STEMedicine

RESEARCH ARTICLE

Involvement of microRNA-138-5p in cardiac surgery-induced postoperative cognitive dysfunction

Pavan Bandhu and Kartik Das*

Department of Biotechnology, Utkal University, Vani Vihar, Bhubaneswar, Odisha, India

Abstract

***Background*:** Despite being one of the main concerns in cardiac surgery, the molecular basis and regulatory mechanisms of postoperative cognitive dysfunction (POCD) are still unclear. In this study, we demonstrate the critical role of miR-138-5p in POCD in mice.

***Methods*:** We first established an animal model for POCD caused by cardiac surgery. We then used quantitative reverse transcription polymerase chain reaction to examine the expression levels of miR-138-5p and its target mRNAs. The protein level of sirtuin 1 (SIRT1) was determined using Western blot assays. To assess the mice's recognition abilities, we performed the Morris water maze (MWM) test. Enzyme-linked immunosorbent assays were used to evaluate the expression levels of hippocampal inflammatory cytokines. Finally, we used a luciferase assay to confirm that miR-138-5p directly targeted the mRNA of SIRT1.

***Results*:** MiR-138-5p was upregulated in the hippocampus of mice following cardiac surgery. Inhibiting miR-138-5p reduced the occurrence of POCD and the hippocampus inflammation in the mice. MiR-138-5p targeted the mRNA of SIRT1, thereby suppressing its expression in the hippocampus of mice following cardiac surgery.

***Conclusion*:** Our findings suggest that miR-138-5p contributes to cardiac surgery-induced POCD by directly targeting and suppressing the expression of SIRT1 in the hippocampus.

Keywords: *postoperative cognition dysfunction*; *miR-138-5p*; *cardiac surgery*; *sirtuin 1*; *hippocampus*

Received: 6 February 2023; Revised: 15 February 2023; Accepted: 15 February 2023; Published: 3 April 2023

Postoperative cognitive dysfunction (POCD) is a prevalent syndrome that can be induced by various types of surgery. Its symptoms, such as casual attention distraction, amnesia of varying degrees, deficits in learning and recall, and motor disorders, significantly impact the recovery and long-term health of patients (1–3). Although much research has focused on the predisposing factors and underlying mechanisms of POCD, and potential risk factors such as diabetes and neural trauma have been revealed, the high frequency of POCD in clinical settings (typically 15–56% in the first week after surgery) and its financial burden on society are still driving the need for a more efficient target for the prevention and treatment of POCD (4–6).

Cardiac surgery has been revealed to be one of the crucial contributions to the neural cognitive complications and it is reported that over 20 to 50% of patients undergoing cardiac surgery has been diagnosed with POCD, compared to 5 to 10% with non-cardiac surgery (7, 8). Among all the predisposing factors in cardiac surgery, cerebral thrombosis, shock and inflammation have been considered as most significant etiology underlying POCD (9–11). The cerebral hypoperfusion and anoxia following by these complications frequent in cardiac surgery induce the decline of cerebral oxygen saturation (rScO2) and lead to irreversible damage in amygdala and hippocampus of the patients' cerebrum (12, 13). Besides, hippocampal inflammatory and microglial activation and inflammatory cytokines such as nuclear factor κB (NF-κB) and p38 mitogen activated protein kinase (p38MAPK) have been proved to participated in the regulation of cerebral postsurgical impairment and POCD (14–16).

MicroRNA (miR) is a kind of non-coding RNA which can target and induce the degradation of other mRNAs and thus regulate the expression of certain genes (17).

Citation: STEMedicine 2023, 4(2): e163 - http://dx.doi.org/10.37175/stemedicine.v4i2.163

In recent years, miR-138-5p has been well documented to participate in the progression and regulation of several cancer types including osteosarcoma, breast cancer, pancreatic cancer and the significant mRNA targets of miR-138-5p including FOXC1, RHBDD1 (18, 19). However, the role of miR-138-5p in the occurrence of POCD remains unclear.

Methods

Animals

All experiments and procedures performed on animals in this research were examined and approved by Utkal University. All mice were cultured in the animal facility with a virus/antigen-free ventilation system and an air conditioning system with constant temperature and humidity. The mice had free access to food and water. The procedure of the cardiac surgery was performed as the former research (20). The surgical procedure involved exposing the ventricle and ligating the left coronary artery to simulate ischemia during cardiac surgery.

Novel location and novel object recognition test

Ten days after the cardiac surgery, the mice were subjected to a novel location and object recognition test. The experiment was conducted using a gray box with dimensions of 40 × 40 × 60, which contained two smell-free objects of the same color. The mice were placed in the box for 2 min to explore the location of the objects and then removed. One of the objects was moved, and the mice were re-placed in the box.

For the object recognition test, one object was kept in the same place, while the other was changed to a novel new object. The time that the mice took to explore and identify the difference was recorded.

Quantitative real-time PCR

RNA from the hippocampus of mice with POCD was extracted using TRIzol reagent (Invitrogen Life Technologies, Carlsbad, CA) following the instructions. The reverse transcription was performed using 2 μg of RNA from each sample and Reverse Transcription Kits (Fermentas, St. Leon-Rot, Germany) to generate cDNA. For real-time PCR, 2 μg of cDNA and 0.5 μM of each primer were used to establish a 20 μl system. The mixtures were detected using an S1000 PCR Thermal Cycler.

The primers used in this assay were shown as follows:

SIRT1 sense: 5′-CAGCCGTCTCTGTGTCACAAAC-3′,
antisense: 5′-GCACCGAGGAACTACCTGAT -3′.

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)
sense: 5′-GGCCAGATCCTGTCCAAGC-3′,
antisense: 5′-GTGGGTTTCCACCATTAG CAC-3′,

Western blot assay

Cells were collected after 48 h of incubation, and the protein was extracted from the cell lines using radioimmunoprecipitation assay buffer (ATCC, Manassas, VA). All the samples were mixed with loading buffer and boiled for 10 min to denature the proteins. Proteins were separated using 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis and NC membranes (Invitrogen Life Technologies, Carlsbad, CA) were used for protein transfer. The membranes were then incubated with anti-SIRT1 and anti-GAPDH (Sigma, St. Louis, MO) respectively overnight at 4°C. After washing with phosphate buffered saline with Tween 20, secondary antibodies (Abcam, Shanghai, China) were incubated with the membranes at 37°C for 1 h.

Luciferase assay

The luciferase reporter plasmid used in the assay was pGL-3-basic (Promega, Madison, WI, USA) and the SIRT1 WT/MT luciferase reporters were established based on it. 24-well plates were used for cell seeding and Lipofectamine (Life Technologies, Carlsbad, CA, USA) was used for the transfection of SIRT1WT, SIRT1MT, miR-NC or miR-138-5p and pRL-TK (Addgene, Cambridge, MA, USA). The cells were then collected and examined using the Luciferase Assay Kit (Promega, Madison, WI, USA) 48 h after the transfection.

Morris water maze assay

The mice were divided into three groups with 10 mice per group based on the treatment. The experiment lasted for 5 days, and all mice were trained four times a day for a fixed period of time. During the training, the mice were placed in a pool through four inlet points. The time taken for the mice to enter the water, find the underwater concealed platform, and stand on it was recorded as the incubation period. The mice were allowed to stay on the platform if they found it on their own. If the mice failed to find the platform within 60 s, they were gently pulled onto the platform for 10 s. Each mouse was placed in the pool through a different inlet point with a 30-second interval between training sessions.

On the fifth day, the mice were placed in the water at the same inlet point in each quadrant, and their swimming path was recorded for 120 s. The number of times the mice crossed the target quadrant platform was recorded to evaluate their spatial localization ability.

Enzyme-linked immunosorbent assay (ELISA)

The blood of mice that had undergone cardiac surgery was collected and an ELISA kit (Abcam, Shanghai, China) was used to measure the levels of tumor necrosis factor alpha (TNFα), interleukin-1beta (IL-1β), IL-6, and IL-10 in the blood.

Statistical analysis

All experiments were repeated at least three times, and the data was presented as the mean ± standard deviation (SD). Student's *t*-test, one-way and two-way analysis of variance (ANOVA) followed by a post-hoc test were used to analyze the differences among all the repetitions. Statistical significance was accepted at a *P*-value of less than 0.05.

Results

The alteration of RNA levels in the hippocampus of mice after cardiac surgery

To investigate the impact of the cardiac surgery on the hippocampal region of mice, we performed RNA sequencing to identify alterations in miRNA levels after the surgery. As shown in Fig. 1a, numerous miRNAs were impacted by the cardiac surgery, with miR-138-5p being dramatically upregulated (Fig. 1b). To estimate the expression of SIRT1, quantitative reverse transcription polymerase chain reaction (qRT-PCR) and Western blot assays were performed. Figure 1c–e shows that both the RNA and protein levels of SIRT1 decreased significantly. This figure illustrates the upregulation of miR-138-5p and the downregulation of SIRT1 expression.

Inhibition of miR-138-5p increased the recognition ability after cardiac surgery induced POCD in mice

Since miR-138-5p was upregulated in mice with POCD, we used miR-138 inhibitors to reduce its expression level in the hippocampus of these mice. The novel object and location recognition tests were performed, and as shown in Fig. 2a and b, the recognition ability of the POCD mice significantly increased after treatment with RNA inhibitors, indicating that miR-138-5p may play a role in the progression of POCD following cardiac surgery.

Inhibition of miR-138-5p increased learning ability and memory of POCD mice

To further investigate the role of miR-138-5p in the progression of POCD, a Morris water maze (MWM) test was

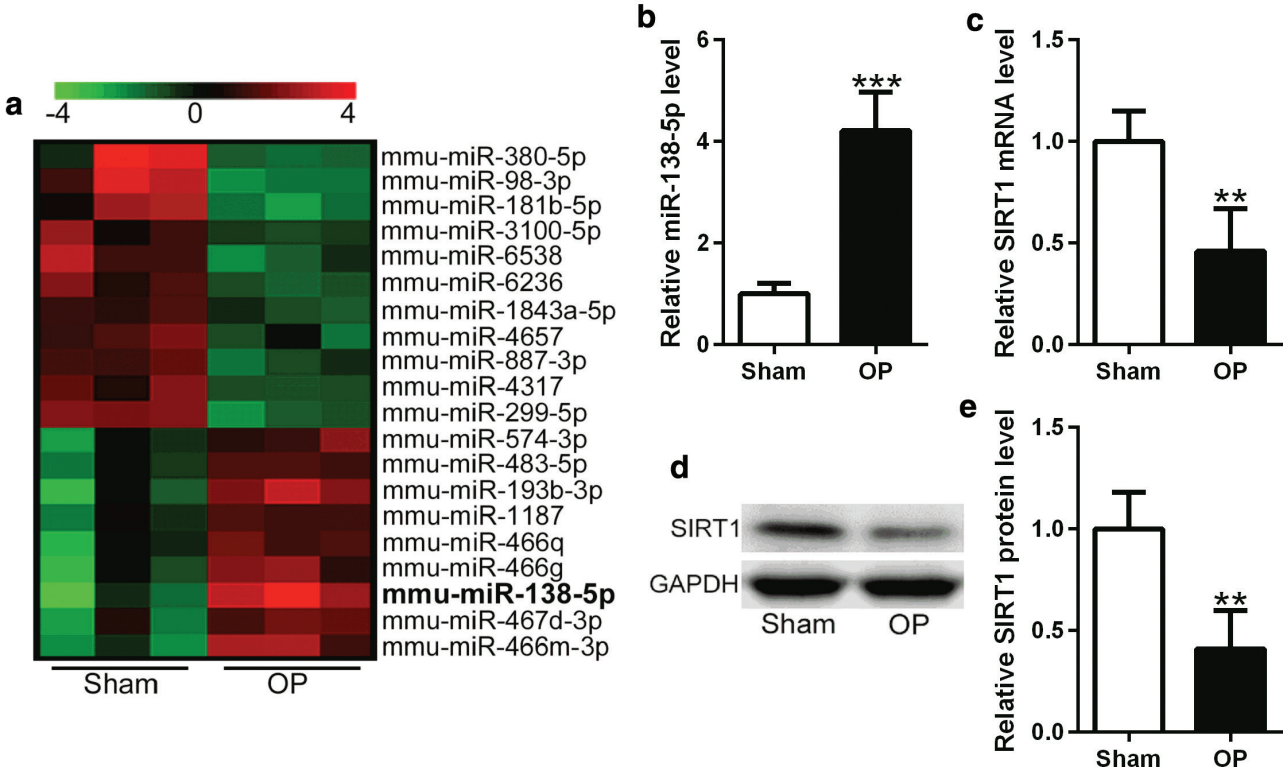

Fig. 1. Effects of cardiac surgery on hippocampal miRNA expression profiles in mice. (a) Heat map for differentially-expressed miRNAs analysis. Each column represents samples and each row represents miRNAs. Red represents upregulated miRNAs and green stands for downregulated miRNAs. The first three columns represent the expression of miRNAs in the Sham group, while the last three columns represent the expression of the corresponding miRNAs expression in the surgery group (OP). (b, c) qRT-PCR was used to measure the expressions of miR-138-5p (b) and SIRT1 mRNA (c) in hippocampus of mice with postoperative cognitive dysfunction (POCD). (d) SIRT1 protein expressions were analyzed by Western blotting. GAPDH was employed as a loading control. Relative expressions were normalized to Sham group (e). Sham: C57BL/6 wild-type mice with sham cardiac surgery; OP: C57BL/6 wild-type mice with cardiac surgery. Data were presented as ± SD. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to sham group.

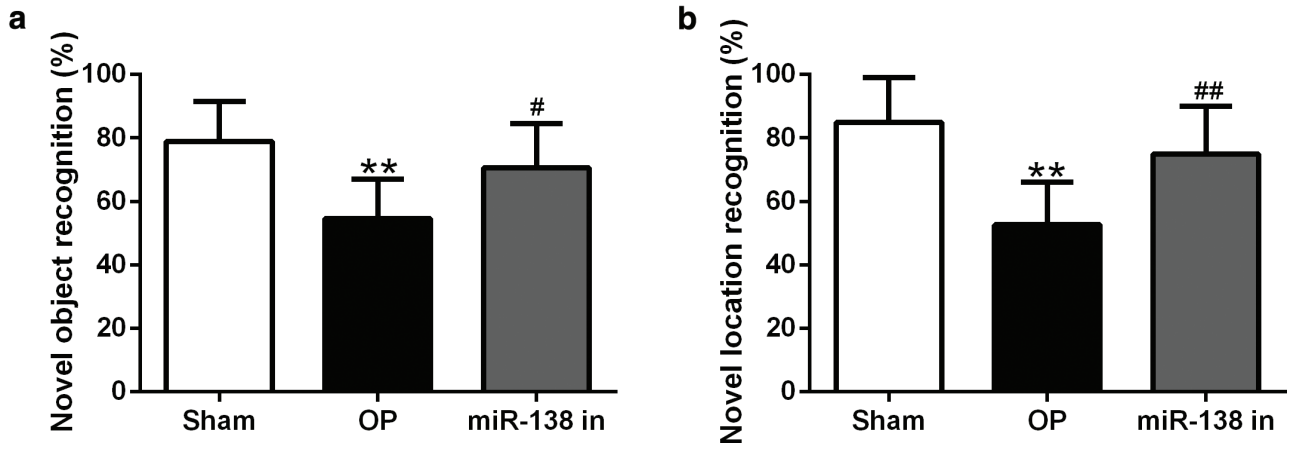

Fig. 2. Inhibition of miR-138-5p increased novel object and novel location recognition after cardiac surgery induced postoperative cognitive dysfunction (POCD) in mice. (a) Novel object recognition in the novel object test. (b) Spatial recognition in the novel location test. Sham: C57BL/6 wild-type mice with sham cardiac surgery; OP: C57BL/6 wild-type mice with cardiac surgery. miR-138 in: C57BL/6 wild-type mice with cardiac surgery treated with miR-138-5p inhibitors. Data were presented as ± SD. $^{**}P < 0.01$ compared to sham group. $\#P < 0.05$, $\#\#P < 0.01$ compared to OP group. $n = 8$ for each group.

performed to evaluate the changes in the learning ability and memory of POCD mice after treatment with a miR-138 inhibitor. As shown in Fig. 3a, the mice in the operation group took the longest time to escape from the maze, indicating that inhibition of miR-138-5p enhances the recovery of the learning ability of POCD mice. In Fig. 3b, the time taken by mice in the miR-138 inhibition group to reach the opposite quadrant was statistically shorter than that taken to reach the target quadrant, indicating that inhibition of miR-138-5p improves the spatial memory of POCD mice. However, the cognitive flexibility of the POCD mice was not affected by the downregulation of miR-138-5p (Fig. 3c and d).

Inhibition of miR-138-5p reduced systemic inflammatory in POCD mice

To demonstrate whether miR-138-5p enhances cognitive dysfunction through hippocampal inflammation, ELISA assays were performed. As shown in Fig. 4a–c, the concentration of plasma pre-inflammatory factors IL-6, IL-10, and TNF-α increased with surgical stimulation. However, the content of IL-6, IL-10, and TNF-α in mouse plasma decreased with the inhibition of miR-138-5p. Similarly, as shown in Fig. 4d–f, the content of IL-6, IL-10, and TNF-α in the hippocampus of POCD mice increased compared to the control groups and the downregulation of miR-138-5p induced a decline of these factors. Mechanically, the inhibition of miR-138-5p induced a decline of IL-6, IL-10, and TNF-α in the hippocampus of POCD mice (Fig. 4g–i). This figure suggests that the inhibition of miR-138-5p reduced inflammation in the hippocampus and thus promoted the recovery of cognitive functions in the POCD mice.

Inhibition of miR-138-5p increased SIRT1 expression in hippocampus of POCD mice

To identify the regulatory network between miR-138-5p and SIRT1, qRT-PCR was performed to assess the changes in the RNA levels of miR-138-5p and SIRT1. As shown in Fig. 5a, the RNA levels of miR-138-5p increased with surgical stimulation and decreased with the treatment of the miR-138 inhibitor. Conversely, the expression of SIRT1 decreased with surgical stimulation but increased with the treatment of the miR-138 inhibitor (Fig. 5b–d).

SIRT1 was a target of miR-138-5p

To determine if miR-138-5p can suppress the expression of SIRT1 by directly targeting its mRNA, we created luciferase reporters with the SIRT1 3′ UTR WT and SIRT1 3′ UTR MUT (Fig. 6a). After transfecting these luciferase reporters and treating with the miR-138 inhibitor, only the fluorescence of the luciferase reporter with the SIRT1 3′ UTR WT was affected by the miR-138 inhibitor, suggesting that miR-138-5p can bind to the 3′ UTR region of SIRT1 mRNA and lead to mRNA degradation (Fig. 6b).

The effects of inhibition of miR-138-5p attenuated cardiac surgery induced POCD were blocked in SIRT1-/- mice

To confirm our previous findings, we used SIRT1-/- mice in this study. As shown in Fig. 7a and b, there was no statistically significant difference in the performance of the novel object and location recognition tests between mice treated with the miR-138 inhibitor and those that were not. Similarly, as shown in Fig. 7c and d, the miR-138 inhibitor did not improve the learning ability and memory of the SIRT1-/- POCD mice. This suggests that

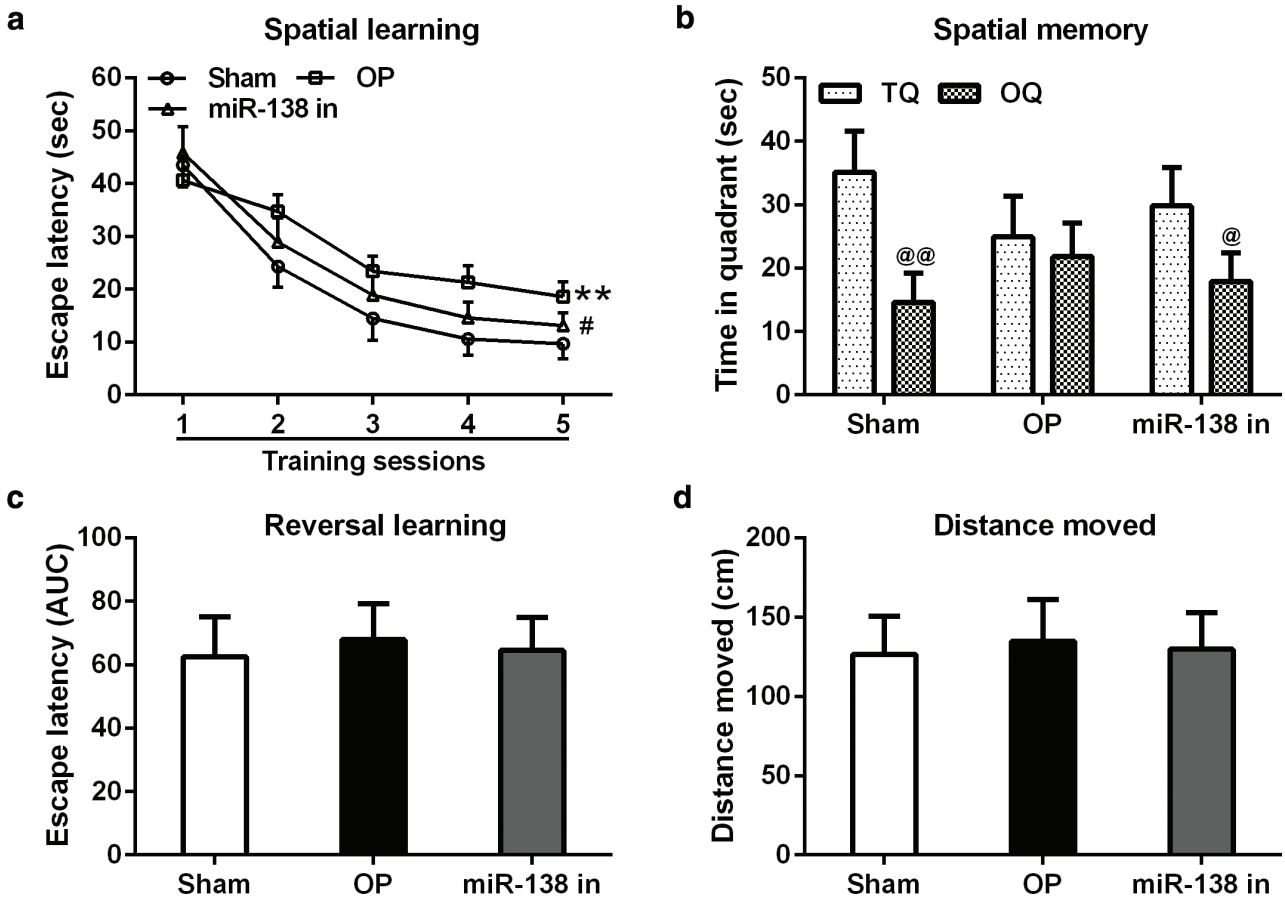

Fig. 3. Inhibition of miR-138-5p increased learning and memory of mice with cardiac surgery in Morris water maze test (MWM). (a) Spatial learning. Average escape latency (sec) is shown for the five training sessions. (b) Spatial memory after a short training period (three training sessions). The time spent in the target quadrant (TQ) and opposing quadrant (OQ) during the probe trial is depicted. (c) Cognitive flexibility. The area under the curve (AUC) for the escape latencies during the two reversal training sessions is shown. (d) Distance moved (m) during the MWM probe trial. Sham: C57BL/6 wild-type mice with sham cardiac surgery; OP: C57BL/6 wild-type mice with cardiac surgery. miR-138 in: C57BL/6 wild-type mice with cardiac surgery treated with miR-138-5p inhibitors. Data were presented as ± SD. $^{**}P < 0.01$ compared to sham group. $\#P < 0.05$, compared to OP group. $@P < 0.05$, $@@P < 0.01$ compared to TQ. $n = 8$ for each group.

miR-138-5p mainly enhances POCD by suppressing the expression of SIRT1.

Discussion

POCD is a well-known complication of surgery that can significantly impact the quality of life of affected patients (21, 22). The occurrence rate of POCD can be as high as 25% in patients over 60 years old within a week after surgery, and its close correlation with increasing rates of long-term disability and mortality makes it a crucial clinical problem that requires resolution (23, 24). Accumulating evidence suggests that the major causes of POCD include cerebral inflammation induced by surgical procedures, glial activation, oxidative stress in the brain, and anesthetic agents, but therapeutic options are limited (25, 26). In clinical practice, drugs commonly used to treat POCD include cyclooxygenase (COX) inhibitors, statins, pregabalin, dexmedetomidine, lidocaine, and ketamine (27, 28). However, very few comprehensive clinical trials have been conducted to thoroughly examine the effects and side effects of these drugs in treating POCD, and research into specific treatments for POCD remains limited. In this study, we first identified the unique role of miR-138-5p in the promotion of POCD. We observed the upregulation of miR-138-5p in the hippocampus of POCD mice and showed that miR-138-5p targeted and suppressed the expression of SIRT1, thus inducing hippocampus inflammation in POCD mice. The miR-138-5p/SIRT1 axis may provide insights into part of the regulatory network of POCD and offer a new target for the prevention and treatment of POCD.

MicroRNAs play a significant role in regulating gene expression through post-transcriptional mediation (29). The alteration in transcription levels of microRNAs has

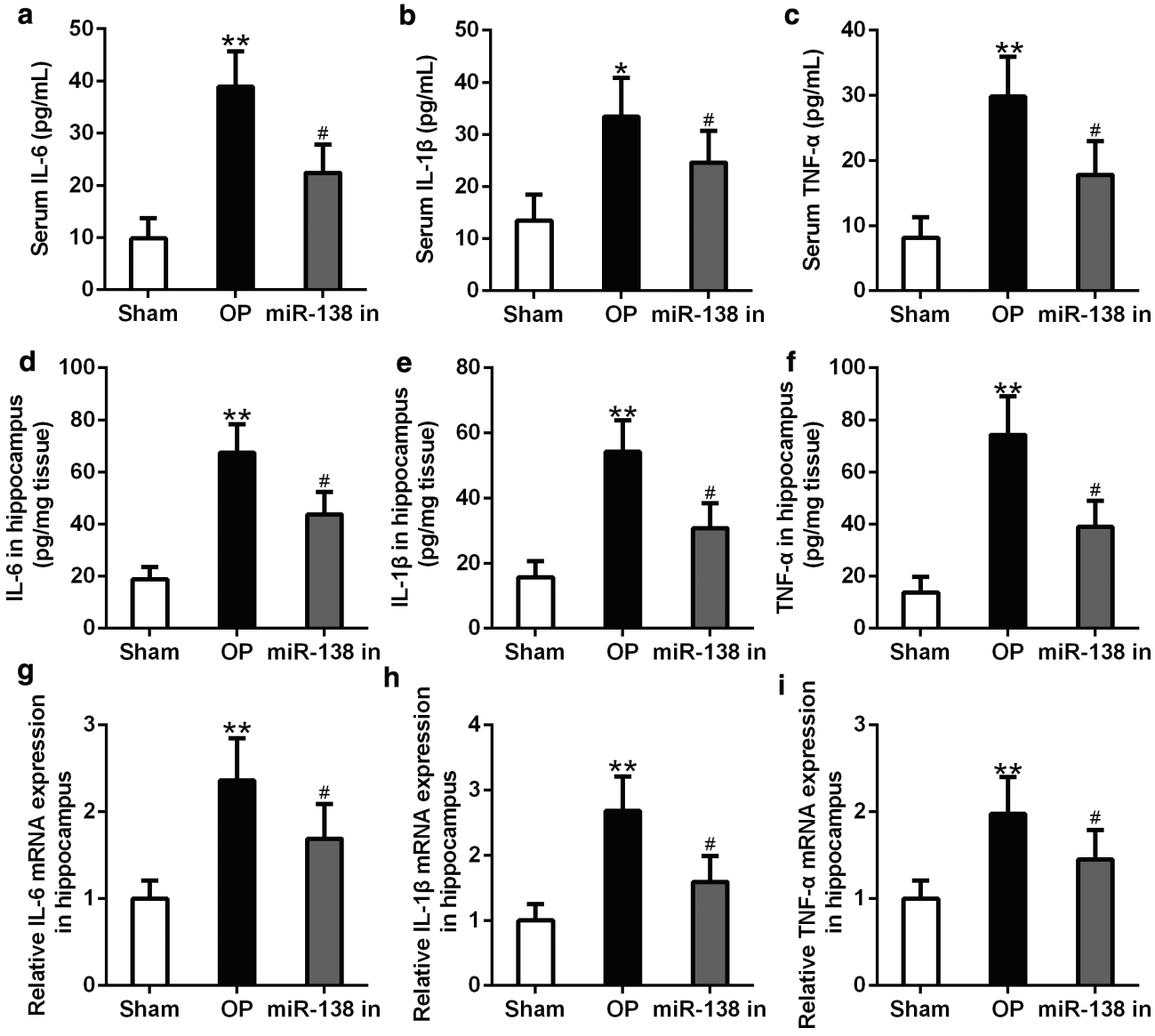

Fig. 4. Inhibition of miR-138-5p reduced systemic inflammatory in cardiac surgery induced postoperative cognitive dysfunction (POCD) mice 24 h after surgery. ELISA was used to analyze the levels of IL-6 (a), IL-1β (b) and TNF-α (c) in serum from indicated mice. ELISA was used to analyze the levels of IL-6 (d), IL-1β (e) and TNF-α (f) in hippocampus from indicated mice. qRT-PCR was used to analyzed the mRNA levels of IL-6 (g), IL-1β (h) and TNF-α (i) in hippocampus from indicated mice. Sham: C57BL/6 wild-type mice with sham cardiac surgery; OP: C57BL/6 wild-type mice with cardiac surgery. miR-138 in: C57BL/6 wild-type mice with cardiac surgery treated with miR-138-5p inhibitors. Data were presented as ± SD. $*P < 0.05$, $**P < 0.01$ compared to sham group. $\#P < 0.05$, compared to OP group. $n = 8$ for each group.

been revealed to be crucial markers for diagnosis and treatment targets in a variety of diseases, particularly cancer (30). In recent years, the regulatory role that microRNAs play in the development and progression of POCD has garnered great attention from the medical community, and various microRNAs have been discovered to be involved in regulating POCD (31, 32). For instance, overexpression of miR-190a has been shown to reduce the symptoms of POCD and improve the learning ability and memory of affected patients by targeting Tiam1 (33). It has also been reported that miR-665 functions as a protector of cerebral neurons by inhibiting glial activation and reducing cognitive dysfunction induced by anesthesia, through targeting the mRNA of chemokine receptor 5 and regulating the PI3K/Akt pathway (34). In addition, miR-181-5p has been shown to relieve the symptoms of POCD by suppressing the inflammatory response in cerebral neurons in mice, which is the opposite of the function of miR-138-5p identified in this study (35). MiR-138-5p has been known as a regulator in several types of tumors for a long time. For example, miR-138-5p has been shown to target the mRNA of PD-L1 and inhibit

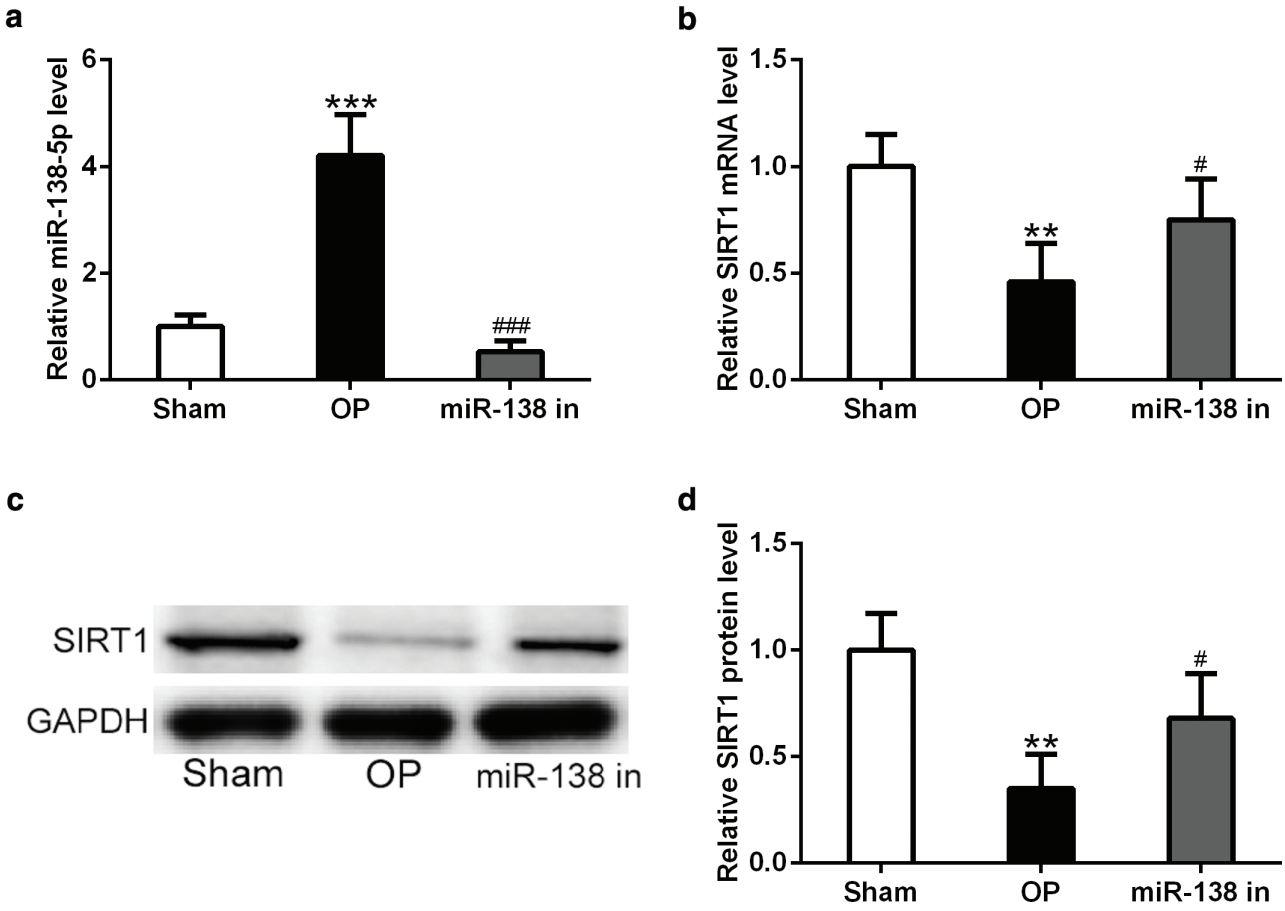

Fig. 5. Inhibition of miR-138-5p increased SIRT1 expression in hippocampus of postoperative cognitive dysfunction (POCD) mice 24 h after surgery. (a, b) qRT-PCR was used to measure the expressions of miR-138-5p (a) and SIRT1 mRNA (b) in hippocampus of indicated mice. (c) SIRT1 protein expressions were analyzed by Western blotting. GAPDH was employed as a loading control. Relative expressions were normalized to Sham group (d). Sham: C57BL/6 wild-type mice with sham cardiac surgery; OP: C57BL/6 wild-type mice with cardiac surgery. miR-138 in: C57BL/6 wild-type mice with cardiac surgery treated with miR-138-5p inhibitors. Data were presented as ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$ compared to sham group. $\#P < 0.05$, $\#\#\#P < 0.001$ compared to OP group. $n = 8$ for each group.

the progression and migration of colorectal cancer cells (36). However, miR-138-5p has also been reported to enhance the progression of cancer, promoting cell viability and proliferation in bladder cancer cells through targeting surviving (37). Interestingly, the direct binding and repression of SIRT1 by miR-138-5p has also been observed in pancreatic cancer cells, where miR-138-5p promotes the progression of pancreatic cancer by suppressing tumor cell autophagy through SIRT1, suggesting that the miR-138-5p/SIRT1 axis may be involved in different physiological processes.

However, our understanding of the relationship between miR-138-5p and POCD is limited. In this research, we showed that miR-138-5p acts as a promoter of the development of POCD. The inhibition of miR-138-5p in mice with POCD resulted in a significant improvement in their learning ability and spatial memory compared to the control group mice. Our findings highlight the critical role of miR-138-5p in the progression of POCD caused by cardiac surgery.

Silent information regulator factor 2-related enzyme 1 (SIRT1) is a type of nicotinamide adenine dinucleotide-dependent deacetylase that belongs to class III histone deacetylases (HDACs) (38). SIRT1 deacetylates histone proteins as well as other transcription factors, thereby regulating various physiological functions in different tissues and cells (39). For example, numerous studies have shown that SIRT1 modulates various signaling pathways, such as the NF-κB pathway, the SIRT1-Foxos pathway, and the SIRT1-PGC-1a pathway, to mediate the metabolic and inflammatory response in cells under ischemic and hypoxic stress (40). SIRT1 is also considered a key regulator of cell senescence and age-related diseases. For instance, recovery of skin tissue integrity after injury and maintenance of homeostasis in granulation tissue require SIRT1 mobilization (41). Additionally, SIRT1 has been linked to brain

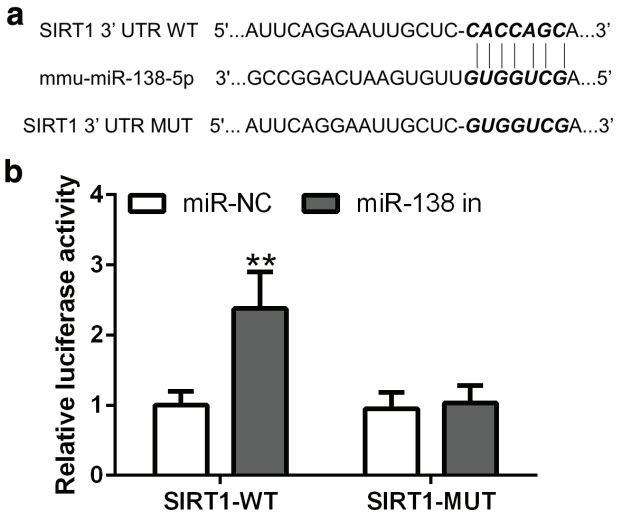

Fig. 6. SIRT1 was a target of miR-138-5p. (a) The target prediction databases, including TargetScan, PicTar and miRanda, were used, and SIRT1 was identified as a target of miR-138-5p. Sequence alignment of the 3′ UTR of SIRT1 shows the complementarity at the 5′ end of miR-138-5p. (b) luciferase reporter system was used by co-transfecting of miR-138-5p inhibitors and SIRT1 3′ -UTR (WT) into 293 cells. The plasmids containing control fragment (miR-NC) or the mutation of SIRT1 3′ -UTR (Mut) were used as controls. Data were presented as ± SD. $^{**}P < 0.01$ compared to miR-NC group.

function and neuronal health, with expression of SIRT1 in the brain modulating axon elongation and repair in cerebral neurons, thus mediating memory formation, motor function, and behavior (42). Due to the close relationship between SIRT1 and neuroinflammation and brain function, the role that SIRT1 plays in regulating POCD has received significant attention. For example, SIRT1 has been shown to regulate neuroinflammation and reduce cognitive dysfunction induced by anesthesia in aged rats (43). Furthermore, overexpression of AMPKa1 alters the AMPK-SIRT1 pathway and enhances POCD (44). Our research has identified that expression of SIRT1 in hippocampal cells of mice with cardiac surgery inhibited the occurrence of POCD. We were able to show for the first time that the mRNA of SIRT1 was a target of miR-138-5p in hippocampal cells of mice, and that expression of SIRT1 was suppressed during POCD. Additionally, we observed alterations in the concentration of pre-inflammatory factors such as IL-6, IL-10, and TNF-α in plasma and hippocampal cells. Consistent with previous studies, upregulation of SIRT1 suppressed cerebral inflammation.

Conclusion

In conclusion, our research revealed, for the first time, a potential molecular and cellular basis for POCD. Surgical

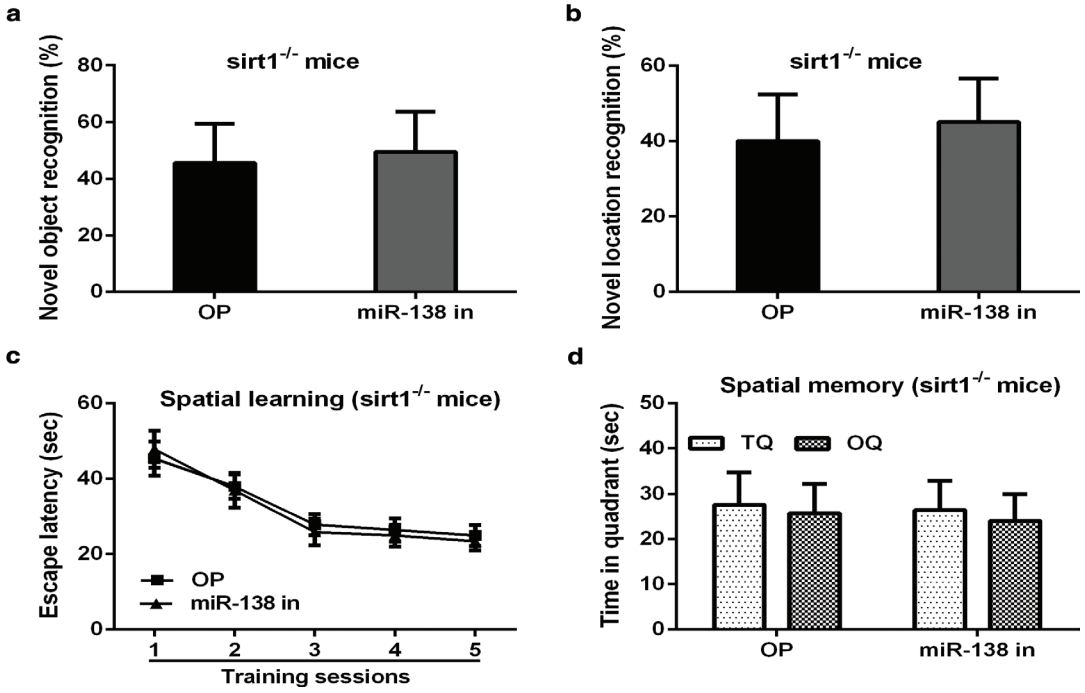

Fig. 7. The effects of inhibition of miR-138-5p attenuated cardiac surgery induced postoperative cognitive dysfunction (POCD) were blocked in sirt1-/- mice. (a) Novel object recognition in the novel object test. (b) Spatial recognition in the novel location test. (c) Spatial learning in the Morris water maze test (MWM). (d) Spatial memory after a short training period (three training sessions). The time spent in the target quadrant (TQ) and opposing quadrant (OQ) during the probe trial is depicted. OP: sirt1-/- mice with cardiac surgery. miR-138 in: sirt1-/- mice with cardiac surgery treated with miR-138-5p inhibitors. Data were presented as ± SD of eight mice in each group. No significant difference between the groups.

factors caused an upregulation of miR-138-5p, which suppressed the expression of SIRT1 in the hippocampal cells of mice and exacerbated the inflammation in the hippocampus, leading to an enhancement of the progression of POCD. This study may provide us with a target for the prevention and treatment of POCD.

Informed consent

Not applicable.

Conflict of interest and funding

The authors have no conflicts of interest to declare. This work was supported by the Department Science Funding.

Data availability statement

Data could be obtained upon request to the corresponding author.

References

1. de Tournay-Jette E, Dupuis G, Bherer L, Deschamps A, Cartier R, Denault A. The relationship between cerebral oxygen saturation changes and postoperative cognitive dysfunction in elderly patients after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2011; 25(1): 95–104. doi: 10.1053/j.jvca.2010.03.019
2. Abbott MW, Gregson RA. Cognitive dysfunction in the prediction of relapse in alcoholics. J Stud Alcohol 1981; 42(3): 230–43. doi: 10.15288/jsa.1981.42.230
3. Grubb NR, Simpson C, Sherwood RA, Abraha HD, Cobbe SM, O'Carroll RE, et al. Prediction of cognitive dysfunction after resuscitation from out-of-hospital cardiac arrest using serum neuron-specific enolase and protein S-100. Heart 2007; 93(10): 1268–73. doi: 10.1136/hrt.2006.091314
4. Hong SW, Shim JK, Choi YS, Kim DH, Chang BC, Kwak YL. Prediction of cognitive dysfunction and patients' outcome following valvular heart surgery and the role of cerebral oximetry. Eur J Cardiothorac Surg 2008; 33(4): 560–5. doi: 10.1016/j.ejcts.2008.01.012
5. Medrzycka-Dabrowska WA, Czyz-Szybenbejl K, Kwiecien-Jagus K, Lewandowska K. Prediction of cognitive dysfunction after resuscitation – a systematic review. Postepy Kardiol Interwencyjnej 2018; 14(3): 225–32. doi: 10.5114/aic.2018.78324
6. Park JH, Park H, Sohn SW, Kim S, Park KW. Memory performance on the story recall test and prediction of cognitive dysfunction progression in mild cognitive impairment and Alzheimer's dementia. Geriatr Gerontol Int 2017; 17(10): 1603–9. doi: 10.1111/ggi.12940
7. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 1991; 41(5): 685–91. doi: 10.1212/WNL.41.5.685
8. Sussman ES, Kellner CP, Mergeche JL, Bruce SS, McDowell MM, Heyer EJ, et al. Radiographic absence of the posterior communicating arteries and the prediction of cognitive dysfunction after carotid endarterectomy. J Neurosurg 2014; 121(3): 593–8. doi: 10.3171/2014.5.JNS131736
9. Salazar JD, Wityk RJ, Grega MA, Borowicz LM, Doty JR, Petrofski JA, et al. Stroke after cardiac surgery: Short- and long-term outcomes. Ann Thorac Surg 2001; 72(4): 1195–201. doi: 10.1016/S0003-4975(01)02929-0
10. Bhamidipati D, Goldhammer JE, Sperling MR, Torjman MC, McCarey MM, Whellan DJ. Cognitive outcomes after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2017; 31(2): 707–18. doi: 10.1053/j.jvca.2016.09.028
11. Hong SW, Shim JK, Choi YS, Kim DH, Chang BC, Kwak YL. Prediction of cognitive dysfunction and patients' outcome following valvular heart surgery and the role of cerebral oximetry. Eur J Cardiothorac Surg 2008; 33(4): 560–5. doi: 10.1016/j.ejcts.2008.01.012
12. Yu Y, Zhang KY, Zhang L, Zong HT, Meng LZ, Han RQ. Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults. Cochrane Database Syst Rev 2018; 1(1): CD010947. doi: 10.1002/14651858.CD010947.pub2
13. Serraino GF, Murphy GJ. Effects of cerebral near-infrared spectroscopy on the outcome of patients undergoing cardiac surgery: a systematic review of randomised trials. BMJ Open 2017; 7(9): e016613. doi: 10.1136/bmjopen-2017-016613
14. Skvarc DR, Berk M, Byrne LK, Dean OM, Dodd S, Lewis M, et al. Post-operative cognitive dysfunction: an exploration of the inflammatory hypothesis and novel therapies. Neurosci Biobehav Rev 2018; 84: 116–33. doi: 10.1016/j.neubiorev.2017.11.011
15. Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of consensus on assessment of neurobehavioral outcomes after cardiac-surgery. Ann Thorac Surg 1995; 59(5): 1289–95. doi: 10.1016/0003-4975(95)00106-U
16. Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP. Neurocognitive function after cardiac surgery from phenotypes to mechanisms. Anesthesiology 2018; 129(4): 829–51. doi: 10.1097/ALN.0000000000002194
17. Ferrante M, Conti GO. Environment and neurodegenerative diseases: an update on miRNA role. Microrna 2017; 6(3): 157–65. doi: 10.2174/2211536606666170811151503
18. Yu C, Wang M, Li ZP, Xiao J, Peng F, Guo XJ, et al. MicroRNA-138-5p regulates pancreatic cancer cell growth through targeting FOXC1. Cell Oncol 2015; 38(3): 173–81. doi: 10.1007/s13402-014-0200-x
19. Zhao C, Ling X, Li X, Hou X, Zhao D. MicroRNA-138-5p inhibits cell migration, invasion and EMT in breast cancer by directly targeting RHBDD1. Breast Cancer 2019; 26(6): 817–25. doi: 10.1007/s12282-019-00989-w
20. Schoemaker RG, Smits JFM. Behavioral-changes following chronic myocardial-infarction in rats. Physiol Behav 1994; 56(3): 585–9. doi: 10.1016/0031-9384(94)90305-0
21. Androsova G, Krause R, Winterer G, Schneider R. Biomarkers of postoperative delirium and cognitive dysfunction. Front Aging Neurosci 2015; 7: 112. doi: 10.3389/fnagi.2015.00112
22. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT, et al. The assessment of postoperative cognitive function. Acta Anaesthesiol Scand 2001; 45(3): 275–89. doi: 10.1034/j.1399-6576.2001.045003275.x
23. Al Hazzouri AZ, Haan MN, Kalbfleisch JD, Galea S, Lisabeth LD, Aiello AE. Life course socioeconomic position and incidence of dementia and cognitive impairment without dementia in older Mexican Americans: results from the Sacramento Area Latino study on aging. Am J Epidemiol 2011; 173: S244. doi: 10.1093/aje/kwq483
24. Ritchie K. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors (vol 341, c3885, 2010). BMJ 2010; 341: c3885. doi: 10.1136/bmj.c3885
25. Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of consensus on assessment of neurobehavioral outcomes after

cardiac surgery. Ann Thorac Surg 1995; 59(5): 1289–95. doi: 10.1016/0003-4975(95)00106-U
26. Patel N, Minhas JS, Chung EM. Risk factors associated with cognitive decline after cardiac surgery: a systematic review. Cardiovasc Psychiatry Neurol 2015; 2015: 370612. doi: 10.1155/2015/370612
27. Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2013; 2013(10): CD004233. doi: 10.1002/14651858.CD010107.pub2
28. Dhanda S, Kaur S, Sandhir R. Preventive effect of N-acetyl-L-cysteine on oxidative stress and cognitive impairment in hepatic encephalopathy following bile duct ligation. Free Radic Biol Med 2013; 56: 204–15. doi: 10.1016/j.freeradbiomed.2012.09.017
29. Mohr AM, Mott JL. Overview of MicroRNA biology. Semin Liver Dis 2015; 35(1): 3–11. doi: 10.1055/s-0034-1397344
30. Acunzo M, Croce CM. MicroRNA in cancer and cachexia – a mini-review. J Infect Dis 2015; 212: S74–7. doi: 10.1093/infdis/jiv197
31. Wei C, Luo T, Zou S, Zhou X, Shen W, Ji X, et al. Differentially expressed lncRNAs and miRNAs with associated ceRNA networks in aged mice with postoperative cognitive dysfunction. Oncotarget 2017; 8(34): 55901–14. doi: 10.18632/oncotarget.18362
32. Wang Y, Huang A, Gan L, Bao Y, Zhu W, Hu Y, et al. Screening of potential genes and transcription factors of postoperative cognitive dysfunction via bioinformatics methods. Med Sci Monit 2018; 24: 503–10. doi: 10.12659/MSM.907445
33. Liu Q, Hou A, Zhang Y, Guo Y, Li J, Yao Y, et al. MiR-190a potentially ameliorates postoperative cognitive dysfunction by regulating Tiam1. BMC Genomics 2019; 20(1): 670. doi: 10.1186/s12864-019-6035-0
34. Lu XH, Lv SG, Mi Y, Wang L, Wang GS. Neuroprotective effect of miR-665 against sevoflurane anesthesia-induced cognitive dysfunction in rats through PI3K/Akt signaling pathway by targeting insulin-like growth factor 2. Am J Transl Res 2017; 9(3): 1344–56.
35. Qu Y, Zhang QD, Cai XB, Li F, Ma ZZ, Xu MY, et al. Exosomes derived from miR-181-5p-modified adipose-derived mesenchymal stem cells prevent liver fibrosis via autophagy activation. J Cell Mol Med 2017; 21(10): 2491–502. doi: 10.1111/jcmm.13170
36. Zhao L, Yu H, Yi S, Peng X, Su P, Xiao Z, et al. The tumor suppressor miR-138-5p targets PD-L1 in colorectal cancer. Oncotarget 2016; 7(29): 45370–84. doi: 10.18632/oncotarget.9659
37. Yang R, Liu MH, Liang HW, Guo SH, Guo X, Yuan M, et al. miR-138-5p contributes to cell proliferation and invasion by targeting Survivin in bladder cancer cells. Mol Cancer 2016; 15: 82. doi: 10.1186/s12943-016-0569-4
38. Kumar S, Kim YR, Vikram A, Naqvi A, Li QX, Kassan M, et al. Sirtuin1-regulated lysine acetylation of p66Shc governs diabetes-induced vascular oxidative stress and endothelial dysfunction. Proc Natl Acad Sci U S A 2017; 114(7): 1714–9. doi: 10.1073/pnas.1614112114
39. Chu HY, Jiang S, Liu QM, Ma YY, Zhu XX, Liang MR, et al. Sirtuin1 protects against systemic sclerosis-related pulmonary fibrosis by decreasing proinflammatory and profibrotic processes. Am J Respir Cell Mol Biol 2018; 58(1): 28–39. doi: 10.1165/rcmb.2016-0192OC
40. Yang H, Bi Y, Xue L, Wang J, Lu Y, Zhang Z, et al. Multifaceted modulation of SIRT1 in cancer and inflammation. Crit Rev Oncog 2015; 20(1–2): 49–64. doi: 10.1615/CritRevOncog.2014012374
41. Qiang L, Sample A, Liu H, Wu X, He YY. Epidermal SIRT1 regulates inflammation, cell migration, and wound healing. Sci Rep 2017; 7(1): 14110. doi: 10.1038/s41598-017-14371-3
42. Herskovits AZ, Guarente L. SIRT1 in neurodevelopment and brain senescence. Neuron 2014; 81(3): 471–83. doi: 10.1016/j.neuron.2014.01.028
43. Yan J, Luo A, Gao J, Tang X, Zhao Y, Zhou B, et al. The role of SIRT1 in neuroinflammation and cognitive dysfunction in aged rats after anesthesia and surgery. Am J Transl Res 2019; 11(3): 1555–68.
44. Yan WJ, Wang DB, Ren DQ, Wang LK, Hu ZY, Ma YB, et al. AMPK1 overexpression improves postoperative cognitive dysfunction in aged rats through AMPK-Sirt1 and autophagy signaling. J Cell Biochem 2019; 120(7): 11633–41. doi: 10.1002/jcb.28443

***Kartik Das**
Department of Biotechnology
Utkal University
Vani Vihar
Bhubaneswar
Odisha 751004
India
Email: Das5525789@outlook.com