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ORIGINAL RESEARCH

Clinical Significance of the Serum lncRNA NORAD Expression in Patients with Neonatal Sepsis and Its Association with miR-410-3p

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Purpose: Neonatal sepsis (NS) is one of the most crucial causes of death in newborns. This investigation aimed to validate the expression level of NORAD and the probable mechanism underlying the function of NORAD in NS.

Patients and Methods: The expression of NORAD and miR-410-3p was identified by qRT-PCR. The diagnostic sensitivity and specificity of NORAD were examined by the ROC curve. The NS cell models were established by the treatment of lipopolysaccharide (LPS) in the macrophage RAW264.7 cells. The luciferase report assay was performed to detect the target relationship between NORAD and miR-410-3p and the association between them was revealed by Pearson correlation.

Results: The expression of NORAD was at a higher level in the NS group than in the pneumonia controls. The levels of NORAD could sever as a diagnostic marker on discriminating NS patients from pneumonia neonates. The expression of IL-6, IL-8, and TNF-α was enhanced in the macrophage cells under LPS circumstances, while NORAD knockdown reversed the overexpression of these pro-inflammatory cytokines. Besides, miR-410-3p was a possible ceRNA of NORAD by the finding that the luciferase activity fell in the co-transfection of miR-410-3p mimics and WT-NORAD group. In vitro, LPS management could inhibit the expression of miR-410-3p, while silenced NORAD ameliorated the suppressed miR-410-3p levels. Decreased expression of miR-410-3p was discovered in NS patients and the changes of miR-410-3p expression were correlated with the levels of NORAD in the NS patients.

Conclusion: We found a raised level of NORAD in the NS patients and it might be a diagnostic indicator for NS patients. NORAD elimination meliorated the inflammation actions steered by LPS. MiR-410-3p was a target of NORAD and lowly expressed in the NS patients.

Keywords: NORAD, miR-410-3p, neonatal sepsis, diagnosis, inflammation

Introduction

Sepsis is a life-threatening systemic inflammatory response syndrome caused by a host of uncontrolled infections, which often leads to multiple organ dysfunction.[1] The incurrence and mortality of sepsis have been increasing in the past few years.[2] Neonatal sepsis (NS) refers to the systemic inflammatory response caused by pathogens entering the neonatal blood circulation, developing, reproducing, and producing toxins in the body.[3] Coagulase-negative staphylococci (CONS) are the most common pathogens in both early-onset NS and late-onset NS.[4] The symptoms of NS at the early stage of the disease are not obvious and specific, which are easily

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confused with other diseases and this increases the difficulty of clinical diagnosis.[5] Considering the immature neonatal function and weak resistance to diseases, failure to timely treatment will increase the mortality of neonates.[6] In the clinic, blood culture is used as the gold standard for early diagnosis of NS, but the longer detection cycle affects the early treatment of newborns, thus delaying the early treatment.[7,8] At present, finding sensitive and efficient diagnostic indicators of neonatal sepsis is the focus of clinical work on NS.

LncRNA is a non-coding RNA with a length of more than 200 bp, which is mainly distributed in the cytoplasm and nucleus and involved in a variety of cellular processes, such as proliferation, apoptosis, and migration.[9] The expression alternation and impacts of lncRNAs on NS have been examined by many researchers. In research of microarray published in 2020, 61 lncRNAs are downexpressed and 28 lncRNAs are overexpressed in NS patients.[10] LncRNA SNHG16 modulates inflammation in NS by sponging miR-15a/16 cluster.[11] LncRAN non-coding RNA activated by DNA damage (NORAD) has been explored in many diseases including immunological diseases. The expression of NORAD is overexpressed in patients with papillary thyroid carcinoma and the NORAD/miR-202-5p axis regulates the growth, invasion, and migration of papillary thyroid carcinoma cells.[12] However, the influence of NORAD in NS needs more investigation.

The current study pursued to assess the expression of NORAD in NS and provide its prognostic significance on NS patients. The expression and impact of NORAD on inflammation were also explored in the RAW264.7 murine macrophage cell line. Moreover, the ceRNA of NORAD was demonstrated to unveil the underlying mechanism.

Patients and Methods

Study Design and Sample Collection

We performed a retrospective cohort study of newborns between 2017 and 2020.A total of 86 pneumonia neonates and 88 late-onset NS patients were included randomly from Weifang Maternal and Child Health Hospital. On the basis of 5% significance level (alpha = 0.05, two-sided) and 80% power (beta = 0.2), at least 62 participants should be enrolled in each group and a total of 142 individuals will be recruited to allow for a 15% dropout rate. A previous protocol for the diagnosis of NS was applied to identify NS patients based on the results of clinic and library tests.[13] All the guardians of participants submitted written informed consent and the design of this study was approved by the Ethics committee of Weifang Maternal and Child Health Hospital. Our experiments were performed in accordance with the Declaration of Helsinki. Serum specimens were collected from each individual and stored at a −80°C refrigerator. All demonstrated information and clinical characteristics were summarized by all participants.

RNA Extraction and Quantitative Real-Time PCR (qRT-PCR)

The total RNA, in the above-mentioned serum specimen, was extracted with TRIzol reagent (ThermoFisher Scientific, MA, USA). The concentration and purity of RNA were measured by a spectrophotometer and the samples with absorbance (A260/280 nm) of 1.8–2.0 were taken. The first line of cDNA for NORAD was synthesized by a reverse kit (Promega, Madison WI, USA). For miR-410-3p, RNA was reverse transcribed into cDNA according to the miRNA reverse transcription kit instructions (Life Technologies, Carlsbad, California, US). Using GAPDH or U6 as the internal references for NORAD or miR-410-3p, the PCR reaction was carried out on the quantitative PCR instrument according to the instructions of the qRT-PCR kit (ThermoFisher Scientific, MA, USA). The primers applied in the qRT-PCR were as follows: NORAD (forward primer, 5′-TGATAGGATACATCTTGGACATGGA-3′; reverse primer, 5′-AACCTAATGAACAAGTCCTGACATACA-3′). GAPDH (forward primer, 5′-GGAGCGAGATCCCTCCAAAAT-3′; reverse primer, 5′-GGCTGTTGTCATACTTCTCATGG-3′), miR-410-3p, forward primer, 5′-GTCAGCGCAATATAACACAG-3′ ‘; reverse primer, 5′-GAGAACAGCTCTGTGTTATAT-3′; and U6, forward primer, 5′-CTCGCTTCGGCAGCACA-3”; reverse primer, 5′-AACGCTTCACGAATTTGCGT-3′). The relative expression of NORAD and miR-410-3p in the serum and cells was calculated by the 2-delta Ct method.

Cell Treatment and Transfection

A murine macrophage cell line RAW264.7 was obtained from American Type Culture Collection (Manassas, VA, USA). The cell line was cultured in Roswell Park Memorial Institute (RPMI) 1640 medium (South Logan, UT, USA) supplemented with 10% fetal bovine serum (FBS) and 1% double-antibody. The condition of the incubator is 37°C and

5% CO2. Lipopolysaccharide (LPS) was used to induce macrophages to simulate the sepsis environment. The culture condition of RAW264.7 was in conformity with the previous method.[14] The ways to screen appropriate time and concentration of LPS were 12-h treatment with 0~2 μg/mL LPS and 0~48-h treatment with 1 μg/mL LPS on RAW264.7 cells.

The fragments of si-NORAD and si-negative controls (si-NCs) were obtained from GenePharma (Shanghai, China). The RAW264.7 cells were seeded into a 6-well plate and cultured until the confluence was 70%. Transfection experiments were carried out using Lipofectamine 3000 reagent (ThermoFisher Scientific, MA, USA).

Enzyme-Linked Immunosorbent Assay (ELISA)

The amount of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) was detected by ELISA kits (all from Abcam, Cambridge, MA, USA) based on their manufacturer's instrument.

Luciferase Activity Assay

The wide type of NORAD (WT-NORAD) sequence containing the binding bases with miR-410-3p was obtained by PCR. The mutation NORAD sequence was synthesized by Sangon Bio (Shanghai, China). The sequences, involving miR-410-3p inhibitors, miR-410-3p mimics, and miR-410-3p NC (miR-NC), were from GenePharma (Shanghai, China). The co-transfection was applied using Lipofectamine 3000 reagent (ThermoFisher Scientific, MA, USA). Luciferase Report Assay Kit (HANBIO, Shanghai, China) was used to access the relative luciferase activity of each group.

Statistical Analysis

SPSS19.0 statistical software and GraphPad Prism 5 were used for statistical analysis. The measurement data were tested by an independent *t*-test. The χ^2 test served as the method to compare the gender between two groups. Pearson correlation was used to explore the relationship between NORAD and miR-410-3p. The value of NORAD in sepsis screening was validated by the ROC curve. The difference was statistically significant when $P < 0.05$.

Results

Baseline Features of the Study Population

The clinical data from the study population were expressed in Table 1. As shown, there were 50 boys and 36 girls with a mean age of 11.84 ± 5.22 days and a mean weight of 3.45 ± 0.57 kg included in the pneumonia group. NS group was constituted by 88 volunteers (48 NS boys and 40 NS girls) with a mean age of 10.61 ± 5.28 days and a mean weight of 3.51 ± 0.45kg. The age, body weight, and gender did not differ between the pneumonia group and NS group (all $P > 0.05$). Whereas, the results of clinical features showed that the concentration of white blood cell (WBC), C-reactive protein (CRP), procalcitonin (PCT), IL-6, IL-8, and TNF-α in the NS group was obviously higher than in the pneumonia group (all $P < 0.01$).

NORAD Was Highly Expressed in NS Patients

The serum expression of NORAD was detected by qRT-PCR and the result was demonstrated in Figure 1. This picture provided that the expression of NORAD was elevated in the NS group when compared with the pneumonia group ($P < 0.001$). Furthermore, the mean relative

Table 1 Clinical Data of the Study Population

Parameters	Subjects (N=174)		Significance Level (*P*)
	Pneumonia Individuals (n = 86)	Neonatal Sepsis (n =88)	
Age (days)	11.84 ± 5.22	10.61 ± 5.28	0.126
Body weight (kg)	3.45 ± 0.57	3.51 ± 0.45	0.413
Gender (male/female	50/36	48/40	0.633
WBC ($\times 10^9$/L)	16.50 ± 6.49	19.64 ± 6.14	<0.001
CRP (mg/L)	10.51 ± 4.36	15.19 ± 4.91	<0.001
PCT (ng/mL)	1.49 ± 0.83	3.64 ± 1.43	<0.001
IL-6 (pg/mL)	302.21 ± 49.17	361.21 ± 62.46	<0.001
IL-8 (pg/mL)	420.85 ± 39.31	449.81 ± 71.98	0.001
TNF-α (pg/mL)	314.08 ± 46.82	369.11 ± 66.16	<0.001

Abbreviations: WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-alpha.

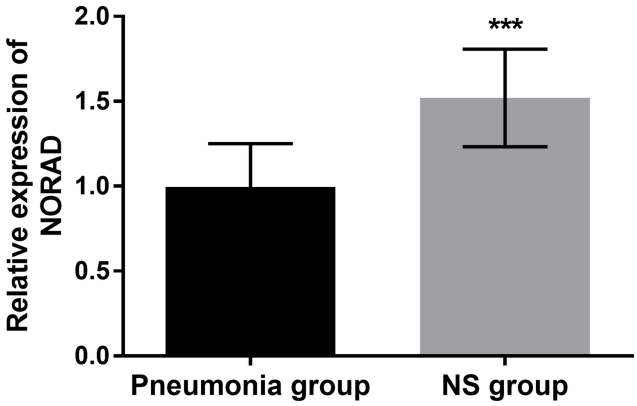

Figure 1 The finding of qRT-PCR elucidated the highly expressed NORAD in the NS group. ***$P < 0.001$.

expression of NORAD was 1.00 ± 0.03 in pneumonia patients and 1.52 ± 0.03 in NS patients.

Relationship of NORAD with Examination Items of NS

The correlations between NORAD expression and characteristics were analyzed using Pearson correlation. As shown in Table 2, no significant correlations between NORAD levels and several demographics, containing age (r = 0.163, $P = 0.130$), body weight (r = 0.039, $P = 0.721$), and gender (r = 0.092, $P = 0.393$). Interestingly, NORAD expression was closely associated with WBC (r = 0.341, $P = 0.001$), CRP (r = 0.554, $P < 0.001$), PCT (r = 0.635, $P < 0.001$), IL-6 (r =0.503, $P < 0.001$), IL-8 (r = 0.559, $P < 0.001$), and TNF-α (r = 0.679, $P < 0.001$), indicating the serum expression of NORAD might appertain to the development of NS.

Table 2 Correlation Between lncRNA NORAD and Clinical Characteristics

Characteristics	Correlation with lncRNA NORAD (r)	*P-value*
Age (days)	0.163	0.130
Body weight (kg)	0.039	0.721
Gender (male/female	0.092	0.393
WBC (×10^9/L)	0.341	0.001
CRP (mg/L)	0.554	<0.001
PCT (ng/mL)	0.635	<0.001
IL-6 (pg/mL)	0.503	<0.001
IL-8 (pg/mL)	0.559	<0.001
TNF-α (pg/mL)	0.679	<0.001

Abbreviations: WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-alpha.

Diagnostic Accuracy of NORAD for NS Patients

The area under the curve (AUC) of NORAD was 0.915, which suggesting the diagnostic possibility of NORAD for forecasting NS patients from pneumonia newborns (Figure 2). Moreover, the sensitivity was 80.7% and the specificity was 88.4%, which showed the high accuracy of NORAD in the discrimination between pneumonia controls and NS patients (Figure 2).

Influence of NORAD on RAW264.7 Cells

Previous research clarifies LPS can activate the inflammatory actions of RAW264.7 macrophages.[15] To establish the cell model for mimicking the damage of NS, the levels of NORAD were validated in the RAW264.7 cells induced by different concentrations and handling time of LPS. In Figure 3A and B, with the increase of concentration and time, the relative levels of NORAD were gradually raised (all $P < 0.05$). To explore whether inflammatory damage contributed to the alternation of NORAD expression, the expression of NORAD was regulated artificially by si-NORAD. In Figure 4A, the si-NORAD reversed the upregulation of NORAD caused by LPS ($P < 0.01$). In addition, the decreased expression of NORAD inhibited the increased concentration of IL-6, IL-8, and TNF-α, suggesting the significance of NORAD levels on inflammation (Figure 4B, $P < 0.001$).

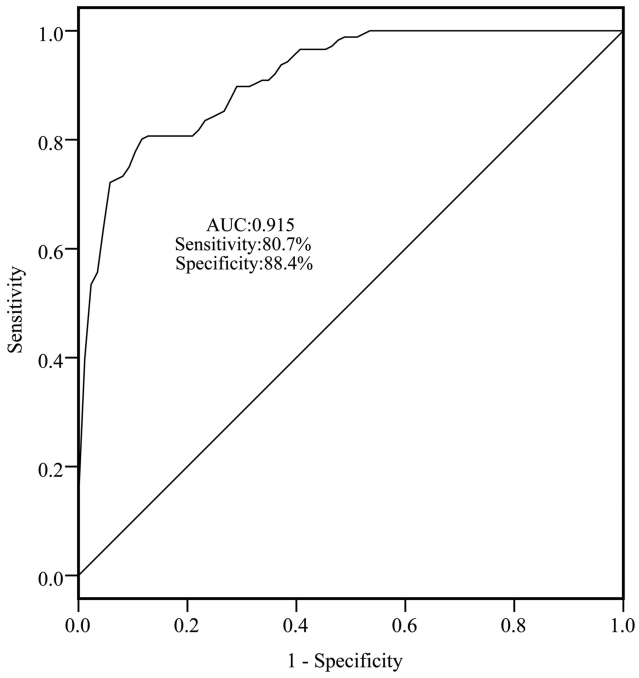

Figure 2 The accuracy of NORAD in distinguishing NS patients.

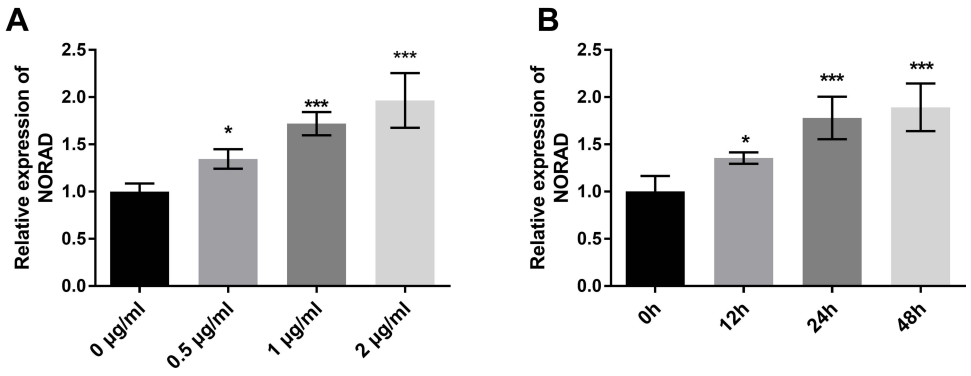

Figure 3 The increasing dosage (**A**) and processing hours (**B**) of LPS contributed to the upregulation of NORAD. *$P < 0.05$, ***$P < 0.001$.

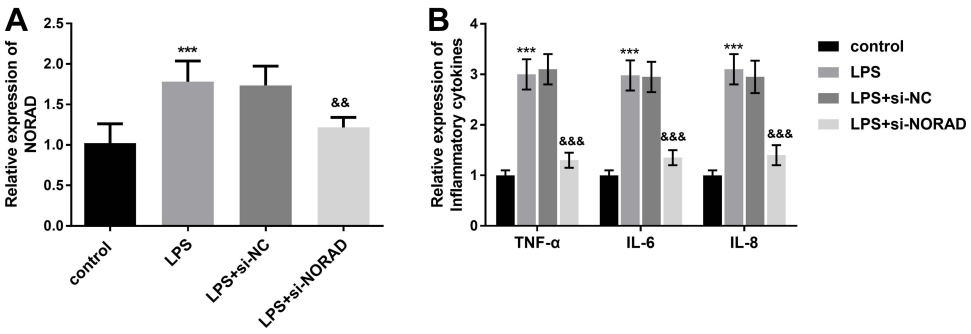

Figure 4 (**A**) Interference of NORAD reversed the elevated levels of NORAD elicited by LPS. (**B**) The concentration of IL-6, IL-8, and TNF-α was increased in LPS-stimulated RAW264.7 cells, while the absence of NORAD reversed the high levels of IL-6, IL-8, and TNF-α. ***$P < 0.001$, compared to control group; $^{\&\&}P < 0.01$, $^{\&\&\&}P < 0.001$, compared to LPS group.

miR-410-3p Serves as a ceRNA of NORAD

The complementary bases between miR-410-3p and NORAD were elucidated in Figure 5A, which showed that miR-410-3p might be a downstream target of NORAD. This relationship was identified by the result of luciferase, that in the group of WT-NORAD, overexpression of miR-410-3p reduced the luciferase activity and silenced miR-410-3p facilitated the activity (Figure 5B, $P < 0.001$). Further analysis found that LPS contributed to the reduced expression of miR-410-3p, while si-NORAD exerted a reversed function on this trend (Figure 5C, $P < 0.001$). Additionally, miR-410-3p was lowly expressed in the NS group compared with the pneumonia group (Figure 5D, $P < 0.001$). Figure 5E provided that the change of miR-410-3p expression was inversely associated with the levels of NORAD in NS newborns ($r = 0.6468$, $P < 0.001$).

Discussion

Uncontrolled inflammatory response and refractory immune dysfunction are the main reasons addressing the progression of sepsis.[16] Pathogen culture is often used to diagnose or evaluate the prognosis of sepsis, but its false positive is high and the diagnostic efficiency is undesirable.[17] It has been found that many kinds of lncRNAs are involved in the regulation of inflammation and the immune process, which can be used in the discrimination of sepsis.[18]

With the development of gene research technology, it has been found that lncRNAs have various functions and play crucial roles in many physiological processes and diseases.[19] LncRNA MALAT1 is highly expressed in sepsis patients and has accuracy in differentiating sepsis patients.[20] In another study published in 2019, lncRNA ZFAS1 is relative to the inflammatory action of sepsis and shows a promising possibility in the diagnosis of sepsis.[21] In our investigation, the expression of NORAD was raised in the NS patients when compared with pneumonia controls, which indicated that NS progression might contribute to the abnormal levels of NORAD. Moreover, aberrant NORAD levels were closely associated with the changes of WBC, CRP, PCT, IL-6, IL-8, and TNF-α, suggesting the alternation of NORAD might be caused by the occurrence of NS. AUC analysis indicated that

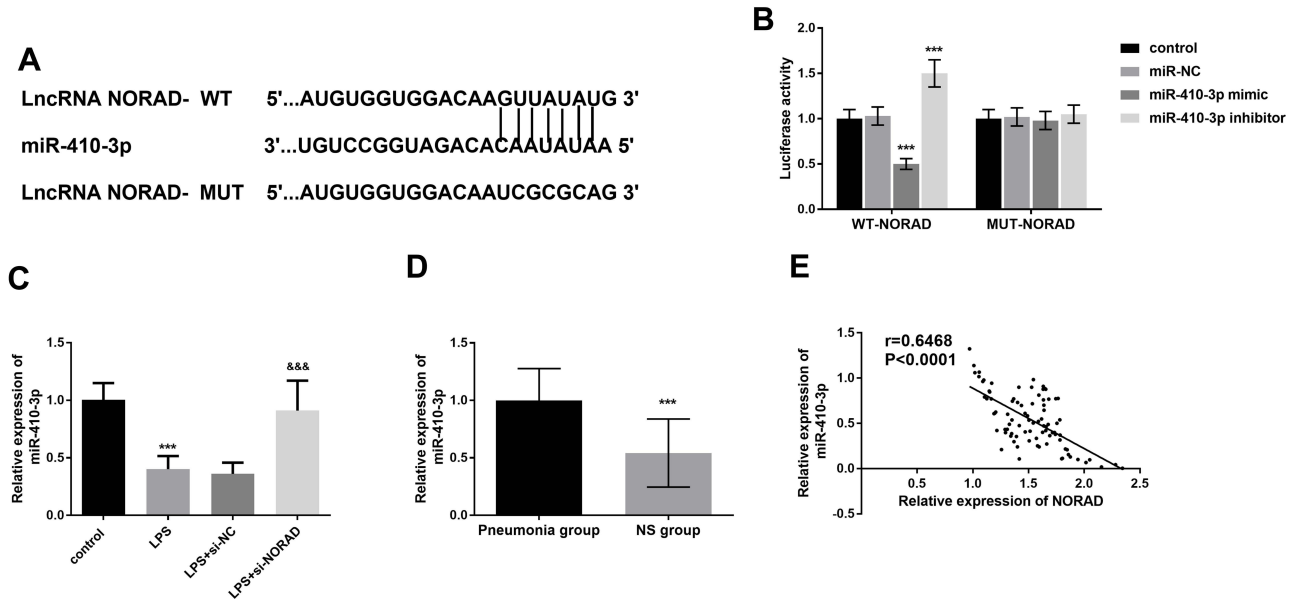

Figure 5 (**A**) The binding bases between miR-410-3p and NORAD. (**B**) The outcome of the luciferase report. (**C**) The reduced expression of miR-410-3p was steered by LPS and downregulation of NORAD inhibited this tendency. (**D**) The expression of miR-410-3p was at a low level in NS patients. (**E**) The analysis result of Pearson correlation. ***$P < 0.001$, compared to control group; $^{\&\&\&}P < 0.001$, compared to LPS group.

NORAD appeared to distinguish NS patients from pneumonia neonates with satisfactory specificity and sensitivity. These findings provided that NORAD might participate in the NS and could predict NS patients efficiently in the management of NS.

Recently, researchers have been paid more and more attention to the function of lncRNAs. Inflammation disorder is the main aspect in NS and lncRNAs play important roles in the process of inflammation.[22,23] For instance, the linkage between lncRNA CRNDE and sepsis is found in a publication, providing that knockdown of CRNDE can inhibit the inflammatory situation in the presence of LPS.[24] Another lncRNA NEAT1 is relative to the inflammatory actions in the LPS-stimulated RAW264.7 cells.[25] In our research, besides the clinical function of NORAD in NS, the impacts of NS on inflammation response were also detected in the LPS-engendered RAW264.7 cells. The present study validated that the expression of NORAD was elevated in the LPS-stimulated cells and the interference of NORAD reversed the increased trend of NORAD expression. Importantly, the LPS management on RAW264.7 cells triggered inflammatory cytokines production, whereas interference of NORAD ameliorated this inflammatory disorder significantly by alleviating the abundant expression of IL-6, IL-8, and TNF-α. In a cell model engendered by high glucose, suppressed NORAD expression inhibits the secretion of pro-inflammatory cytokines, including IL-6.[26] In neuroblastoma cells, NORAD plays a role in the inflammatory condition by sponging miR-204-5p.[27] All these pieces of evidence manifest NORAD expression might participate in NS by mediating inflammatory actions.

CeRNA is an essential segment in the mechanism of lncRNA and miRNA.[28] Our finding showed that miR-410-3p was a probable target of NORAD by the outcome of luciferase activity. And the expression of miR-410-3p was decreased in the LPS-irritated macrophages, whereas the absence of NORAD could reverse the downregulation of miR-410-3p, suggesting the abnormal NORAD expression might regulate the levels of miR-410-3p. The expression and influence of miR-410-3p have been considered by several authors.[29,30] In a previous investigation, the decreased miR-410-3p expression is predictive in the sepsis mice models.[31] Furthermore, our report discovered the levels of miR-410-3p were reduced in the NS group and this trend was reversely associated with the relative expression of NORAD, substantiating NORAD might target miR-410-3p in the regulation of NS development. One of the limitations in our subject was that we did not include healthy patients and compare the expression between healthy controls and NS neonates. Our experiments might provide a theoretical basis concerning NORAD in the exploration and treatment of NS.

Conclusion

Collectively, the abundance of NORAD was confirmed in NS patients and this tendency correlated with several

clinical items concerning NS. In vitro, LPS accelerated the inflammatory response, while silenced NORAD could weaken the enhanced levels of IL-6, IL-8, and TNF-α. What's more, miR-410-3p was proved to be a ceRNA of NORAD and expressed at a high level in NS. The expression of miR-410-3p was regulated by NORAD.

Ethics Statement

All the guardians of participants submitted written informed consent and the design of this study was approved by the Ethics committee of Weifang Maternal and Child Health Hospital.

Disclosure

The authors report no conflicts of interest in this work.

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