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Original Article

Protective effect and mechanism of γ-secretase inhibitor on myocardial injury in sepsis rats

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Abstract: Objective: This study aimed to investigate the mechanism of γ-secretase inhibitor (GSI) in myocardial repair in septic rats. Methods: Thirty-six healthy male Wistar rats were randomly and equally divided into control groups, model group and intervention group. The model group and the intervention group were treated with ligation of cecum and perforation to build sepsis model, and the intervention group received intraperitoneal injection of GSI II (DAPT). Serum levels of Troponin T (cTnT), creatine kinase isoenzyme (CK-MB) and interleukin-17 were measured by ELISA. The Th17 cell percentage in peripheral blood mononuclear cells in $CD4^+$ cells was determined by flow cytometry, and myocardial tissue cells in each group were measured by TUNEL. The mRNA of RORγt was measured by real-time quantitative PCR, and the protein expressions of Notch1, Hes1 and HIF-α in myocardial tissue were measured by Western blot. Results: The cTnT, CK-MB, Th17 and Th17/$CD4^+$ levels in the model group and the intervention group were remarkably higher than those in the control group ($P<0.05$), while those in the intervention group were remarkably lower than those in the model group ($P<0.05$). Myocardial apoptosis rate, myocardial RORγt mRNA and protein expressions of Notch1, Hes1 and HIF-α in the model group and the intervention group were obviously higher than those in control group ($P<0.05$), and those in the intervention group were obvious lower than those in the model group ($P<0.05$). Conclusion: γ secretase inhibitors have clearly protective effects on cardiomyocytes, and the mechanism may be associated with Notch blocking and RORγt expression, which inhibit immune damage induced by abnormal activation of Th17.

Keywords: γ secretase inhibitor, sepsis, myocardial injury, myocardial protection, mechanism

Introduction

Sepsis is a systemic inflammatory response syndrome. It occurs in patients with severe trauma, infection, shock or other pathological conditions, and it is difficult to treat clinically [1]. With the worsening of the disease, patients may have septic shock, multiple organ dysfunction syndrome or death. Patients with myocardial injury have a significantly increased death rate [2]. The activation of systemic inflammatory response, the cascade release of inflammatory mediators and the stress response of the systemic immune system are the pathological features of sepsis and the pathological basis of multiple organ dysfunction syndrome [3, 4]. Studies have illustrated that sepsis can induce immunological reaction of T cells, resulting in an imbalance in the ratio of Th1/Th2 cells, and Th17 also exerts a crucial function in myocardial injury in sepsis [5]. Notch signaling pathway is a ubiquitous signal sequence. It is greatly conserved and can regulate the differentiation and progression of T cells. The γ-secretase inhibitor (GSI) DAPT is a blocker of the Notch pathway [6]. Th17 cells can produce interleukin (IL)-17, and retinoic acid receptor-related orphan nuclear receptor γt (RORγt) is a specific transcription factor of Th17 cells [8]. In this study, we investigated the role of GSI inhibitor DAPT in Th17 cell ratio, RORγt mRNA expression and myocardial injury protection in septic rats.

Materials and methods

Materials and instruments

Thirty-six healthy male Wistar rats with body weight of (220±30) g were procured from the Experimental Animal Center of Guangxi Medical University. The animal license number was

SCXK GUI 2009-0002. GSI II (DAPT) was purchased from Merck Millipore Corporation. cTnT and CK-MB detection kits were purchased from Wuhan Mingde Biological Company. Click-iT™ Plus TUNEL Assay Kits for In Situ Apoptosis Detection, PECF594-CD4 mAb, AF700-CD3 mAb, PE-IL-17 mAb, IL-17 ELISA kits and Trizol reagent were from Invitrogen™, USA. PrimeScript™ II 1st Strand cDNA Synthesis Kits were from Takara Company in Japan. The anti-activated Notch1, anti-Hes1 antibody, anti-HIF-1 alpha antibody, anti-ROR-gamma antibody, Notch1 ELISA kits and HIF-α ELISA kits were from Abcam, USA. Hes1 ELISA kits were from Shanghai Kepeirui Biotechnology Co., Ltd., China, IgG labeled with horseradish peroxidase from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., flow cytometer from BD Company, USA, and microplate reader from Bio-Rad Company, USA. C57BL/6 mice purchased from Shanghai Laboratory Animal Center, Chinese Academy of Sciences.

Experimental grouping

All rats were adaptively fed for 1 week and randomly divided into control group, solvent control group, model group and intervention group, with 8 rats in each group. The rats in the control groups were subjected to sham operation, and the model group and intervention group were subjected to ligation of cecum and perforation to establish a sepsis model. The rats were anesthetized by intraperitoneal injection of pentobarbital sodium 30 mg/kg, and the caecum was separated after laparotomy. Ligation was performed with surgical suture at 1 cm from the end of the cecum, and the needle passed through the ligation 3 times. The intestine was then returned to abdominal cavity, and the incision was closed in layers. The control group and the model group were intraperitoneal injected with 2 ml of normal saline at 0 h and 8 h after modeling. The intervention group was intraperitoneal injected with 2 mg/kg DAPT. The injection volume was based on previous literature [7] and a certain pre-experimental analysis by us. At 0 h and 8 h after modeling, the solvent control group was intraperitoneally injected with the same amount of DMSO as the intervention group. The rats were sacrificed 48 hours after modeling to collect peripheral blood and myocardial tissue.

Determination of cTnT, CK-MB and IL-17 levels in rats

The peripheral blood of the rats was collected 48 h after modeling, and centrifuged at 3000 r/min for 10 min to separate the serum. Then, cTnT, CK-MB and IL-17 levels were tested by ELISA following the kit instruction.

Detection of cardiomyocyte apoptosis

Paraffin sections of myocardium of rats in each group were made 48 hours after modeling, and click-IT™ Plus TUNEL Assay Kits for In Situ Apoptosis Detection were used for detection. TUNEL positive cells were observed under the microscope and counted after staining, then, the apoptosis rate of each group was calculated accordingly.

Detection of Th17 cell proportion in peripheral blood

The peripheral blood mononuclear cells (PBMCs) of rats in each group were collected 48 hours after modeling, and isolated by lymphocyte separation solution. The cells were incubated with PECF594-CD4 mAb, AF700-CD3 mAb and PE-IL-17 mAb respectively, for 30 min at 37°C. Th17 cell percentage in $CD4^+$ cells were measured by flow cytometry after rinsing with phosphate buffer solution.

Detection of myocardial RORγt mRNA

Total RNA from myocardial tissue of each group was extracted using Trizol reagent 48 hours after modeling and reverse transcribed into cDNA. The RORγt mRNA levels of IL-17 related transcription factors were detected by real-time quantitative PCR. The PCR reaction system volume was 20 μl, and 35 rounds were performed. The dissolution curve conditions were 95°C for 10 s and 60°C for 10 s. The target gene was normalized with GAPDH as the internal reference gene, and RORγt mRNA relative expression was expressed by $2^{-\Delta\Delta Ct}$. The primers were synthesized by Shanghai Sangong Bioengineering Co., Ltd. The sequences are as follows. GAPDH: forward 5'-TGTGATGGGTGTGAACCACG-3', reverse 5'-CAGTGAGCTTCCCGTTCACC-3'; RORγt: forward 5'-ACCAGGCATCCTGAACTTGG-3', reverse 5'-CGTGAAAAGAGGTTGGTGCG-3'.

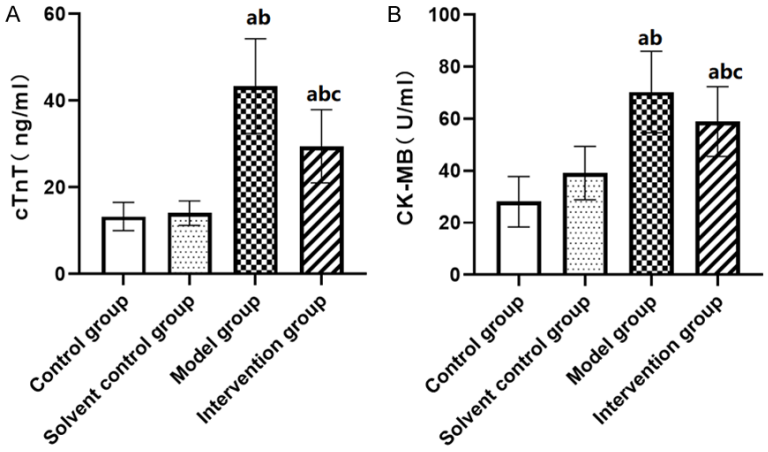

Figure 1. Serum cTnT and CK-MB levels of rats in each group. A: Serum cTnT; B: Serum CK-MB. Compare with the control group, aP<0.05; Compare with the solvent control group, bP<0.05; Compare with the model group, cP<0.05.

Expression of Notch signaling pathway and RORγt protein in myocardial tissue

Notch1, Hes1, HIF-α and RORγt protein expressions were tested by Western blot 48 hours after modeling. The myocardial tissue in each group of rats was homogenized in lysis buffer and centrifuged for 15 min (12000 r/min). Tissue lysates were collected, and total protein was extracted for SDS-polyacrylamide gel electrophoresis. The lysates were transferred to PVDF membranes, blocked with blocking solution, and incubated overnight with Notch1 (1:2000), Hes1 (1:1000), HIF-α (1:1000) antibodies. Then, the lysates were rinsed with TBST for 3 times and incubated with horseradish peroxidase labeled IgG (1:3000) at room temperature for 2 h. The results were developed and observed after rinsing with TBST for 3 times.

ELISA detection of myocardial tissue homogenate

The myocardial tissue of each group was taken 48 h after modeling, and the tissue was cut up with surgical scissors and homogenized with a homogenizer. The supernatant of the tissue was obtained by centrifugation at a speed of 10000 r/min for 5 min. The ELISA detections were performed according to the kit instructions. The absorbance value was measured at a wavelength of 450 nm with the enzyme label, and the expressions of Notch1, Hes1 and HIF-α in the tissue homogenate were detected.

Effects of DAPT on proliferation of Th17 cells

Bone marrow cells were extracted from the femur and tibiofibula of C57BL/6 mice, and their red blood cells were lysed. The cells were cultured in 24-well plates at a density of 1.5×10^6-2.0×10^6/ml per well. The medium contained 20 ng/ml granulocyte-macrophage colony-stimulating factor (mGM-CSF). The unattached cells were removed every day, and fresh medium containing mGM-CSF was added. The adherent cells were collected after 6 days of culture. $CD4^+$ T cells were sorted by flow cytometry. T cells induced Th17 differentiation by 1 ng/ml transforming growth factor-β1 + 20 ng/ml IL-6. The effect of DAPT on the proliferation and division of Th17 cells was detected by flow cytometry.

Statistical calculation

Data analyses were managed by statistical software SPSS 25.0. Measurement data were expressed as $\bar{x} \pm sd$ and compared using analysis of variance and LSD-t test. P<0.05 was considered statistically significant.

Results

Comparison of cTnT and CK-MB levels

The cTnT and CK-MB levels in the model group and the intervention group were remarkably higher than those in the control group and the solvent control group (*P<0.05*), and the levels in the intervention group were apparently lower than those in the model group (*P<0.05*) (**Figure 1**).

Comparison of cardiomyocyte apoptosis

The apoptosis of myocardial cells in the model group and the intervention group were notably higher than that in the control group (*P<0.05*), and the intervention group had remarkably lower apoptosis rate than the model group did (*P<0.05*) (**Figure 2**).

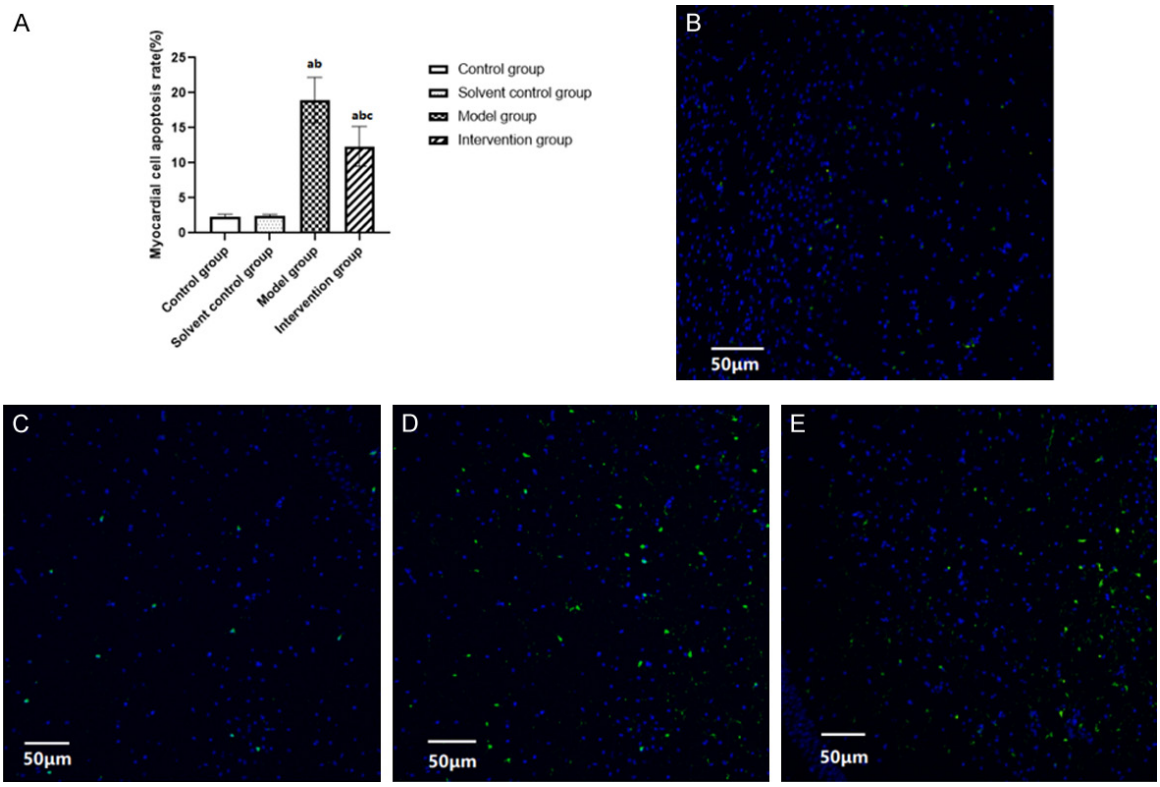

Figure 2. Comparison of myocardial cell apoptosis rates among groups. A: Comparison of apoptosis rates; B: Myocardial cell apoptosis of the control group; C: Myocardial cell apoptosis of the solvent control group; D: Myocardial cell apoptosis of the model group; E: Myocardial cell apoptosis of the intervention group. 400×. Compare with the control group, aP<0.05; Compare with the solvent control group, bP<0.05; Compare with the model group, cP<0.05.

Comparison of Th17 cells proportion

Th17/CD4$^+$ proportion in PBMCs in the model group and the intervention group exceeded that in the control group (*P<0.05*), and the intervention group had apparently lower percentage than the model group did (*P<0.05*) (**Figure 3**).

Comparison of IL-17 level

The model group and the intervention group had higher serum IL-17 level than the control group did (*P<0.05*), and the level in the intervention group was apparently lower than that in the model group (*P<0.05*) (**Figure 4A**).

Comparison of RORγt mRNA in myocardium of rats

Myocardial RORγt mRNA in the model group and the intervention group were obviously higher than that in the control group (*P<0.05*), and the intervention group had significantly lower relative expression than the model group did (*P<0.05*) (**Figure 4B**).

Notch signaling pathway and RORγt protein expressions in myocardial tissue

The relative expression of Notch1, Hes1 and HIF-α proteins in the model group and the intervention group were obviously higher than those in the control group (*P<0.05*), and the intervention group had lower expressions than the model group did (*P<0.05*) (**Figure 5**).

Expressions of Notch signal pathway and its downstream factors in myocardium of rats

The levels of Notch1, Hes1 and HIF-α in the myocardial tissue homogenate in the model group and the intervention group were apparently higher than those in the control group and the solvent control group (*P<0.05*). Also, the levels in the intervention group were significantly lower than those in the model group (*P<0.05*) (**Table 1**).

Effects of DAPT on Th17 cell proliferation and IL-17 secretion in vitro

The addition of DAPT significantly inhibited the proliferation and division of Th17 cells, and

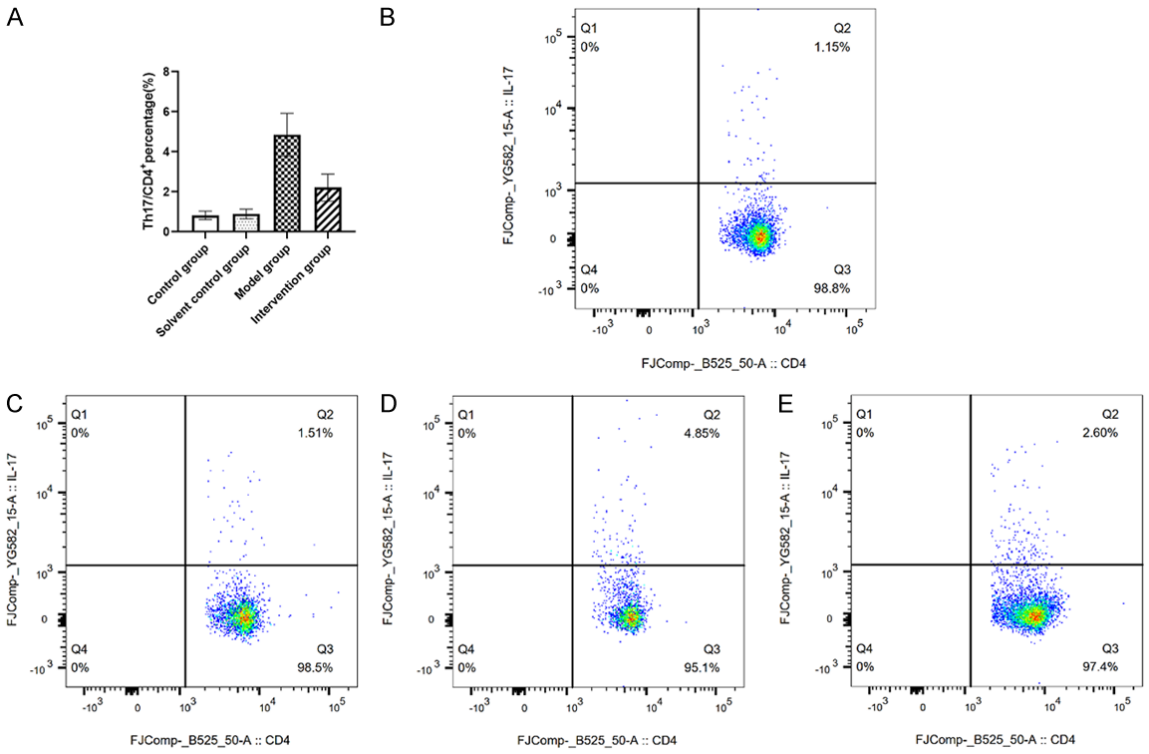

Figure 3. Comparison of the Th17/CD4$^+$ cell percentage among groups. A: Percentage of Th17/CD4$^+$ cells in each group; B: Percentage of Th17/CD4$^+$ cells in the control group; C: Percentage of Th17/CD4$^+$ cells in the solvent control group; D: Percentage of Th17/CD4$^+$ cells in the model group; E: Percentage of Th17/CD4$^+$ cells in the intervention group. Compare with the control group, aP<0.05; Compare with the solvent control group, bP<0.05; Compare with the model group, cP<0.05.

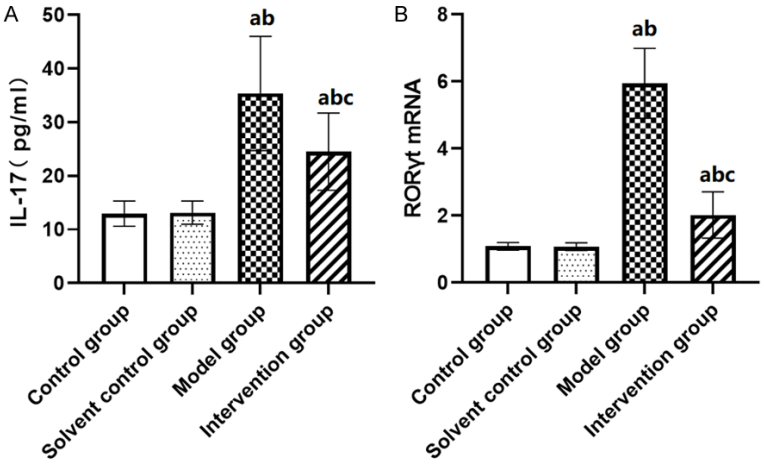

Figure 4. Comparison of Th17 and RORγt mRNA relative expression levels among groups. A: Comparison of Th17 levels; B: Comparison of RORγt mRNA relative expression levels. Compare with the control group, aP<0.05; Compare with the solvent control group, bP<0.05; Compare with the model group, cP<0.05.

meanwhile reduced the secretion level of IL-17 in Th17 cells. See **Figures 6** and **7**.

Discussion

Sepsis is a clinically critical illness caused by infection. It is characterized by the activation of systemic inflammatory response. The massive release of inflammatory factors triggers septic shock and multiple organ dysfunction. The mortality of patients with sepsis is high, while the clinical treatment is difficult. Myocardium is a common organ involving in sepsis. A number of animal studies have confirmed that the apoptosis and inflammatory responses in the myocardium of rats with sepsis are overactivated [9]. Sepsis with myocardial injury is an important cause of sepsis shock and multiple organ failure. In clinical practice, the probability of myo-

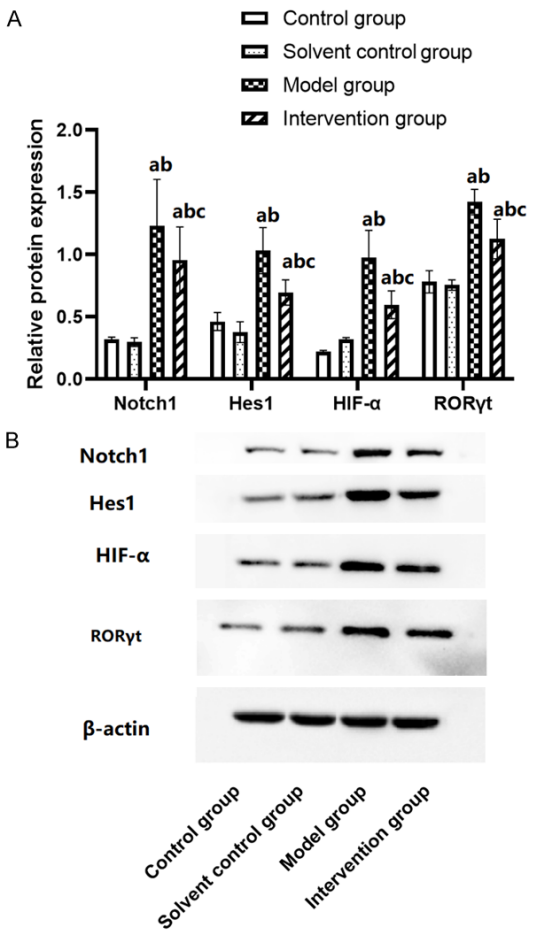

Figure 5. Relative expression levels of Notch signaling pathway-related proteins in myocardial tissues of rats in each group. A: Relative protein expressions; B: Expression of Notch signaling pathway-related proteins. Compare with the control group, aP<0.05; Compare with the solvent control group, bP<0.05; Compare with the model group, cP<0.05.

cardial injury in patients with sepsis is very high, and the lack of specific monitoring indicators leads to an increased mortality [10]. CTnI and CK-MB are molecules specifically expressed in cardiomyocytes. Among them, cTnI is involved in the formation of cytoskeleton, and CK-MB is involved in the catalysis of energy metabolism. Cardiomyocyte injury can lead to the rupture of cardiomyocytes, allowing cTnI and CK-MB in the cytoplasm to enter the blood circulation. Therefore, cTnI and CK-MB can be used as landmark indicators of myocardial injury [11]. In view of this research, cTnT and CK-MB in the model group and the intervention group were obviously higher than those in the control group. This indicates that ligation of the cecum and puncture modeling can lead to myocardial injury, which is consistent with the results of previous studies [13]. Serum cTnT and CK-MB in the intervention group were significantly lower than those in the model group, suggesting that GSI had a great protective effect against myocardial injury in sepsis rats.

Th17 cells, another population of $CD4^+$ T cells, stimulate inflammatory responses and enhance immune responses to extracellular bacteria, fungi, and viral acquired cells by activating the differentiation of specific transcription factor RORγt [14, 15]. RORγt induces immature $CD4^+$ T cells to produce IL-17, thereby regulating Th17 cell differentiation [16]. IL-17 is primarily secreted by Th17. It induces epithelial cells, endothelial cells and fibroblasts to secrete IL-6, IL-8 and PEG2, and promotes the expression of ICAM-1. Studies have shown that in rats with traumatic sepsis, the proportion of Th17 cells increased significantly on the 3rd day after trauma, and began to decline on the 7th day. This suggests that Th17 cells are involved in the inflammatory process of sepsis. In addition, similar changes were observed in the level of RORγt mRNA [17]. In this study, the peripheral blood Th17/$CD4^+$ T cell percentage, IL-17 level and RORγt mRNA expression in the model group and the intervention group were significantly higher than those in the control group. This suggests that Th17 cytokine IL-17 and transcription factor RORγt play an important role and can further aggravate the disease process.

Notch signaling pathway, as a widespread pathway in mammals, is known to play a crucial role in the occurrence, development, pathology and physiological processes of the cardiovascular system, including vascular remodeling, vascular stability and heart development. The Notch signaling pathway determines the maintenance of normal structure and function and the repair of damaged tissues and organs in adult animals. Notch signal may recruit stem cells, promote the formation of new blood vessels and mediate further differentiation of cells. In a mouse model of myocardial infarction, Notch signaling pathway was shown to protect the heart by activating the PI3K/Akt signaling pathway, and to promote the survival and regeneration of damaged cardiomyocytes [18]. In addition, studies have shown that activation of the

Table 1. Expression of Notch signal pathway in myocardial tissue homogenate of rats in each group

Group	Notch1 (ng/ml)	Hes1 (pg/ml)	HIF-α (ng/ml)
Control group	2.38±0.47	36.52±8.39	27.59±5.49
Solvent control group	2.44±0.59	35.94±9.28	28.11±6.44
Model group	5.63±1.25a,b	68.42±7.39a,b	45.63±7.21a,b
Intervention group	4.36±1.22a,b,c	57.44±10.82a,b,c	36.52±8.23a,b,c

Compare with the control group, aP<0.05; Compare with the solvent control group, bP<0.05; Compare with the model group, cP<0.05.

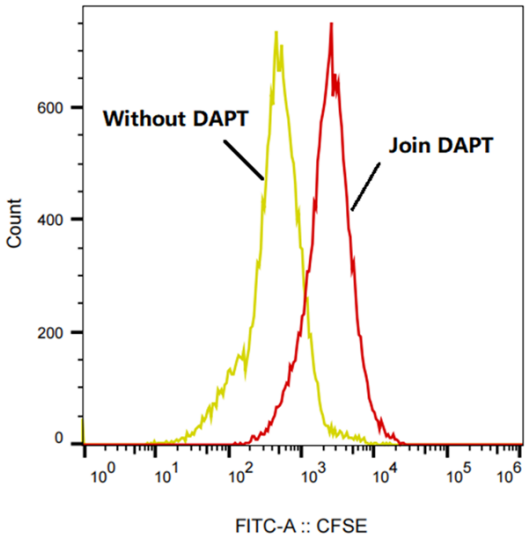

Figure 6. Effect of DAPT on proliferation and division of Th17 cells in vitro. Adding DAPT inhibited the proliferation and division of Th17 cells.

endogenous Notch signaling pathway can improve the cardiac function, reduce myocardial fibrosis and promote angiogenesis in mice with myocardial infarction [19]. Studies have also shown that the reactivity of the Notch signaling pathway can be upregulated in the process of myocardial ischemic reinjury in rats, which may be based on the compensatory protective response of cardiomyocytes [20]. In addition, the Notch signaling pathway is important for the proliferation and differentiation of T cells and the regulation of cell functions. As a blocker of Notch signaling pathway, GSI can therefore regulate the immune response of T cells [21]. Notch is a key signaling pathway that controls the survival and apoptosis of Th17 cells. The Notch pathway directly activates the transcription factor RORγt, which is essential for Th17 cells differentiation. In addition to RORγt, the Notch signaling pathway can also directly regulate the changes of IL-17 in the body, so IL-17 and RORγt can reflect the changing trend of Th17 cells to a certain extent [22-24]. In the process of sepsis, the Notch pathway may participate in inflammation by regulating Th17-related cytokines and transcription factors [25].

The Notch signaling pathway is the transduction pathway of key signals controlling Th17 cell survival and apoptosis mode. Notch directly activates transcription factor RORγt, which is essential for Th17 cell differentiation. In addition, studies have shown that Notch signaling can also directly regulate IL-17 secretion in addition to RORγt [26]. Therefore, IL-17 and RORγt can reflect the changes of Th17 cells to a certain extent. It was found that inhibition of Notch signaling activation resulted in decreased differentiation of Th17 cells when induced in vitro. Th17 cells were also significantly reduced when GSI was used to treat asthmatic mice. This indicates that Notch signaling pathway can affect the occurrence and progression of asthma by regulating the Th17 cell count [27]. Hes1 is a key gene downstream of Notch1 signaling pathway. In inflammatory injury of the body, Hes1 is jointly regulated by upstream signaling pathways and cytokines, which affect the myocardial injury process. In this study, our results showed that compared with the model group, the intervention group had significantly reduced apoptosis rate, Th17/$CD4^+$ T cell percentage, IL-17 level, RORγt mRNA, and protein expressions Notch1, Hes1 and HIF-α. This suggests that GSI can effectively inhibit Notch signaling pathway and its downstream genes, thereby reducing RORγt level and blocking the Th17 immune response induced by sepsis inflammation, thus playing a corresponding protective role in myocardial injury. The above studies provide a new idea for the treatment and prevention of myocardial injury in sepsis [28, 29].

In conclusion, γ secretase inhibitors have obvious protective effects on myocardial cells in

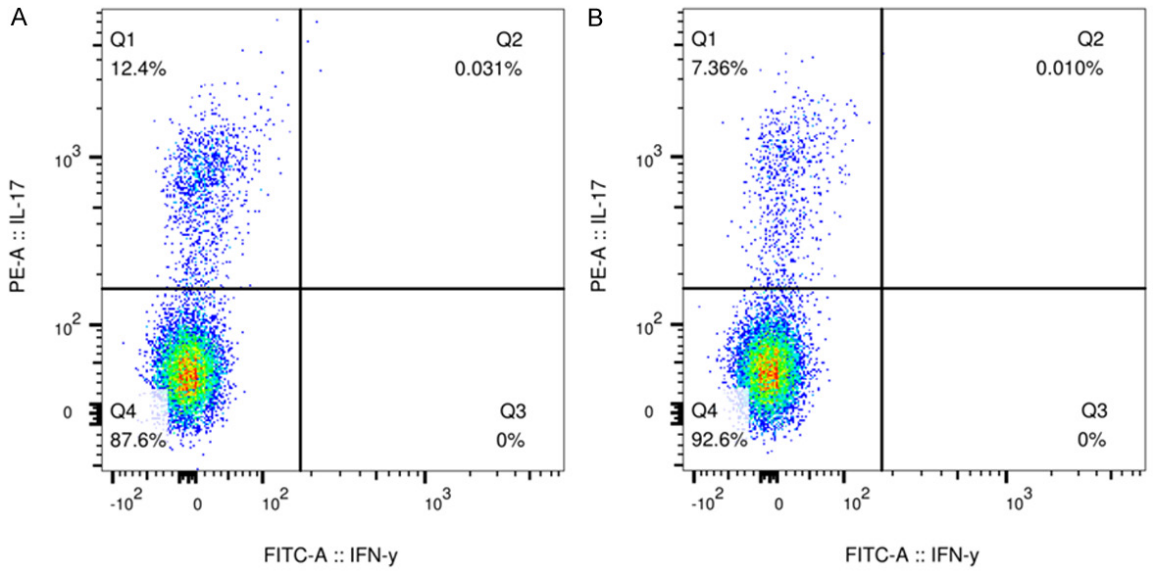

Figure 7. Effect of DAPT on IL-17 secretion in Th17 cells. A: Not in DAPT; B: After adding DAPT, the IL-17 secreted by TH17 cells decreased.

septic rats. The mechanism may be related to Notch blocking and RORγt expression, thus inhibiting the immune damage caused by abnormal activation of Th17.

Disclosure of conflict of interest

None.

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