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Original Article

Influence of interleukin-1 beta gene polymorphisms on the risk of myocardial infarction and ischemic stroke at young age *in vivo* and *in vitro*

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Abstract: In this study, by using vivo and vitro model, we assessed whether interleukin (IL)-1beta gene polymorphisms influence on the risk of myocardial infarction and ischemic stroke at young age. 147 patients (age < 45 years) with a first episode of MI and 56 patients (age < 45 years) with first-ever cerebral ischemia consecutively were admitted to this study from the Department of Chinese PLA General Hospital. Meanwhile, 91 normal volunteers without MI or stroke were deeded as control group and greed to give blood samples for DNA analysis and biochemical measurements by written informed consent. IL-1β-511 wild type (WT, CC) and SNP (TT) were established and transfected into Rat myocardial H9c2 cell and Mouse brain endothelial bEND.3 cells. In Young Age MI or stroke patients, the IL-1β levels of patients with 511CC are higher than that of patients with 511TT. In our study, NF-κB miRNA, iNOS activity, NF-κB, iNOS and Bax protein expressions of MI-induced H9c2 cell or stroke-induced bEND.3 cells in IL-1β-511TT group were lower than those of IL-1β-511CC. Additionally, the protein expression of MMP-2 of MI-induced H9c2 cell or stroke-induced bEND.3 cells in IL-1β-511TT group were higher than that of IL-1β 511CC group. In conclusion, our data indicate that IL-1β-511TT/CC influence on the risk of myocardial infarction and ischemic stroke at young age through NF-κB, iNOS, MMP-2 and Bax.

Keywords: IL-1β gene polymorphisms, IL-1β-511TT/CC, myocardial infarction, ischemic stroke

Introduction

With the gradual rising of morbidity and fatality rate, myocardial infarction (AMI) has already become the first killer of threatening national health seriously [1]. The main cause of death for acute myocardial infarction is acute heart failure. Nowadays, with the improvement of medical level, internal medicine thrombolysis, interventional stent and surgical bypass surgery dramatically decrease the probability for acute myocardial infarction to develop into acute heart rate and then lead to death, and such a disease is developed into the chronic stage with the further development of condition [2]. Chronic stage mainly gives priority to cardiac fibrosis remodeling, which will trigger chronic heart failure and result in death, if fibrosis remodeling is excessive [3]. However, there have been no good methods to prevent and cure cardiac fibrosis remodeling until now.

Stroke is an acute cerebrovascular disease, which is sudden onset, caused by local hemodynamic disorders of brain, and has the common characteristic of focal neurologic deficits, is one of three major diseases of death, due to high morbidity, death rate, disability rate and recurrence rate, ranks the first place in the cause of death for urban residents and second place in the cause of death for rural residents in our country, and is also the first disease of causing disability [4]. Ischemic stroke (IS) occupies 70%-80% of all IS and has high morbidity, critical condition, higher death rate and disability rate, because etiology and pathogenesis haven't been definite completely yet and clinically ideal treatment is limited [5]. At present, clinical treatment on IS mainly can be divided into thrombolytic drug therapy, which has been the only confirmative effective method so far, and drug therapy of neuroprotection [6]. However, only 5% of patients can acquire effective thrombolytic therapy, because of shorter

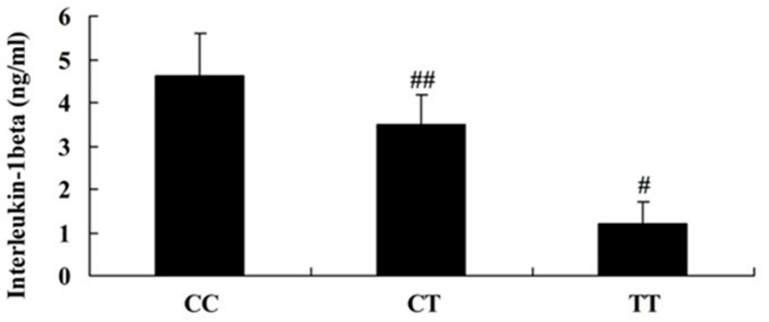

Figure 1. IL-1β-511 WT and SNP and Risk of MI at Young Age. CC, IL-1β-511CC (WT/WT); CT, IL-1β-511 CT (WT/SNP); TT, IL-1β-511 TT (SNP/SNP). ##P < 0.01 compared with CC group; #P < 0.01 compared with CT group.

therapeutic window and higher bleeding risk [7].

Interleukin-1 (IL-1) includes two different subtypes of ligand: IL-1α and IL-1β and can play a role by combining with IL-1 type receptor (IL-1RI) and using G-protein coupling mechanism. The biological activity of IL-1ci and IL-10 currently can't be distinguished, IL-1α displays biological activity in the form of membrane correlation, while IL-1P mainly appears in blood circulation and plays a leading role in cardiovascular system. In addition, human body has natural IL-1 receptor antagonist (IL-Ira) to restrain conduction of IL-1 signal through 1L-1RI of competitive binding.

IL-1 is defined as "the first endogenous pyrogen", because it was originally discovered with function of inducing fever of rabbits and humans [8]. IL-1β has the pro-inflammatory function and its important role in multiple cardiovascular diseases is gradually realized by people with the further study [9]. IL-1β participates in the progress of atherosclerosis, including local lesion formation of atherosclerosis, inflammatory reaction of vascular wall, unbalanced plaque and vulnerable plaque rupture, etc., a series of pathological process [10]. IL-1β takes part in post-inflammatory reaction of myocardial infarction, enhances expression of matrix metalloproteinase, and participates in poor myocardial remodeling [11]. Lots of recent studies show that IL-1β participates in the occurrence and development of heart failure, while IL-1β takes part in inflammatory reaction in the process of heart failure, plays a direct toxic effect on cardiac muscle, promotes apoptosis of cardiac muscle cells, and participates in left ventricle remodel of heart failure [12, 13]. Therefore, in this study, we assessed whether IL-1beta gene polymorphisms influence on the risk of myocardial infarction and ischemic stroke at young age in vivo and in vitro.

Materials and methods

Study population

A total of 147 patients (age < 45 years) with a first episode of MI consecutively were admitted to this study from the Department of Chinese PLA General Hospital. All patients were defined as resting chest pain lasting 30 min accompanied with ST-segment elevation evolving into pathological Q waves. Meanwhile, they also detected total creatinine kinase (CK) or muscle brain fraction levels of more than twice the upper normal limit.

A total of 56 patients (age < 45 years) with first-ever cerebral ischemia consecutively were admitted to this study from the Department of Chinese PLA General Hospital. All patients were defined as a sudden loss of global or focal cerebral function that persisted with a probable vascular cause for 24 h and confirmed by brain CT or MRI. 91 normal volunteers without MI or stroke were deeded as control group and greed to give blood samples for DNA analysis and biochemical measurements by written informed consent.

Cultivation cells

Rat myocardial H9c2 cell and Mouse brain endothelial bEND.3 cells were cultured in Dulbecco's modified Eagle's medium (DMEM, Gibco, Billings, MT, USA) supplemented with 10% (v/v) fetal bovine serum (HyClone-Thermo Scientific, Germany) at 37°C in a humidified atmosphere of 5% (v/v) CO_2. Mouse brain endothelial bEND.3 cells were cultured in DMEM (4500 mg/L glucose, Gibco, Billings, MT, USA) supplemented with 10% (v/v) fetal bovine serum (HyClone-Thermo Scientific, Germany) at 37°C in a humidified atmosphere of 5% (v/v) CO_2.

To induce hypoxia, H9c2 cell was incubated with 1% O_2, 5% CO_2 and 92.5% N_2 for 4 h and serum was deprived as described previously

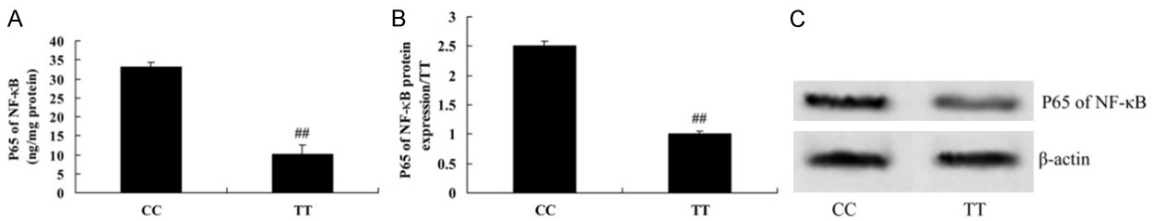

Figure 2. The effect of IL-1β-511 WT and SNP on NF-κB in MI-induced cell. NF-κB activity (A), NF-κB protein expression using Western blotting assays (B) and NF-κB protein expression using Statistical Analysis (C). $^{\#\#}P < 0.01$ compared with CC group.

[14], in which was deeded as MI cell model. bEND. 3 cells were incubated in a hypoxia chamber (Changjin Institute of Applied Technology, China) supplemented with 10% (v/v) fetal bovine serum (HyClone-Thermo Scientific, Germany) at 37°C in a humidified atmosphere of 5% (v/v) CO_2 for 12 h and then incubated under normal conditions at 37°C for another 24 h.

IL-1β-511 wild type (WT, CC) and SNP (TT), transfection

Full lengths of IL-1β-511 SNP (TT) forward and reverse primers were amplified: 5'-ACCAAACCTCTTCGAGGCACAAGGCACA-3' and 5'-TGAAATAAACTTCACTGAAGAAAAAAAAA-3'. Full lengths of IL-1β-511 SNP (TT) forward and reverse primers were amplified: 5'-TATGCATATTCTCTTTCTCTCTCTCTTTCT-3' and 5'-ATACGTATAAGAGAAAGAGAGAGAAAGA-3'. Then, DNA fragments were ligated into plasmid vector pcDNA3.1/IL-1β-511TT and pcDNA3.1-IL-1β-511CC (Invitrogen) to structure pcDNA3.1-IL-1β-511TT and pcDNA3.1-IL-1β-511CC. H9c2 cell and bEND.3 cells were transfected with either pcDNA3.1-IL-1β-511TT and pcDNA3.1-IL-1β-511CC using lipofectamine 2000 (Invitrogen).

Enzyme-linked immunosorbent assay

All cells were collected and lysed in Laemmli sample buffer (Bio-Rad). The homogenates were centrifuged at 4°C at 12,000 g for 15 min, and supernatants were collected and evaluated the levels of IL-1β, p65 of NF-κB and iNOS using ELISA Kits, In accordance with the manufacturer's guidelines.

Western blotting assays

All cells were collected and lysed in Laemmli sample buffer (Bio-Rad). The protein content was determined through the BCA protein assay kit (Thermo Scientific), and then loaded in 10-12% SDS-PAGE gel and separated through electrophoresis, which was followed by transferring them to a PVDF membrane (Roche). The membrane was incubated with primary antibodies: anti-NF-κB (1:2000, Cell signaling, USA), anti-iNOS (1:2000, Cell signaling, USA), anti-MMP-2 (1:3000, Cell signaling, USA), anti-Bax (1:3000, Cell signaling, USA) and β-actin (1:4000, Cell signaling, USA) overnight at 4°C. The membrane was washed and the horseradish peroxidase-conjugated anti-mouse secondary antibodies were incubated for 2 hrs in room temperature and visualized using the enhanced chemiluminescence kit (Thermo Scientific, USA).

Statistical analysis

Data was presented as the mean ± SD and analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL). Comparisons among multiple sets of data were performed using single-factor analysis of variance. $P < 0.05$ was considered to be statistically significant.

Results

IL-1β-511WT and SNP and Risk of MI at young age

As shown in **Figure 1**, the IL-1β levels of young age MI patients carrying 511CC were highest in all patients carrying three genes. Meanwhile, the IL-1β levels of Young Age MI patients with 511TC were higher than that of patients with 511TT (**Figure 1**). These results showed that IL-1β 511TT may inhibit the IL-1β levels in Young Age MI patients.

The effect of IL-1β-511WT and SNP on NF-κB in MI-induced cell

To explore the effect of IL-1β-511 gene polymorphism on NF-κB expression level in MI-induced cell, we established MI-induced

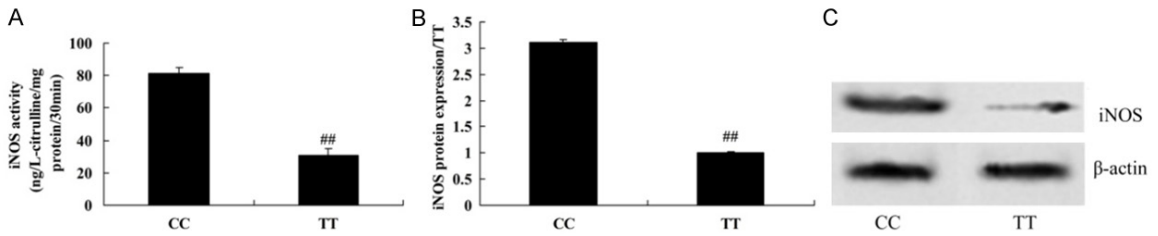

Figure 3. The effect of IL-1β-511 WT and SNP on iNOS in MI-induced cell. iNOS activity (A), iNOS protein expression using Western blotting assays (B) and iNOS protein expression using Statistical Analysis (C). ##P < 0.01 compared with CC group.

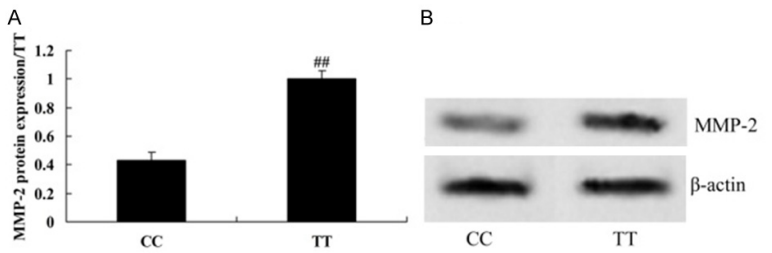

Figure 4. The effect of IL-1β-511 WT and SNP on MMP-2 in MI-induced cell. MMP-2 protein expression using Western blotting assays (A) and iNOS protein expression using Statistical Analysis (B). ##P < 0.01 compared with CC group.

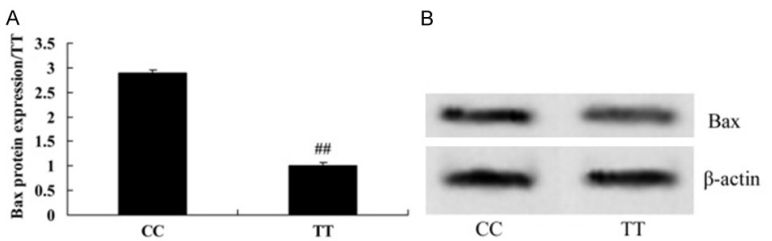

Figure 5. The effect of IL-1β-511 WT and SNP on Bax in MI-induced cell. Bax protein expression using Western blotting assays (A) and Bax protein expression using Statistical Analysis (B). ##P < 0.01 compared with CC group.

H9c2 cell model to study mechanism. We found that IL-1β 511TT memorably suppressed the NF-κB miRNA and protein expression level in MI-induced H9c2 cell, compared with IL-1β 511CC (**Figure 2**).

The effect of IL-1β-511WT and SNP on iNOS in MI-induced cell

We researched that the role of IL-1β-511WT on iNOS in MI-induced cell. As shown in **Figure 3**, the iNOS miRNA and protein expression level of IL-1β 511TT in MI-induced H9c2 cell was lower than that of MI-induced H9c2 cell transfected with IL-1β 511CC.

The effect of IL-1β-511WT and SNP on MMP-2 in MI-induced cell

MMP-2 protein expression in MI-induced H9c2 cell was analyzed for the effect of IL-1β-511WT and SNP on MMP-2 in MI-induced cell. There was a remarkable increase in MMP-2 protein expression of MI-induced H9c2 cell, compared with IL-1β 511CC (**Figure 4**).

The effect of IL-1β-511WT and SNP on Bax in MI-induced cell

Additionally, to investigate the effect of IL-1β-511WT and SNP on Bax in MI-induced cell, Bax protein expression was measured. As shown in **Figure 5**, Bax protein expression of IL-1β 511TT was very lower than that of MI-induced H9c2 cell transfected with IL-1β 511CC.

IL-1β-511WT and SNP and Risk of Ischemic stroke at young age

Figure 6 showed that IL-1β-511WT and SNP had different influence on the ischemic stroke at young age patients. Firstly, in young age patients with ischemic stroke, the IL-1β levels in IL-1β 511CC group were also highest. Next, the IL-1β levels of young age ischemic stroke patients with 511TT were also lowest in all genotypes (**Figure 6**).

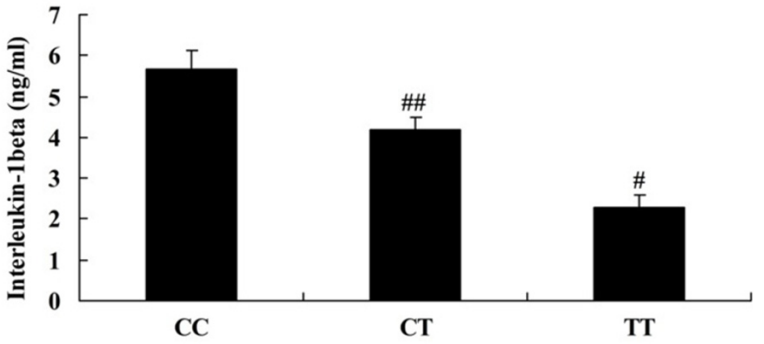

Figure 6. IL-1β-511 WT and SNP and Risk of Ischemic Stroke at Young Age. CC, IL-1β-511CC (WT/WT); CT, IL-1β-511 CT (WT/SNP); TT, IL-1β-511 TT (SNP/SNP). ##P < 0.01 compared with CC group; #P < 0.01 compared with CT group.

The effect of IL-1β-511WT and SNP on NF-κB in stroke-induced cell

After stroke, the effect of IL-1β-511WT and SNP on NF-κB in stroke-induced cell was explored in our study. The activity and protein expression of NF-κB were markedly suppressed in IL-1β-511TT, compared with IL-1β 511CC (**Figure 7**).

The effect of IL-1β-511WT and SNP on iNOS in stroke-induced cell

Furthermore, to explore the effect of IL-1β-511WT and SNP on iNOS in stroke-induced cell, iNOS activity and iNOS protein expression were measured. As shown in **Figure 8**, iNOS activity and iNOS protein expression of stroke-induced bEND.3 cells in IL-1β-511TT group were lower than those of IL-1β-511CC.

The effect of IL-1β-511WT and SNP on MMP-2 in stroke-induced cell

Furthermore, as shown in **Figure 9**, the protein expression of MMP-2 memorably increased in IL-1β-511TT group was observed in stroke-induced bEND.3 cells, compared with IL-1β 511CC.

The effect of IL-1β-511WT and SNP on Bax in stroke-induced cell

Interestingly, when compared with the IL-1β 511CC group, Bax protein expression of stroke-induced bEND.3 cells was markedly diminished in 511TT group (**Figure 10**).

Discussion

MI is caused by myocardial necrosis of a part, because myocardial blood circulation is suspended suddenly and completely [15]. With the gradual rising of morbidity and fatality rate, MI has already become the first killer of threatening national health seriously [15]. The main cause of death for acute myocardial infarction is acute heart failure. Nowadays, with the improvement of medical level, internal medicine thrombolysis, interventional stent and surgical bypass surgery dramatically decrease the probability for acute myocardial infarction to develop into acute heart rate and then lead to death, and such a disease is developed into the chronic stage with the further development of condition [16]. Chronic stage mainly gives priority to cardiac fibrosis remodeling, which will trigger chronic heart failure and result in death, if fibrosis remodeling is excessive [17]. However, there have been no good methods to prevent and cure cardiac fibrosis remodeling until now. We found that the IL-1β levels of Young Age MI or stroke patients with 511TC were higher than that of patients with 511TT.

IS is one of the commonest reasons for death and causing disability of adults in a majority of countries and one of three major diseases with the highest death rate in the world, except for coronary heart disease and cancer [18]. Ischemic stroke occupies 70%-80% of all IS, not only brings psychosomatic destruction to patients, but also causes a white elephant to the society and family [18]. Thus, a major important mission of modern medical field is to carry out prevention and treatment of IS positively. In recent 20 years, domestic and overseas have carried out lots of studies on epidemic disease and preventive control of IS [19]. It is noted that morbidity of IS has the rising trend. The statistical data from ministry of health show that IS ranks the first place and second place in urban male and female causes of death, respectively and ranks the second place and third place in rural male and female causes of death [20]. In recent years, with the

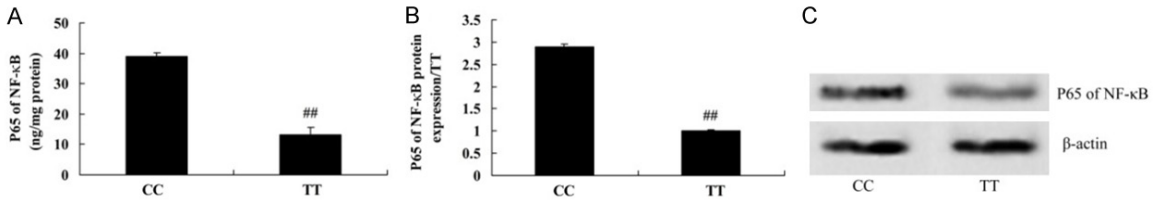

Figure 7. The effect of IL-1β-511 WT and SNP on NF-κB in Stroke-induced cell. NF-κB activity (A), NF-κB protein expression using Western blotting assays (B) and NF-κB protein expression using Statistical Analysis (C). ##P < 0.01 compared with CC group.

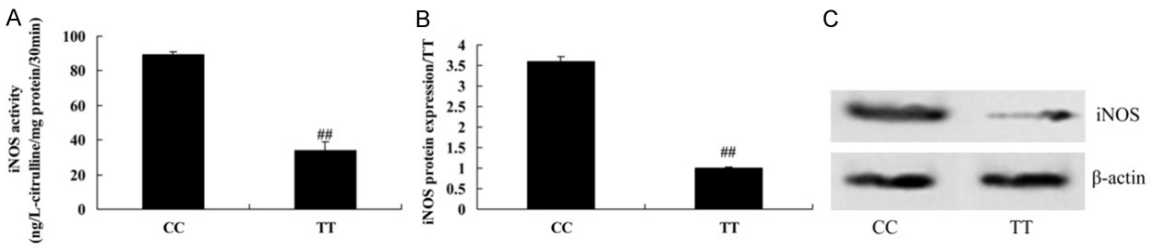

Figure 8. The effect of IL-1β-511 WT and SNP on iNOS in Stroke-induced cell. iNOS activity (A), iNOS protein expression using Western blotting assays (B) and iNOS protein expression using Statistical Analysis (C). ##P < 0.01 compared with CC group.

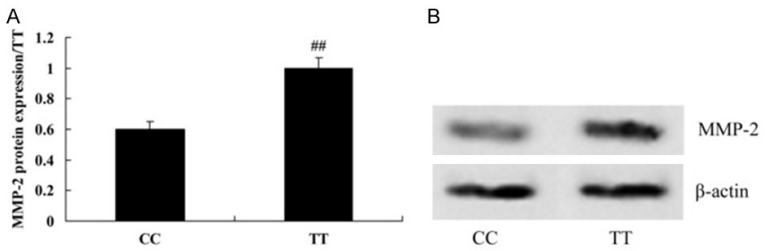

Figure 9. The effect of IL-1β-511 WT and SNP on MMP-2 in Stroke-induced cell. MMP-2 protein expression using Western blotting assays (A) and iNOS protein expression using Statistical Analysis (B). ##P < 0.01 compared with CC group.

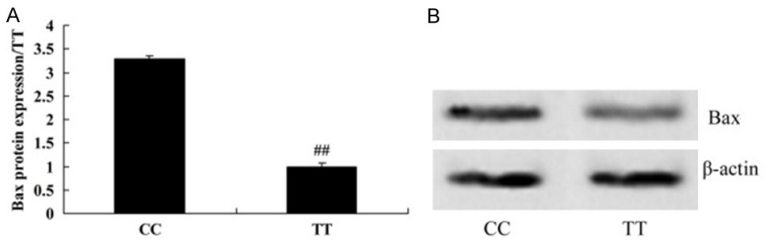

Figure 10. The effect of IL-1β-511 WT and SNP on Bax in Stroke-induced cell. Bax protein expression using Western blotting assays (A) and Bax protein expression using Statistical Analysis (B). ##P < 0.01 compared with CC group.

further study on pathogenesis of IS, an increasing number of scholars have valued the inflammation theory [20]. Many studies mention that inflammation plays an extremely important role on the occurrence, development and prognosis of IS [21]. One of hotspots in the study field is the relation between IS and 1L-1β, because 1L-1β is a multifunctional cell factor with the anti-inflammatory function [22]. In this study, we found that IL-1β 511TT memorably suppressed the NF-κB miRNA and protein expression level in MI-induced H9c2 cell or stroke-induced bEND.3 cells, compared with IL-1β 511CC.

Though existing studies have already observed the acceleration of IL-1β on the ischemic myocardial apoptosis, specific molecular mechanism currently has been poorly understood [23]. IL-1β induces myocardial apoptosis of mice by activating Bax and Bcl-xL, etc., BCL family members of Nitric oxide (NO) mediation.

Inflammatory cytokines-IL-1α and IL-β can develop complicated biological effect by regulating gene expression and behavior of multiple cell types [24]. Multiple inflammatory diseases (including rheumatoid arthritis and inflammatory bowel disease) are induced to generate and activate IL-1RI, trigger multiple phosphorylations successively, and result in nuclear translocation of transcription factors, after tissue damage [25]. Though most of cells have low expression of IL-1RI, IL-1 signal can transmit effectively after amplifying receptors. As the substrate of Mitogen-Activated Protein Kinase (MAPK), serine and threonine residues are activated by IL-1 continuously [26]. Afterwards, protein kinase suffers from phosphorylation, ultimately resulting in rapid phosphorylation of IkB, and finally transcription factors have nuclear transition [27]. In our study, iNOS activity, iNOS and Bax protein expressions of MI-induced H9c2 cell or stroke-induced bEND.3 cells in IL-1β-511TT group were lower than those of IL-1β-511CC. Meanwhile, the protein expression of MMP-2 memorably increased in IL-1β-511TT group was observed in MI-induced H9c2 cell or stroke-induced bEND.3 cells, compared with IL-1β 511CC.

IL-1β enhances the ability of Dermal Microvascular Endothelial Cells to form tubular structure, increases P-2 expression of cardiac microvascular endothelial cells, and promotes substrate degradation directly [28]. In addition, IL-1β stimulates cardiac microvascular vascular endothelial growth factors [29]. Collectively, these data clearly indicate that IL-1β-511TT/CC influence on the risk of myocardial infarction and ischemic stroke at young age through NF-κB, iNOS, MMP-2 and Bax.

Acknowledgements

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Disclosure of conflict of interest

None.

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