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Relationship between *SIRT1* gene and adolescent depressive disorder with nonsuicidal self-injury behavior

Based on gene methylation and mRNA expression

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Abstract

Objective: The incidence of non-suicidal self-injury (NSSI) behavior in adolescents is increasing year by year. Patients with a history of both depression and NSSI behavior tend to be at greater risk for suicide. At present, the mechanism of adolescent depressive disorder with NSSI behavior is not clear and still in research and exploration. The expression of the Silent Information Regulator 2 Related Enzyme 1 (*SIRT1*) gene is closely related to the level of serotonin in molecular mechanisms, and may be closely related to the occurrence and development of depressive disorder. This study aimed to explore the relationship between the *SIRT1* gene and NSSI behaviors in adolescents with depressive disorder.

Methods: A total of 15 adolescent depressed patients with NSSI behavior and 15 healthy controls were enrolled in the study. Bisulfite Sequencing PCR (BSP) was used to test the methylation level of *SIRT1* gene promoter region of the participants. The real-time fluorescent quantitative PCR was conducted to measure the mRNA expression level of *SIRT1* gene.

Results: Our study found that the methylation level of *SIRT1* gene promoter region at cytosine-guanine dinucleotide 5 (CpG5) site in depression group was higher than that of control group. Compared with that of control group, the plasma concentration of Sirt1 protein significantly decreased in depression group.

Conclusion: Our study investigated the methylation level and the mRNA expression of *SIRT1* gene in adolescent depressive patients with NSSI behavior. The study points towards finding an in vivo molecular marker for those adolescent patients.

Abbreviations: 5-HT = 5-hydroxy trptamine, CpG5 = cytosine-guanine dinucleotide5, DSM-5 = 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, MAO-A = Monoamine oxidase A, NSSI = nonsuicidal self-injury, PCR = polymerase chain reaction, SIRT1 = silent information regulator 2 related enzyme 1.

Keywords: adolescent, bisulfite sequencing PCR, depressive disorder, DNA methylation, nonsuicidal self-injury behaviors, *SIRT1* gene

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LW and DZ contributed equally to this work.

This study, which strictly implemented the principle of informed consent, was approved by the Ethics Committee of School of Clinical Medicine, Cheeloo College of Medicine, Shandong University. The informed consent forms were used to explain in concise terms the contribution and benefits to the subjects and how to protect their rights and interests prior to their participation in the research.

Researchers interested in the study may contact corresponding author to obtain relevant data via email: qiaovincent@163.com.

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1. Introduction

Nonsuicidal self-injury (NSSI) behavior refers to a series of unacceptable behaviors that directly and deliberately harm one's body without suicidal intentions.[1] Usually at the beginning of adolescence, it is mostly related to problems with family members and peers. Community surveys have found that 14% to 17% of the adolescents and 4% of the adults engaged in NSSI behaviors.[2] And other studies suggested that between 15 million and 30 million adolescents would likely to have NSSI behavior by 2020.[3,4] In recent years, the mental health level of children and adolescents has been constantly improved worldwide, which has aroused public concern. And adolescent depressive disorder patients with NSSI behavior deserve more attention in the field of psychiatry.

Depressive disorder is a group of diseases characterized by depression, and may be associated with varying degrees of cognitive behavior changes, psychotic symptoms, suicidal and self-injurious behaviors. According to the World Health Organization, depressive disorder will become the second cause of disability worldwide by 2020.[5] Adolescent patients with depressive disorder may have NSSI behavior, the relationship between depression and NSSI behavior is complex and still under exploitation. Some studies suggest that depression is an important risk factor for NSSI behavior.[6,7] And anhedonia may be one of the motivations of NSSI behavior.[8] Severe depressive symptoms are related to self-injurious functions, including self-punishment, dissociation and confrontation, and interpersonal relationship boundary and so on.[9] There are also studies suggest that patients with NSSI behavior may have emotional management disorders. NSSI behavior may be an emotional regulation strategy for depressive patients.[10] NSSI behavior can be involved in regulating emotions, self-punishment, or generating emotional needs to regulate social interaction and self-experience.[11] Although the relationship between NSSI behavior and depressive disorder is unclear, NSSI behavior has been found to be one of the best predictors of suicide in adolescents,[1] the patients who had a history of depressive disorder and NSSI behavior at the same time may have a greater risk of suicide.[12] Therefore, further identifying the psychological characteristics of NSSI behavior in adolescents with depressive disorder will contribute to early detection, prevention, and guidance of individualized treatment.[13]

The pathogenesis of depressive disorder is complicated. Studies have shown that epigenetic mechanisms may be involved in the occurrence, development, and outcome of depressive disorder.[14,15] The most studied type of modification in the epigenetics is DNA methylation. Studies suggested that silent information regulator 2 related enzyme 1 (*SIRT1*) gene[16] may be related to depressive disorder. Sirt1 protein can deacetylate helix-loop-helix transcription factor-2, thereby activating the binding of it and monoamine oxidase A (MAO-A) promoter region. It can promote the transcription of MAO-A, increase the activity of MAO-A and the degradation of 5-hydroxy trptamine (5-HT), reduce the level of 5-HT in the brain, and cause depression.[17]

Studies have shown that *SIRT1* gene polymorphism may be associated with clinical symptoms such as cognitive impairment, sleep disturbance, guilt, suicide, systemic symptoms, and sexual symptoms in patients with depression. Gene polymorphisms and gene expression levels may be related to the clinical symptoms of depression and antidepressant efficacy.[18] The *SIRT1* gene polymorphism site rs12415800 may be a predictor of antidepressant efficacy in Han patients with depression.[19] There is a genetic association between site rs12415800, rs4746720 and suicide.[20] Gene expression study[21] found that the mRNA level of *SIRT1* gene in peripheral blood of depressive patients after electroconvulsive treatment was increased, so the decrease of *SIRT1* gene expression level may be a biological feature of depressive disorder.[22] Animal experiments of Lo, Iacono L et al[23] showed that mice exposed to stress in childhood showed depression-like behaviors in adulthood, which may be related to the decrease of Sirt1 protein levels in the brain and peripheral blood mononuclear cells. The expression of *SIRT1* gene seems to have a protective effect on depressive patients. Studies have suggested that a good living environment can activate the SIRT1/microRNA-134 pathway, thereby inhibiting depression and cognitive deficits.[24] Sirt1 protein may also improve the depression-like behavior in mice by promoting the conversion of microglia to M2 type.[25] In addition, the *SIRT1* gene expression in the nucleus accumbens region can be induced, and the activity of Sirt1 protein can be altered by pharmacological or genetic methods to regulate anxiety and depression-like behaviors.[26] At present, there has been no research on the methylation level of *SIRT1* gene in depressive patients. However, considering that NSSI behavior may be related to adolescent traumatic events,[27] abnormal attachment patterns,[28] etc, it is speculated that epigenetics may be involved in the occurrence and development of NSSI behavior, and the *SIRT1* gene may be related to the long-term consequences of children's adverse experiences. Therefore, we can propose the following hypothesis on the above research status: *SIRT1* gene DNA methylation and mRNA expression may be related to the mechanism of depression and NSSI behavior, and such effect may be related to the patients' past growth experience, family environment, parenting style, attachment patterns, and emotional expression. Those interactions can participate in the development of NSSI behavior in depressive disorder.

2. Material and methods

This study was approved by the Ethics Committee of School of Clinical Medicine, Cheeloo College of Medicine, Shandong University.

A total of 15 adolescent depressive patients with NSSI behavior and 15 normal healthy individuals were enrolled in this study. Comply with the diagnostic criteria for major depressive disorder in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5); the age range is 10 to 19 years old, male or female; Volunteer to participate in the research and obtain written informed consent of the legal guardian. The above is the criteria for the experimental group. The exclusion criteria of the experimental group were as follows: the score of third item among Hamilton depression scale-24 (suicide) $\geq$2 points (2 points means wishing to have died, or often thinking about things related to death); mood disorders, such as bipolar disorders or related to it, persistent, unspecified mood disorders, or mental disorders caused by psychoactive substances; some patients who had received special therapy in the last 3 months, such as modified electroconvulsive therapy, transcranial magnetic stimulation therapy or systematic psychotherapy; other mental disorders defined in DSM-5. The inclusion criteria for the control group were as follows: healthy volunteers recruited from the community during the same period; those who must match the age, gender, and education level of the experimental group;

understand and sign written informed consent. The exclusion criteria were as follows: schizophrenia spectrum, bipolar or related disorders, depression, anxiety, obsessive-compulsive, separation, physical symptoms, and other related disorders specified in DSM-5; First-degree relatives have mental and neurological diseases; previously implemented NSSI behaviors.

3. Molecular analysis

3.1. DNA methylation detection

The samples were EDTA anticoagulated blood collected from cubital vein and 2 mL blood was centrifuged to collect leukocyte layer. Using online software CpG Island Searcher (http://cpgislands.USC.edu) to analyze the gene promoter region CpG island, ranging from 2000 bp upstream to 1000 bp downstream of the transcription start point, to obtain sequence information. The SequenomEpiDesigner software was used to analyze and design methylated primers, and synthesize primers. Genomic DNA was treated with the bisulfite sequencing polymerase chain reaction (PCR). All unmethylated cytosines are converted into uracils, while the methylated cytosines remain unchanged; then primers with PCR after designing at both ends of the CpG island. Then purify the target product to perform TA cloning. From each clone, the positive clones were selected for sequencing, and finally the measured sequence was compared with the original sequence to count the methylation sites and numbers, and analyze the degree of methylation. The extraction of DNA was performed using the DNA Kit (GENERAY, GK0122). DNA samples were bisulfite-converted using the Bisulfite Kit (QIAGEN, cat; 59824).

The primers for the promoter region of *SIRT1* gene are as follows: F: TTTTTTGAGTAGTTGGGATTATAGG; R: AAACCTTAAAACCATCTTTAATTAC.

3.2. mRNA expression detection

A total of 3 mL whole blood with RNA preservation solution was collected and mononuclear cells were carefully separated from the peripheral blood. Then perform cell viability and cell count detection on the separated cell suspension, select samples with cell concentrations above $1–3 \times 10^6$ orders of magnitude for RNA extraction. Take RNA solution to test the concentration and absorbance value; the OD260/280 value is 1.8 to 2.0 as qualified purity, otherwise, the RNA needs to be re-extracted. After RNA electrophoresis, the photo shows 3 bands of 28S, 18S, and 5S, and no contaminated bands appear. Then perform RNA reverse transcription and save complementary DNA for preservation. The real-time fluorescent quantitative PCR reaction was conducted for RNA amplification. After the reaction, check the melting curve to check whether the amplified product is single specific. If the melting curve has multiple peaks, the reaction system may be contaminated, and the reaction system can be reconfigured to start again. Finally confirm the amplification curve and cycle threshold values of all genes, and use the $2\text{-}^{\Delta\Delta}$Ct method to analyze the gene expression level.

3.3. Statistical analysis

SPSS 21.0 software was used to establish a database and perform statistical analysis of data. The continuous variables were expressed as mean ± standard deviation and the categorical variables were expressed in frequency. One-way analysis was used to compare the continuous variables between groups. The chi-square test was used to compare the categorical variables between groups. $P < .05$ considered the result to be statistically significant.

Table 1

General clinical data of depression and control group.

Group	Male	Female	χ^2, *P*	Average age	*F*, *P*
Depression group	6	9	0.871, 1	16.00 ± 1.309	0.786, .385
Control group	7	8		16.73 ± 2.120	

4. Results

There is no statistical difference in age and gender of the 15 adolescent depressive patients with NSSI behavior and 15 normal controls (Table 1).

Compared with that in control group, the degree of cytosine-guanine dinucleotide5 (CpG5) site methylation in *SIRT1* gene promoter region in depression group was significantly higher (Table 2).

In order to further explore the abnormal methylation in the promoter region of the *SIRT1* gene, the depression group used enzyme-linked immunosorbent assay to detect the plasma Sirt1 protein concentration of the 2 groups. The results showed that the plasma concentration of Sirt1 protein in depression group was significantly lower than that of control group (Table 3).

5. Discussion

According to the above research results, *SIRT1* gene is related to the occurrence and development of depressive disorder. However, there is no epigenetic method to study whether this gene methylation is related to adolescent depressive disorder patients with NSSI behavior. Therefore, in our study a case-control study method was used to compare the methylation degree of *SIRT1* gene between adolescent depressive disorder patients with NSSI behavior and normal controls.

Our results found that the degree of CpG5 site methylation in the *SIRT1* gene promoter region was statistically different in adolescent depressive disorder patients with NSSI behavior. The results of the study suggest that there was an abnormal methylation level of *SIRT1* gene promoter region in adolescent depressive patients with NSSI behavior, and this abnormality may be an in vivo molecular marker for adolescent depression patients with NSSI behavior. In order to further explore the abnormal methylation in the promoter region of the *SIRT1* gene, enzyme-linked immunosorbent assay was used to detect the Sirt1 protein concentration in the plasma of both groups. The results showed that the plasma concentration of Sirt1 protein in depression group was lower than that of the control group, and the difference was statistically significant.

One possibility is that our results show that the methylation degree of CpG5 site in the *SIRT1* gene promoter region was abnormal, and the concentration of Sirt1 protein in plasma is low. It may be that these patients have experienced long-term adverse life stimuli during childhood and adolescence, which led to the alterations in *SIRT1* gene expression. Therefore, we can assume that these patients themselves carry abnormal *SIRT1* gene methylation before the occurrence of NSSI behavior. So, we hypothesized that NSSI behavior may affect the early epigenetic regulation of *SIRT1* gene, and may contribute to the occurrence

Table 2

Comparison of methylation degree of *SIRT1* gene CpG sites between depression and control group.

Sites	Group	Mean	Standard	*F*	*P*
CpG1	Control group	9.67	0.488	0.000	1.000
	Depression group	9.67	0.488		
CpG2	Control group	9.73	0.458	0.093	.762
	Depression group	9.73	0.594		
CpG3	Control group	9.60	0.828	0.000	1.000
	Depression group	9.60	0.737		
CpG4	Control group	9.6	0.632	0.676	.418
	Depression group	9.73	0.594		
CpG5	Control group	9.87	0.352	5.206	**.030**[*]
	Depression group	9.67	0.617		
CpG6	Control group	10.00	0.000	0.577	.456
	Depression group	9.80	0.414		
CpG7	Control group	9.93	0.258	1.513	.232
	Depression group	9.75	0.463		
CpG8	Control group	9.80	0.414	0.707	.408
	Depression group	9.73	0.458		
CpG9	Control group	9.67	0.724	2.431	.130
	Depression group	9.80	0.414		
CpG10	Control group	9.73	0.458	3.422	.075
	Depression group	9.87	0.352		

$P < .05$ represented the statistical significance at CpG5 site in the promoter region of *SIRT1* gene of depression and control groups.
[*] $P < .05$.

and development of NSSI behavior. However, we have not yet collected relevant data on the adverse experiences of these patients in childhood and adolescence, and we cannot provide further evidence for this hypothesis. Therefore, we need to conduct more animal studies under controllable conditions to provide evidence that certain negative environmental conditions in early life have affected the epigenetic patterns of adolescent depression patients for multiple generations.

Another possibility is that the NSSI behavior is the protection mechanism that caused the body to reach a steady state after CpG5 site methylation in promoter region of *SIRT1* gene has altered. Studies have shown that Sirt1 protein can deacetylate helix-loop-helix transcription factor-2, thereby activating its binding to the MAO-A promoter region. It can promote the transcription of MAO-A, increase the activity of MAO-A, and increase the degradation of 5-HT, reduce the level of 5-HT in the brain, and cause depression.[17] The reduction of 5-HT in patients with depression can lead to anhedonia. Anhedonia may be one of the motivations of NSSI behavior,[8] which promotes NSSI behavior in adolescents with depression. NSSI behavior, as a stress mediator, can stimulate the production of 5-HT in adolescent patients with depression. Meanwhile, after electroconvulsive treatment, the *SIRT1* mRNA level in peripheral blood of depressed patients was found increased.[21] As a result, NSSI behavior, as a body protection mechanism, which increases 5-HT in the patient's body, and at the same time increases the *SIRT1* mRNA level in the patient's peripheral blood, which may lead to corresponding alterations in the degree of CpG5 site methylation of the *SIRT1* gene promoter region, make the body reach a stable state, thereby improving the depressive mood of adolescent patients.

Table 3

Comparison of the plasma Sirt1 protein concentration (ng/mL) in depression and control group.

Group	Mean	Standard	*F*	*P*
Control group	1.63687	0.152618	9.103	**.007**[†]
Depression group	1.46213	0.076931		

$P < .05$ represented the statistical significance at plasma Sirt1 protein concentration (ng/mL) in depression and control group.
[*] $P < .05$.
[†] $P < .01$.

6. Limitations

There are limitations of our work. The present study includes only a small number of depressed adolescents with NSSI behavior and healthy controls. Nevertheless, it reached nominally significant results. Based on the above results, there may be bias considering that the sample size is small, so whether this abnormality can be used as an in vivo marker needs to be further expanded samples and more clinical data to verify this abnormality and possible epigenetic feedback regulation mechanism, and we will do future studies to strive for the early detection of biological markers applied in clinical work. In addition, in future studies, we will add a group of adolescent depressive patients without NSSI behavior to better understand the relationship among adolescent depression, NSSI behavior, and changes of *SIRT1* gene DNA methylation and gene expression.

7. Conclusion

We conclude that there are some significant differences in the methylation degree and the mRNA expression of the *SIRT1* gene in adolescent depressive patients with NSSI behavior. Compared with that in control group, the methylation degree of CpG5 site in the promoter region of *SIRT1* gene in depression group was significantly higher, and the plasma concentration of Sirt1 protein was significantly lower. So, we believe that there is a

certain relationship between *SIRT1* gene and adolescent depressive patients with NSSI behavior.

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