Research Article

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lncRNA SNHG6 regulates neuroinflammation in traumatic brain injury by inhibiting the expression of miR-101-3p

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Abstract

Objectives: This study was to investigate the altered expression of SNHG6 in individuals suffering from traumatic brain injury (TBI), as well as the correlation between varying degrees of injury severity and patient's prognosis, and to explore the impact of SNHG6 on oxygen-glucose deprivation (OGD)-induced cell damage.

Methods: A cohort of 121 patients with TBI were included in this study, including 71 mild patients and 50 severe patients. Reverse Transcription-Polymerase Chain Reaction (RT-qPCR) was used to determine the levels of SNHG6 and miR-101–3p. Receiver Operating Characteristic (ROC) curves were used to analyze the role of SNHG6 in distinguishing TBI patients with different degrees and TBI patients with different prognosis. The cell model was constructed by OGD damage, the cell proliferation capacity was detected by Cell Counting Kit-8 (CCK-8) assay, and the concentrations of inflammatory factors in the cells were detected by ELISA kit.

Results: Patients with severe TBI had higher levels of SNHG6 expression than those with mild TBI. And the expression of SNHG6 in patients with poor prognosis was higher than that in patients with good prognosis. SNHG6 could distinguish severe TBI patients from those mild TBI patients and predict the prognosis of patients with TBI. SNHG6 regulated cell proliferation and inflammation after OGD injury by inhibiting the expression of miR-101–3p.

Conclusions: SNHG6 may be a biomarker for TBI, SNHG6 may affect TBI by regulating the expression of miR-101–3p.

Keywords: SNHG6; miR-101–3p; traumatic brain injury; diagnosis; prognosis

Introduction

Traumatic Brain Injury (TBI) originates from a knock, strike, or shaking of the head, or a head-penetrating injury that interrupts the regular brain activity [1]. TBI ranks second in terms of both incidence and fatality rates, following only cancer and cardiovascular conditions, and it is the primary factor contributing to traumatic fatalities [2, 3]. Failure to promptly diagnose and therapy may lead to irrevocable nervous system harm, thereby markedly deteriorating the patient's life quality and hampering their productivity [4]. Presently, the ascertainment of TBI in clinical settings chiefly relies on an integration of the patient's exhibited symptoms and signs, neurological assessments (such as the Glasgow Coma Scale, GCS), neuroimaging assessments, along with pertinent laboratory tests [5]. Nevertheless, the limitations in differential diagnosis persist due to the sensitivity of imaging methods and the non-specificity of diagnostic markers. Accordingly, the discovery of precise and readily accessible biomarkers to direct the diagnostic process, predict outcomes, and inform treatment strategies for individuals with TBI represents a critical medical necessity [6].

Research has further shown that lncRNAs are capable of influencing a multitude of physiological and pathological pathways by means of epigenetic, transcriptional, and post-transcriptional modulations [7]. LncRNAs have been associated with a range of human illnesses, including TBI [8]. The study identified multiple differentially expressed lncRNAs in TBI mice [9]. Investigation of the gene expression profile revealed that the expression of lncRNAs in rats, mice, and humans was altered following TBI. It is proposed that

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lncRNAs could be implicated in numerous pathological and physiological processes that occur following TBI, potentially assuming a pivotal role in the complexities of TBI [10].

One study reported altered lncRNAs in rats after TBI, including the up regulation of lncRNA SNHG6 in TBI rats [11]. The levels of SNHG6 expression in neurons were substantially raised following oxygen-glucose deprivation (OGD) and middle cerebral artery occlusion (MCAO) in mice [12]. Nonetheless, the expression of SNHG6 in individuals with TBI and its relevance to the clinical state of TBI remain elusive.

We systematically identified potential miRNA targets regulated by SNHG6 utilizing established online databases. Among these candidates, miR-101–3p emerged as a particularly noteworthy target warranting further investigation. miR-101–3p is reduced in the cerebral tissue of young mice after transient MCAO, and the elevation of miR-101–3p has the potential to enhance recovery from cerebral infarction, as well as to improve neuronal structure and reduce neuronal apoptosis in these mice [13]. Reduced expression level of miR-101–3p is observed in the blood of individuals suffering from ischemic stroke (IS), and it serves as a promising indicator of neurological rehabilitation in IS patients [14]. However, the binding relationship between SNHG6 and miR-101–3p and their regulatory role in TBI have not been confirmed.

The investigation delved into the altered expression of SNHG6 in individuals suffering from TBI, as well as the correlation between varying degrees of injury severity and patient outcomes. Additionally, this study explored the effect of SNHG6 on OGD-induced cell damage. This research contributed useful insights and direction for assessing the extent of trauma and forecasting recovery in those with TBI.

Materials and methods

Research population

A cohort of 121 patients with TBI who were treated at Guangzhou Panyu District Hexian Memorial Hospital were included in this study. In addition, 110 healthy volunteers who underwent physical examinations in Guangzhou Panyu District Hexian Memorial Hospital were selected as control group. Venous blood was collected from all people, serum was collected after centrifugation and stored at −80 °C.The inclusion of TBI patients met the diagnostic criteria for TBI [15] and were admitted to our hospital within 24 h after injury. In addition, patients with a clear history of cerebral infarction, cerebral hemorrhage, and transient ischemic attacks, major psychiatric disorders (such as schizophrenia) or neurological disorders, and neurodegenerative diseases were excluded. Each participant signed an informed consent form. The Ethics Committee of Guangzhou Panyu District Hexian Memorial Hospital gave its approval for this study (202200694).

Individuals suffering from TBI were evaluated using the GCS score, which provided a measurement of their neurological status. The assessment of their nervous system function was carried out by observing their responses to movement, verbalizations, and eye-opening responses. According to the GCS score, the subjects were divided into a severe group (n=50, 3–8 points) and a mild group (n=71, 9–15 points).

All TBI patients were followed up for 12 weeks. The outcomes of patients were evaluated by Glasgow Outcome Scale (GOS) score and the patients were categorized into two groups: a good prognosis group (n=79, 4–5 points) and a poor prognosis group (n=42, 1–3 points) [16].

In addition, the basic information of the patients included age, gender, BMI, history of hypertension, history of diabetes, body temperature, respiratory rate, heart rate, and time from trauma to admission were recorded (Table 1).

Cell culture and treatment

The BV2 cell line was procured from the Cell Center of the Chinese Academy of Sciences. BV2 cells were maintained in DMEM (Gibco, MA, USA) supplemented with 10 % FBS (Thermo Fisher Scientific, MA, USA). The cells were incubated in an environment containing 5 % carbon dioxide at 37 °C.

Construction of an OGD model

An *in vitro* model of OGD was developed to mimic the activation of BV2 microglial cells. In summary, BV2 cells were subjected to three-time washes with a glucose-free DMEM (Gibco, MA, USA). The cells were then cultivated in DMEM devoid of glucose and placed in an incubator containing 1 % oxygen, 5 % carbon dioxide, and 94 % nitrogen. They were then maintained at a temperature of 37 °C for a duration of 1.5 h. The control group was subjected to cultivation in a same culture medium within an incubator that provided a normal oxygen atmosphere and maintained a 5 % carbon dioxide concentration for the same duration.

Cell transfection

The BV2 cells were transfected with a siRNAs targeting SNHG6 (si-SNHG6), siRNA control (si-NC), a miR-101–3p inhibitor and miRNA control (miR-NC) (GenePharma Co., Ltd,

Table 1: General information of the enroll participants.

Parameters	TBI			p-Value	
	Healthy (n=110)	Mild (n=71)	Severe (n=50)	Healthy vs. mild	Mild vs. severe
Age	46.51 ± 10.75	47.37 ± 11.71	45.82 ± 10.89	0.616	0.463
Gender, female/male	51/59	35/36	24/26	0.790	0.888
BMI, kg/m^2	23.05 ± 1.95	23.35 ± 2.16	22.77 ± 2.54	0.342	0.179
Hypertension, n, %	35,31.82 %	19, 26.76 %	17, 34.00 %	0.468	0.391
Diabetes, n, %	38,34.55 %	22, 30.99 %	14, 28.00 %	0.619	0.724
Body temperature, °C	36.48 ± 1.04	36.50 ± 0.43	36.52 ± 0.40	0.872	0.797
Respiratory rate (breaths/minute)	16.22 ± 2.44	15.80 ± 2.81	16.36 ± 2.50	0.292	0.264
Heart rate (beats/minute)	67.18 ± 4.57	66.51 ± 6.15	65.42 ± 6.13	0.400	0.359
Time from trauma to admission, h	–	1.57 ± 0.52	2.88 ± 0.74	–	<0.001
GCS score	–	12.00 ± 2.15	5.80 ± 1.77	–	<0.001
GOS score	–	4.18 ± 0.87	3.08 ± 1.35	–	<0.001

BMI, body mass index; GCS, glasgow coma scale; GOS, glasgow outcome scale.

Shanghai, China) via Lipofectamine 3000 (Invitrogen, CA, USA).

Extraction of RNA and RT-qPCR

Total RNA was isolated with the TRIzol regent (Invitrogen, CA, USA) and reverse transcribed to cDNA using a reverse transcription kit (Invitrogen, MA, USA). The levels of SNHG6 and miR-101–3p were determined employing RT-qPCR with SYBR Green kit (Invitrogen, MA, USA). qPCR was conducted utilizing the SYBR Green Realtime PCR Master Mix on an ABI 7500 Fast Real-Time PCR System (Toyobo Biologics, Japan). The endogenous controls that were employed were U6 and β-actin. The $2^{-\Delta\Delta Ct}$ technique was used to calculate the results.

Cell Counting Kit-8 assay

CCK-8 kit was utilized to assess the viability of BV2 cells. In brief, 1×10^3 BV2 cells were seeded in a 96-well plate per well. The CCK-8 regent (10 μL) (Do Jindo Laboratories, Japan) was subsequently added to each well, after which the plate was placed in an incubator for a 2-h duration. Thereafter, a microplate reader was employed to measure the optical density at a wavelength of 450 nm.

ELISA assay

The concentration of IL-1β, TNF-α, IL-6, IL-4 and IL-10 in cells were determined using an ELISA kit (R&D Systems, Minneapolis, USA). The experiments were carried out in triplicate sets.

Luciferase reporter assay

StarBase was used to predicte the binding sites between SNHG6 and miR-101–3p online. SNHG6 was cloned into pGLO vector to generate a wild-type SNHG6 reporter vector (wt-SNHG6). A mutant-type SNHG6 reporter vector (mut- SNHG6) was created through site-directed mutagenesis. The wt-SNHG6 or mut-SNHG6 vectors were co-transfected with miR-101–3p mimics or miR-101–3p inhibitor into BV2 cells for 48 h, Then the relative luciferase activity was measured. The Dual Luciferase Reporter Assay Kit (Promega) was utilized for the quantification of luciferase activity.

Statistical analysis

The data analysis was done by employing GraphPad Prism 9.0 and SPSS v.26.0. The data were displayed as mean±SD The one-way ANOVA was utilized for comparing means across multiple groups, and the Student's t-test was used for pair-wise comparisons between two distinct groups. The ROC analysis was conducted to assess the diagnostic value of SNHG6 in TBI, and its prognostic value was estimated using the ROC analysis and Cox regression analysis. The statistically significant difference was indicted by $p<0.05$.

Results

The general information of TBI patients and healthy controls

Age, sex, BMI, history of diabetes, body temperature, respiratory rate, heart rate and history of hypertension did not

significantly differ from one another. GCS, GOS, and trauma to hospital admission scores varied significantly across the three groups (Table 1).

The expression of SNHG6 in patients with TBI

TBI patients had increased SNHG6 expression, and those with severe TBI had greater SNHG6 levels than those with moderate TBI (Figure 1A). Moreover, the levels of SNHG6 in the serum of poor prognosis patients were noticeably higher in comparison to those with a good prognosis (Figure 1B).

Clinical value of SNHG6 in TBI

The AUC of the ROC curve for SNHG6 to distinguish patients with severe TBI from those with mild TBI was 0.849, the sensitivity was 74.0 %, and the specificity was 77.5 % (Figure 2A). Furthermore, SNHG could differentiate between TBI patients with a good prognosis and those with poor prognosis. The AUC of ROC curve reached 0.881, with a sensitivity of 78.6 % and a specificity of 82.3 % (Figure 2B).

Based on their average SNHG6 levels, two groups of TBI patients were created: those with low expression and those with high expression. The level of SNHG6 was significantly correlated with the time from trauma to hospital admission, GCS score, and GOS score (Table 2). In addition, In TBI patients, SNHG6 was a risk factor for a bad outcome (Table 3).

Relationship between miR-101–3p and SNHG6

In TBI patients, the expression of miR-101–3p was downregulated, and the level was lower in severe patients (Figure 3A). In addition, the level of miR-101–3p was negatively correlated with SNHG6 (Figure 3B). Furthermore, miR-101–3p mimic reduced the luciferase activity of wt-SNHG6, while miR-101–3p inhibitor enhanced the luciferase activity of wt-SNHG6 (Figure 3C).

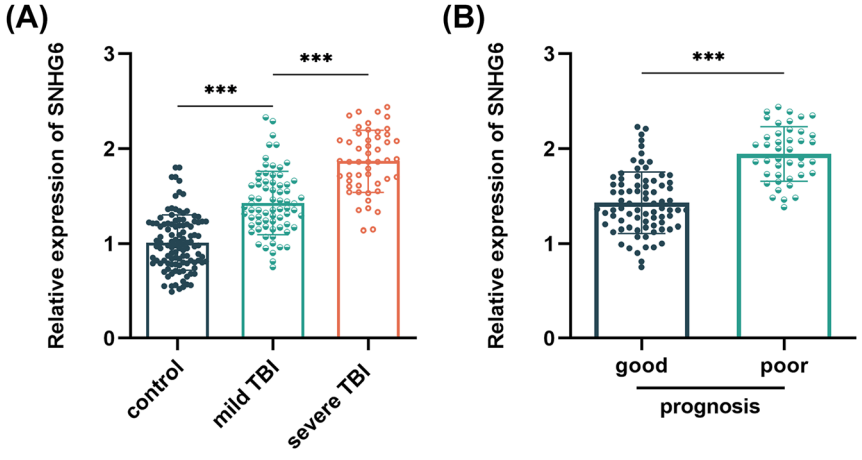

Figure 1: The expression of SNHG6 in patients with TBI. ***p<0.001. Expression of SNHG6 in healthy controls, mild TBI patients, and severe TBI patients (A). Expression of SNHG6 in TBI patients with good and poor prognosis (B).

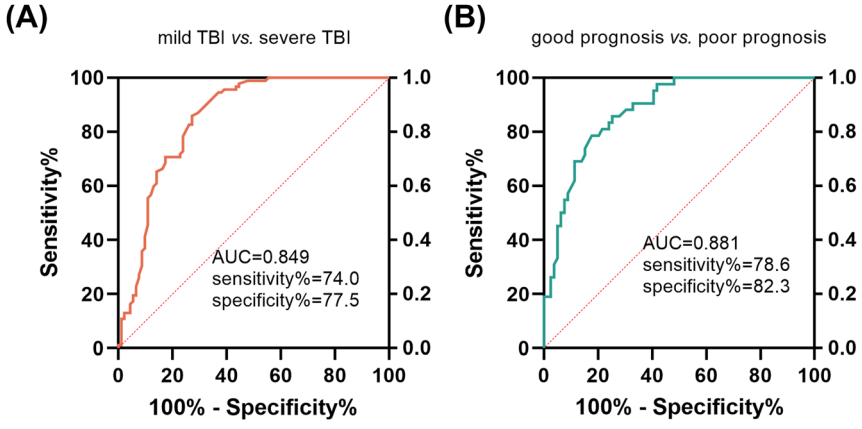

Figure 2: Clinical significance of SNHG6. The ROC curve of SNHG6 differentiates patients with mild TBI from those with severe TBI (A). The ROC curve of SNHG6 distinguishes between good and poor prognosis TBI patients (B).

Table 2: Correlation of SNHG6 with patients' clinicopathological features.

Characteristics	Cases (n=121)	SNHG6 expression		p-Value
		low(n=60)	high(n=61)	
Age, years				0.315
<48	63	34	29	
≥48	58	26	32	
Gender				0.526
Female	62	29	33	
Male	59	31	28	
BMI, kg/m^2				0.315
<22.9	58	26	32	
≥22.9	63	34	29	
History of hypertension				0.735
No	85	43	42	
Yes	36	17	19	
History of diabetes				0.953
No	85	42	43	
Yes	36	18	18	
Body temperature, °C				0.773
<36.5	52	25	27	
≥36.5	69	35	34	
Respiratory rate (breaths/minute)				0.650
<16	60	31	29	
≥16	61	29	32	
Heart rate (beats/minute)				0.527
<66	64	30	34	
≥66	57	30	27	
Time from trauma to admission, h				<0.001
<2.2	69	46	23	
≥2.2	52	14	38	
GCS score				<0.001
<9	50	11	39	
≥9	71	49	22	
GOS score				<0.001
>3	79	55	24	
≤3	42	5	37	

Table 3: Multivariate Cox analysis of clinical characteristics in relation to poor prognosis.

Characteristics	HR	95 %CI	p-Value
SNHG6	8.328	3.161–21.936	<0.001
Age	1.407	0.730–2.712	0.308
Gender	1.381	0.649–2.936	0.402
BMI	1.542	0.760–3.130	0.230
History of hypertension	1.434	0.666–3.087	0.357
History of diabetes	1.429	0.647–3.155	0.377
Body temperature	1.042	0.508–2.136	0.911
Respiratory rate	1.238	0.641–2.389	0.525
Heart rate	0.889	0.471–1.679	0.716
Time from trauma to admission	2.989	1.255–7.120	0.013
GCS score	0.383	0.158–0.931	0.034

BMI, body mass index; GCS, glasgow coma scale.

SNHG6 and miR-101–3p regulated the proliferation and inflammatory response of BV2 cells

The expression of SNHG6 was significantly elevated after the cells were treated with OGD, while miR-101–3p expression was down-regulated in the OGD cell model. Additionally, si-SNHG6 could enhance the expression level of miR-101–3p and miR-101–3p level was inhibited after transfection with miR-101–3p inhibitor (Figure 4A).

After OGD treatment, the proliferation capacity of BV2 cells decreased, and SNHG6 knockdown improved the proliferation capacity of BV2 cells. However, miR-101–3p inhibitor partially offset the enhancement of the proliferation capacity of BV2 cells induced by si-SNHG6 (Figure 4B). Additionally, the concentration of IL-1β, IL-6, and TNF-αin BV2 cells were elevated after OGD treatment, this increase was reversed by inhibiting the expression of SNHG6, transfection of miR-101–3p inhibitor led to a subsequent rise in these cytokines once more (Figure 4C). On the contrary, the concentration of IL-4 and IL-10 in BV2 cells decreased after OGD treatment. Moreover, SNHG6 knockdown upregulated the levels of IL-4 and IL-10, and miR-101–3p inhibitor reversed this upregulation (Figure 4D).

Discussion

Given the profound impact of TBI on patients' quality of life, precise assessment of TBI is critically important for diagnostic, therapeutic, and prognosticative purposes [17]. According to certain research, TBI is associated with aberrant expression of lncRNAs, such as MALATI overexpression improves TBI-induced brain edema [18]. Some studies have also reported lncRNAs as diagnostic or prognostic markers for TBI, such as the level of MEG3 is decreased in TBI patients, serving as a potential biomarker for the detection and management of TBI [19]. Overexpression of AK046375 enhanced the restoration of motor, learning, and memory capabilities in C57BL/6 mice following TBI [20].

Our investigation focused on the expression levels of SNHG6 in both healthy individuals and patients suffering from TBI with varying degrees of severity. We observed that the level of SNHG6 was increased in the serum of those with TBI, this is highly consistent with previous studies [11]. Furthermore, SNHG6 correlated with the time interval from trauma to admission, GCS score, and GOS score, this may imply a strong correlation between SNHG6 and the degree of brain damage as well as the clinical status of the patients. The GCS is a measure used to evaluate consciousness levels

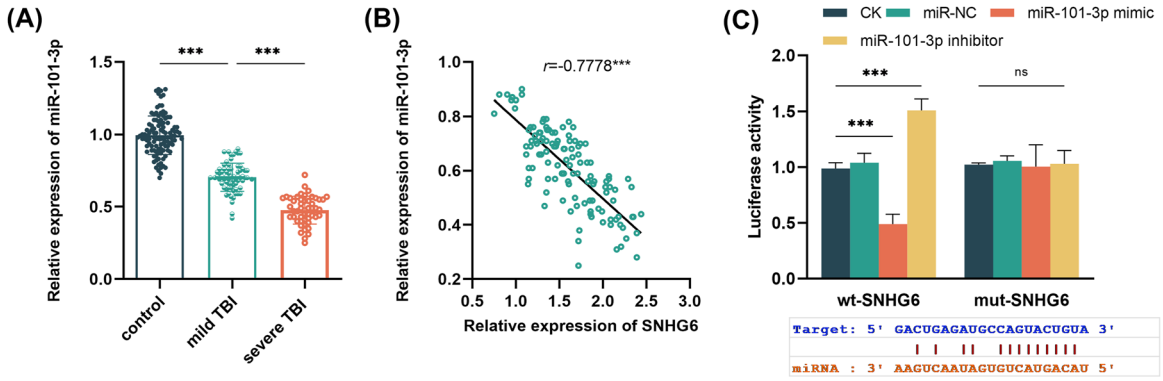

Figure 3: Relationship between miR-101–3p and SNHG6. ***p<0.001. miR-101–3p expression in healthy controls, patients with mild TBI, and patients with severe TBI (A). Correlation between expression levels of SNHG6 and miR-101–3p (B). Dual luciferase reporter gene assay shows the interaction between SNHG6 and miR-101–3p (C).

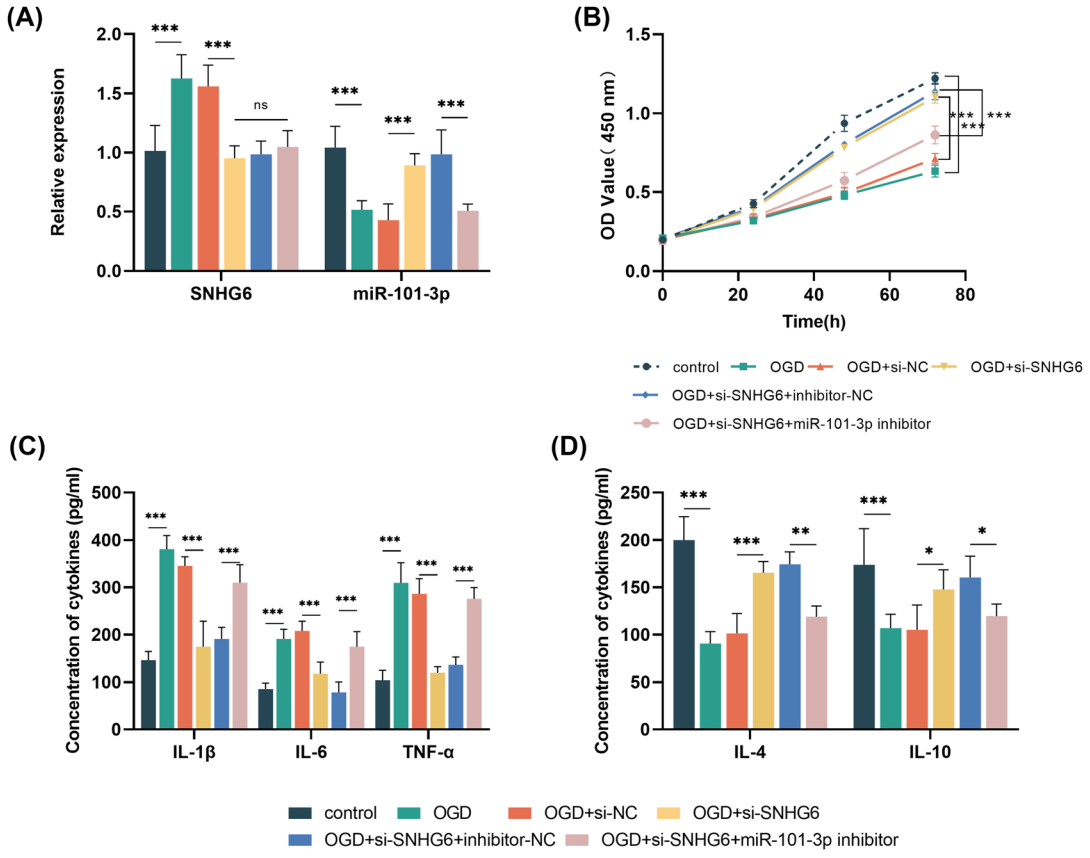

Figure 4: SNHG6 and miR-101–3p regulated the proliferation and inflammatory response of BV2 cells. ***p<0.001, *p<0.05. miR-101–3p inhibitor showed no effect on the expression of SNHG6 but reversed its enhancement by SNHG6 silencing (A). Effect of SNHG6 and miR-101–3p on OGD-induced BV2 cell proliferation (B). Effect of SNHG6 and miR-101–3p on DGR-induced BV2 cell inflammatory response (C–D).

after a brain injury, with lower scores indicating greater disability and more extreme cases of TBI [21]. It has also been reported that GCS score is a prognostic risk factor for severe TBI patients [22]. GOS serves as a reliable tool for the quantitative evaluation of functional recovery following TBI [23]. The study also found significant differences in the time from trauma to hospital admission among with different degrees of TBI patients [5]. SNHG6 was correlated with these key indicators significantly, so we conclude that SNHG6 may be associated with the progression of TBI. Furthermore,

SNHG6 was also shown to distinguish patients with different severities of TBI and predict the prognosis of TBI patients, further confirming our hypothesis. Thus, SNHG6 may be able to serve as a diagnostic and prognostic marker for TBI.

Previous studies have also reported the regulatory role of multiple miRNAs in the progression of TBI. For instance, miR-124 attenuates neuroinflammatory responses following TBI [24]. The suppression of miR-491–5p facilitates angiogenesis, reestablishes cerebral perfusion, and enhances neurological recovery following TBI [25]. These studies showed that miR-101–3p is relevant in the context of brain injury. More importantly, miR-101–3p was downregulated in TBI patients. In order to verify whether SNHG6 regulates miR-101–3p expression, we constructed an OGD model *in vitro* to explore the mutual regulatory relationship between SNHG6 and miR-101–3p in TBI. Through *in vitro* experiments, we also found that inhibiting the expression of SNHG6 could alleviate the decrease of cell proliferation and the increase of inflammatory factors caused by OGD injury, while inhibiting the expression of miR-101–3p could reverse the influence on cell proliferation and inflammatory response.

Inflammatory responses are central to the pathogenesis of secondary brain injury after TBI [26]. Enhanced microglial activation is the main immune cells in the central nervous system and is implicated in the production and secretion of several pro-inflammatory cytokines and chemokines. The released cytokines serve to activate additional inflammatory cells and attract them to the site, thereby intensifying the inflammatory reaction [27]. This study found that SNHG6 may regulate the inflammatory response in TBI by regulating miR-101–3p and thus participate in the disease progression of TBI.

Overall, this study explored the clinical significance of SNHG6 in TBI as well as its role in cells. However, this study still has some limitations, such as the insufficient number of patients included, and more patients as well as more experimental data may be needed to demonstrate the role of SNHG6 in TBI. In addition, SNHG6 may affect the progression of TBI through multiple mechanisms, and SNHG6 may regulate multiple miRNAs, it is of great significance to the integrity of this study to identify more miRNAs regulated by SNHG6. Therefore, whether SNHG6 participates in the regulatory mechanism of TBI by regulating other miRNAs requires further experiments for verification.

Research ethics: This study was approved by the Ethics Committee of Guangzhou Panyu District Hexian Memorial Hospital.

Informed consent: All the participants signed informed consent forms.

Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Changtong Zhao, Jiawei He and Wenhui Huang. The first draft of the manuscript was written by Xizhong Xie and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest: The author states no conflict of interest.

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Data availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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