3. The length of stay in the intensive care unit and inhospital were similar in both groups. There was no inhospital death detected. In two patients of the POAF group, the intraaortic balloon pump had to be used. One patient in the POAF group, who suffered from stroke, had to be reintubated. The use of inotropic agents was equally distributed in both groups.

3.2. MiRNA expression

A decreased expression of miR-199a was found in tissue samples of patients with POAF compared to the non-POAF group (POAF 0.77 ± 0.27 vs. non-POAF 1.11 ± 0.69, $P=.022$) (Fig. 1). MiR-195 was also less expressed in samples of the POAF group without showing a significant difference compared to the non-POAF group (POAF 0.64 ± 0.28 vs. non-POAF 0.85 ± 0.44, $P=.055$) (data not shown).

SIRT 1 protein expression

SIRT1 protein was markedly elevated in samples of the POAF group compared to the non-POAF group ($P<.001$) (Fig. 2).

4. Discussion

The molecular mechanisms underlying the early development of atrial fibrillation remain poorly understood. To date, a few micro RNA

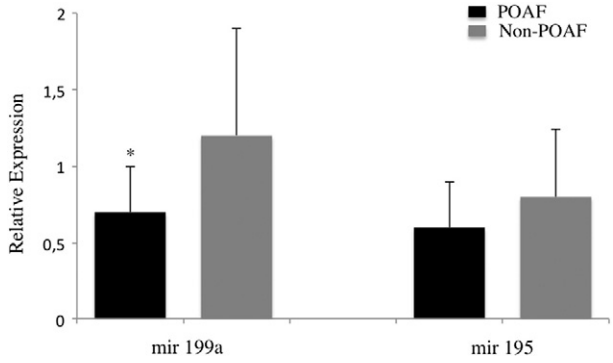

Fig. 1. Relative expression of micro RNAs 199a and 195 in cardiac tissue probes of the study groups. Statistical evaluation by Student's *t* test. The results are shown as mean± standard deviation (SD). *$P<.05$.

studies in AF have provided useful information in gene characterization of AF [1,19,22,23]. However, these studies were focused on chronic AF patients, in whom extensive atrial remodeling processes have already taken place. Thus, many molecular changes in chronic AF patients may result from these remodeling processes and thereby confound the interpretation of their findings. In contrast, our study focused on postoperative AF, showing a specific miR–protein interaction, which may play a role in early AF pathogenesis without confounding structural remodeling.

We have demonstrated that miR-199a is significantly down-regulated in tissue probes of patients suffering from POAF, paralleled by an increase of its target protein SIRT1 (Figs. 1 and 2).

In a recently published transcriptomic analysis, miR-199a was identified as a dysregulated micro RNA in patients with paroxysmal AF after cardiac operation [24].

Moreover, FKBP5- or the FK506-binding protein 5 was identified as a target of miR-199a. FKBP5 is a 51 kDa protein with peptidylprolyl cis-trans isomerase (PPIase) and co-chaperone activities [24] that interacts with heat-shock protein 90 (HSP90) and plays a role in intracellular trafficking and microtubule stabilization [25]. Regulation of steroid hormone receptor function [26], inhibition of apoptosis in cancer cells [27], promotion of Akt dephosphorylation and down-regulation of Akt pathways [28] are known functions of FKPB5 in other organs, although the function in the heart remains unknown. Besides, FKBP5 contains c-terminal tetratricopeptide repeat domains inhibiting store-operated calcium entry through the ISOC channel [25].

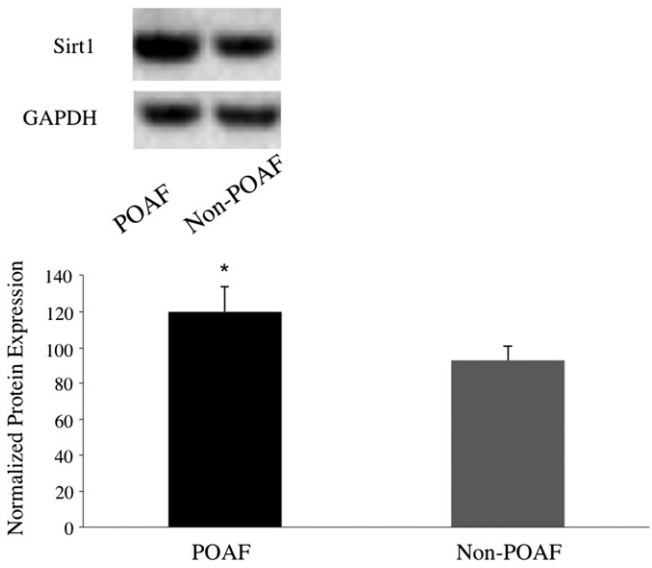

Fig. 2. Representative western blot analysis of SIRT1 protein (POAF $n=8$; non-POAF $n=8$). The relative SIRT1 expression was normalized against GAPDH. Statistical evaluation by Student's *t* test. The results are shown as mean±standard deviation (SD). *$P<.05$.

The cardio-protective protein SIRT1 is another miR-199a predicted target [21], and its expression is enhanced in cardiac tissue of patients with AF [7] and in sera of patients with chronic CAD [8]. It is supposed that the disease-related overexpression of SIRT1 is a compensatory mechanism to inhibit the process of oxidative stress, which contributes to the pathogenesis of AF [3,7,8] and CAD [9].

In cardiomyocytes, overexpression of miR-199a reduced endogenous SIRT1 by 50%, whereas its knockdown enhanced its expression 2.2 times [21].

In tissue, hypoxia or ischemia decreases miR-199a, yielding an increase in SIRT1 in cardiacmyocytes. SIRT1 in turndown down-regulates prolylhydroxylase 2 (PHD2), which stabilizes HIF-1α and initiates hypoxia signaling. Thus, it was concluded that miR-199a is a master regulator of a hypoxia-triggered pathways and can be considered for preconditioning.

What might be the mutual pathomechanism yielding increased SIRT1 levels in AF and CAD?

Risk factors for AF are similar to those of atherosclerosis; these risk factors, such as hypertension, aging, diabetes and coronary artery bypass surgery, are paralleled by increased systemic markers of oxidation [29,30]. Further, there is also evidence of increased cardiac oxidation of myofibrillar protein [31,32] and membrane lipids [33] with AF or with risk factors related to AF. Although it is not possible to elucidate whether the cardiac oxidation leads to systemic markers of oxidation or whether systemic oxidation leads to cardiac oxidation, the association of oxidative stress and AF is clear.

Sun et al. have shown that besides enhanced tissue concentration of SIRT1, levels of oxidative stress markers like malondialdehyde, metallothionein and the activity of superoxide dismutase were elevated in patients with AF compared to patients with sinus rhythm [7]. Further AF was shown to be closely associated with an atrial up-regulation of hypoxic and angiogenic markers [34].

Whether cardiac ischemia associated with oxidative stress yields down-regulation of miR-199a with subsequent overexpression of SIRT1 protein, which in turn compensates the deleterious effects of tissue hypoxia, has to be clarified in further experiments.

Intriguingly, although miR-199a and −195 are expressed in cardiac tissue, targeted and inhibited the same protein, SIRT1, there was no clear association between miR-195 and POAF (Fig. 1).

MiR-195 promotes apoptosis through down-regulation of SIRT1, Bcl-2 and increase of ROS production [20]. Further, it is involved in the pathogenesis of cardiac hypertrophy [35] and contributes to the pathogenesis of aortic aneurysmal disease [36]. In contrast to miR-199a, it is not regulated by hypoxia or cardiac ischemia, which can occur during placing the atrial suture and cannulas in an open cardiac operation.

To summarize, we conclude that decreased steady state levels of miR-199a with subsequent activation of SIRT1 protein might predict postoperative atrial fibrillation.

The postulated pathway hypoxia/hypoxia-derived oxidative stress — miR-199a — SIRT1, which might play a role in the pathogenesis of early POAF, has to be elucidated in further studies.

Study limitations

The number of the study groups might be increased. Markers for hypoxia or oxidative stress were not determined.

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Disclosures

The authors declare that there is no conflict of interest.

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