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Effects of Uric Acid on Myocardial Fibrosis

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Abstract: Background. Myocardial fibrosis is a serious complication and outcome of long time ischemia and necrosis of heart. The deposition of collagen fibers is the pathological basis. Inflammatory cytokines participate in and promote the process of myocardial fibrosis. The effect of uric acid on cardiovascular disease has been confirmed. However, the effect of uric acid on myocardial fibrosis and cardiac fibroblasts is not well understood. This study aimed to explore the effect of uric acid on collagen synthesis and inflammatory response in cardiac fibroblasts. Methods. The cardiac fibroblasts of neonatal rats were isolated and cultured and divided into a normal control group and groups of different concentration of uric acid intervention (200, 400, 600, 800μmol/L). MTT assay was performed to measure the proliferation of cardiac fibroblasts. The content of collagen was detected by hydroxyproline kit. The secretions of IL-6, IL-1 β and TNF- α were detected by ELISA. And Real-time quantitative PCR was used to analyze the mRNA levels of IL-6, IL-1 β, TNF- α, Col- Ⅰ,Col-Ⅲ, respectively. Results. Compared with the normal control group, the cell proliferation and collagen secretion of cardiac fibroblasts were increased in groups of high concentration uric acid. Uric acid also promoted the release of IL-6, IL-1β and TNF-α in cardiac fibroblasts. Besides, Uric acid treatment significantly enhanced the mRNA expression of IL-6, IL-1 β, TNF- α, Col- Ⅰ, Col-Ⅲ, compared with the control group. Conclusion. These results suggest that uric acid could promote collagen synthesis and inflammatory response in cardiac fibroblasts.

Keywords: Cardiac fibroblasts; Uric acid; Collagen; Inflammatory cytokine.

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1. INTRODUCTION

Heart failure is the ultimate destination of many cardiovascular diseases. Cardiac remodeling and inflammation are the key pathological symbols in the development of heart failure. Myocardial fibrosis is the crucial cause of ventricular remodeling, and it is also a common pathological change in the development of various heart diseases to a certain stage (1, 2). Effective prevention and treatment of myocardial fibrosis has great clinical significance in reducing the mortality of cardiovascular disease and improving the quality of life of patients

with heart disease (3). Cardiac fibroblasts are the most numerous cells in the heart, and their main function is to regulate extracellular matrix (ECM) homeostasis. When the heart suffers damage, of which the cause may be ischemia, hypoxia, physical and chemical stimulation, cardiac fibroblasts get activated and proliferate rapidly, secrete inflammatory cytokines and synthesize collagen, which are the main pathological processes of myocardial fibrosis (4, 5).

Hyperuricemia is a high level of plasma uric acid caused by abnormal purine metabolism and abnormal excretion of uric acid in the body. With the improvement of people's living standard, the change of dietary structure and the aging of population, the prevalence of hyperuricemia is increasing year by year (6). A large number of epidemiological studies suggest that hyperuricemia is an independent risk factor for cardiovascular disease and is closely related to the occurrence and development of cardiovascular diseases (7). Hyperuricemia often occurs in patients with chronic heart failure, and is associated with the severity of heart failure (8). Recent studies revealed that elevated plasma uric acid level can increase the risk of heart failure and poor prognosis, and is strongly associated with ventricular remodeling (9). In recent years, the study of uric acid's effect on cardiovascular disease is mainly focused on the damage of cardiomyocyte (10, 11), little has been done to find out the effect of uric acid on myocardial fibrosis and cardiac fibroblasts.

In this study, we investigated the effects of uric acid on the secretion of inflammatory cytokines and collagen synthesis in cardiac fibroblasts. Our results show that uric acid can promote the release of IL-6, IL-1β, and TNF-α in rat cardiac fibroblasts, also with expression of Col- I and Col- III. These findings confirmed the feasibility of uric acid in myocardial fibrosis models in vitro, further clarified the effect of uric acid on myocardial fibrosis and cardiac remodeling, and provided a new molecular biological confirmation of the role of uric acid in the development of heart failure.

2. METHODS

2.1 Materials

Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS) and 0.25％trypsin were obtained from Hyclone (USA). Uric acid was obtained from Sigma-Aldrich (USA). MTT kit was purchased from Solarbio (China). Hydroxyproline kit was purchased from NJJCBIO (China). Rat IL-6, IL-1β, and TNF-α were purchased from Neobioscience (China). Total RNA kit was purchased from Omega (USA). PrimeScript™ RT reagent Kit with gDNA Eraser and SYBR® Premix Ex Taq™ II (Tli RNaseH Plus) were from TaKaRa (Japan). The primers were designed by Sangon Biotech (China).

2.2 Isolation and culture of cardiac fibroblasts

The 1–3-day-old Wistar rats were obtained from Qingdao Daren Fortune Animal Technology Co.Ltd, china. The study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals issued by the National Institutes of health, and the guidelines of Affiliated Hospital of the Qingdao University. Primary cardiac fibroblasts were isolated from neonatal rats as described previously. Briefly, the hearts were taken out under aseptic condition and

washed into the pre-cooled D-Hanks solution to remove congested blood. The ventricles were cut into fragments about 1 mm3 in size. The tissue was digested repeatedly by trypsin and collagenase II until it disappeared completely. After the cell suspension was filtered and centrifuged, the cells were resuspended with the DMEM containing 10% FBS. The cells were put into a culture flask and incubated at 37 °C in 5% CO2 for 60min. The unattached cardiomyocytes were abandoned. The remaining cells continue to be cultured in DMEM with 10% FBS. The second to fourth passage of cardiac fibroblasts were used for our experiments.

2.3 Measurement of cell proliferation

Cells were plated in 96-well plates (1×10^5/well) and incubated at 37 °C for 24 h, then treated with uric acid at concentrations of 0, 200, 400, 600, and 800μmol/L for 24h or 48h. After treatments, MTT solution (10μL/well) was added in, after 4h, culture supernatants were changed into DMSO solution (100μL/well). Cells oscillated at low speed on a shaker for 10 minutes. The absorbance at 490nm was measured by a microplate reader.

2.4 Measurement of collagen

Cells were plated in 6-well plates and incubated for 24 h, then treated with uric acid at concentrations of 0, 200, 400, 600, and 800μmol/L for 24h or 48h. The levels of collagen in the culture supernatants were measured by hydroxyproline kit following the manufacturer's protocol.

2.5 Measurements of TNF-α, IL-1β, and IL-6

Cells were plated in 6-well plates and incubated for 24 h, then treated with uric acid at concentrations of 0, 200, 400, 600, and 800μmol/L for 24h. The content of IL-6, IL-1β, and TNF-α in the culture supernatants were measured by rat ELISA kits according to the instructions of the manufacturers.

2.6 Real-time quantitative PCR (qPCR)

Total RNA was extracted from cardiac fibroblasts using the kit according to the manufacturer's instruction. Total RNA was reversely transcribed using RT reagent Kit and cDNA was synthesized according to the protocol provided by the manufacturers. The cDNA template was used for RT-PCR by Premix Ex Taq as guided by the manufacturer. The measurement of IL-6, IL-1β, TNF-α, Col-Ⅰ, and Col-Ⅲ mRNA expressions was performed by a Real-Time PCR Instrument (Bio-Rad,USA). The qPCR program was followed by two stage: 1 cycle of 95℃ for 30s and 40 cycles of 95℃ for 3s, 60℃ for 30s. After the reaction, the dissolution curve and amplification curve of PCR were determined, and the results were analyzed by $2^{-\Delta\Delta Ct}$ method. The sequences of primers were as follows.

Col-Ⅲ, forward:

5'-GACACGCTGGTGCTCAAGGAC -3';

Col-Ⅲ, reverse:

5'-GTTCGCCTGAAGGACCTCGTTG-3';

Col-Ⅰ, forward:

5'-TACCCTCAAGAGCCTGAGCC-3';

Col-Ⅰ, reverse:
5'-GGCACATCTTGAGGTCACGG-3';
TNF-α, forward:
5'-GCATGATCCGAGATGTGGAACTGG-3';
TNF-α, reverse:
5'-CGCCACGAGCAGGAATGAGAAG-3';
IL-1β, forward:
5'-ATCTCACAGCAGCATCTCGACAAG-3';
IL-1β, reverse:
5'-CACACTAGCAGGTCGTCATCATCC-3';
IL-6, forward:
5'-AGGAGTGGCTAAGGACCAAGACC-3';
IL-6, reverse:
5'-TGCCGAGTAGACCTCATAGTAACC-3';
GAPDH, forward:
5'-GACATGCCGCCTGGAGAAAC-3';
GAPDH, reverse:
5'-AGCCCAGGATGCCCTTTAGT-3'.

2.7 Statistical analysis

All statistical analyses were processed using SPSS22. 0 software. The results were reported as the mean±SD. Differences among groups were performed by one-way ANOVA followed by post-hoc multiple comparison test (LSD). Data were considered statistically significant when the value of $P < 0.05$.

3. RESULTS

3.1 Effect of uric acid on the proliferation of cardiac fibroblasts

We studied the effects of uric acid with different concentrations on the proliferation of cardiac fibroblasts by MTT assay. We found that when cardiac fibroblasts were treated with uric acid for 24h, uric acid at concentrations of 400μmol/L, 600μmol/L, and 800μmol/L significantly increased the proliferation of cardiac fibroblasts ($P < 0.05$), but uric acid at 200μmol/L had no obvious effect on the cell proliferation (Fig. 1). When cardiac fibroblasts exposed to uric acid for 48h, uric acid at concentrations of 400μmol/L, 600μmol/L, and 800μmol/L significantly promoted cell proliferation ($P < 0.05$), but uric acid at 200μmol/L had no obvious effect (Fig. 1).

3.2 Effect of uric acid on the synthesis of collagen in cardiac fibroblasts

We first examined the effect of uric acid with different concentrations on the synthesis of collagen in cardiac fibroblasts by hydroxyproline assay. The secretion of collagen significantly increased in cardiac fibroblasts which have been exposed to uric acid (400μmol/L, 600μmol/L, and 800μmol/L) for 24h and 48h ($P < 0.05$), but the synthesis of collagen was not significantly different in uric acid (200μmol/L) compared with the control (Fig. 2A). According to the

hydroxyproline assay, we next chose uric acid at concentration of 600μmol/L for Real-time qPCR, to investigate the effects of uric acid on the expression of Col-Ⅰand Col-Ⅲ mRNA in cardiac fibroblasts. We found that when cardiac fibroblasts were treated with uric acid for 24h, uric acid at concentration of 600μmol/L significantly increased the synthesis of Col-Ⅰand Col-Ⅲ in cardiac fibroblasts ($P < 0.05$) (Fig. 2B).

3.3 Effect of uric acid on the production of IL-6, IL-1β, and TNF-α in cardiac fibroblasts

To determine whether uric acid could induce the production of inflammatory cytokines in cardiac fibroblasts, cardiac fibroblasts were treated with uric acid (0μmol/L, 200μmol/L, 400μmol/L, 600μmol/L, and 800μmol/L) for 24h. As shown in Fig. 3, the production of inflammatory cytokines significantly increased in all groups compared with the control ($P < 0.05$). It should be noted that uric acid induced a dose-dependent increase in inflammatory cytokines within a certain concentration range. Furthermore, compared with the control, the mRNA levels of IL-6, IL-1β, and TNF-α in cardiac fibroblasts treated with uric acid (600μmol/L, 24h) were higher ($P < 0.05$).(Fig. 3D)

4. DISCUSSION

It is well known that hyperuricemia is a common metabolic disease. It is a metabolic syndrome associated with hypertension, dyslipidemia and impaired glucose metabolism (12). Recent studies have shown that the prevalence of hyperuricemia is increasing year by year (7). Not only can hyperuricemia lead to gout, gouty arthritis and kidney disease, but evidence is mounting that hyperuricemia is an important and independent risk factor for cardiovascular disease (such as ischemic heart disease and heart failure) (6, 13, 14). Clinical studies have shown that the level of serum uric acid is independently associated with left ventricular hypertrophy in the general population (15). In patients with heart failure, the level of serum uric acid is significantly related to ventricular remodeling and independent of renal function (14, 16). These studies support the notion that increased production of uric acid might promote or even lead to ventricular remodeling. Experimental investigates indicate that the increase of serum uric acid can induce ventricular remodeling, inflammation, myocardial fibrosis and abnormal secretion of enzymes-related collagen in mice (17, 18). Uric acid can promote the increase of cell proliferation, the endothelin-1 (ET-1) expression and reactive oxygen species (ROS) production in cardiac fibroblasts (19), which indicates that hyperuricemia can induce oxidative stress accompanied by the fibrogenesis in cardiac tissue. However, the effect of uric acid on collagen synthesis and inflammatory response in cardiac fibroblasts has not been reported.

Myocardial fibrosis is one of the main manifestations of ventricular remodeling. It is a pathological process of inflammation mediated apoptosis and necrosis of cardiomyocyte, abnormal increase and over deposition of ECM after cardiac injury. Myocardial fibrosis can lead to the increase of myocardial stiffness, ventricular systolic dysfunction, the decrease of ventricular compliance, cardiac ejection fraction and stroke volume, decompensation of heart function, and eventually lead to heart failure. The cardiac ECM is mainly composed of

collagen, proteoglycan, glycoprotein, cytokine, growth factor and protease, among which collagen is mainly Col-Ⅰand Col-Ⅲ, accounting for about 80% and 10%, respectively (20). The main function of collagen is to provide skeleton support for the heart, transmit mechanical signals to cardiomyocytes, and promote the orderly contraction of the heart. Cardiac fibroblasts can effectively regulate ECM levels by synthesizing collagen and secreting collagen hydrolases. Cardiac fibroblasts are one of the main cells of cardiac tissue and the main effectors of myocardial fibrosis (21). In physiological state, cardiac fibroblasts secrete cytokines, collagenase, and synthesize new collagen to replace aging collagen, thus stabilizing the composition and structure of the cardiac ECM. After the heart damage, the cardiac fibroblasts are regulated by a variety of bioactive factors secreted by autocrine and paracrine. These bioactive factors can change the gene expression of cardiac fibroblast, making cardiac fibroblasts active and proliferate rapidly and migrate to the damaged area and secrete ECM (mainly collagen), thus promoting the healing and scar formation of the wound (22). It can lead to excessive deposition of collagen and myocardial fibrosis when the heart continues to receive external stimulation (23). In this study, we investigated the effect of uric acid on the proliferation of cardiac fibroblasts and the secretion of collagen. We found that some concentrations of uric acid can promote cell proliferation and collagen synthesis. These findings suggest that uric acid can induce cardiac fibroblasts' oversynthesis of collagen and lead to the occurrence of myocardial fibrosis.

Cardiac inflammation can trigger the phenotypic transformation of cardiac fibroblasts and increase myocardial collagen deposition, which is a pathological key to cardiac remodeling (24). Activated cardiac fibroblasts can produce a series of bioactive factors and are secreted into the interstitium, acting not only on the other cells in the heart but also on themselves. TGF-β1, Ang-Ⅱ, IL-6, TNF-α, IL-1β and other cytokines were detected in cultured cardiac fibroblasts (25). After heart injury, cardiac fibroblasts produce pro-inflammatory cytokines, chemokines such as IL-6, IL-1β, and TNF-α, to raise inflammatory cells (neutrophils, macrophages, mononuclear cells, etc.) into the cardiac tissue (26, 27). The interaction between cardiac fibroblasts and inflammatory cells leads to a vicious cycle of heart inflammation. Therefore, the inflammatory response of cardiac fibroblasts plays a key role in myocardial fibrosis and heart failure induced by a series of pathological processes after heart damage. Inflammation may be a pathogenic mechanism of hyperuricemia in cardiovascular diseases (28). Elevated serum inflammatory markers in patients with hyperuricemia indicate probability of inflammation in body, caused by hyperuricemia (29). Recent studies revealed that activation of the NLRP3 inflammasome in cardiac fibroblasts is pivotal in cardiac inflammatory response (30-32). Previous studies revealed that uric acid can activate the NLRP3 inflammasome, release pro-inflammatory cytokines to the extracellular domain, and mediate inflammatory responses (33). Therefore, we conclude that uric acid can induce the inflammatory reaction of cardiac fibroblasts. In this study, our results demonstrated that the release of inflammatory cytokines (IL-6, IL-1β, and TNF-α) increased with the increase of uric acid concentration in a certain range. Thus, uric acid might promote the development of cardiac inflammation to some

extent by stimulating cardiac fibroblasts. Further experiments are needed to clarify the pathway of uric acid's action.

In conclusion, this study demonstrates that uric acid enhances the cell proliferation; promotes collagen synthesis, and Col- I and Col- III expression; induces release of IL-6, IL-1β, and TNF-α in cardiac fibroblasts, which all lead to fibrosis of the cardiac tissue. Our results discover the role of uric acid in the heart and the pathophysiological mechanism of uric acid to promote ventricular remodeling and heart failure, thereby contributing to the research of the relationship between hyperuricemia and cardiovascular disease.

Figure legends

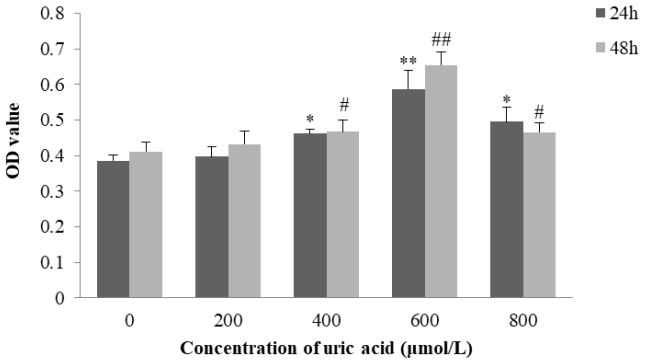
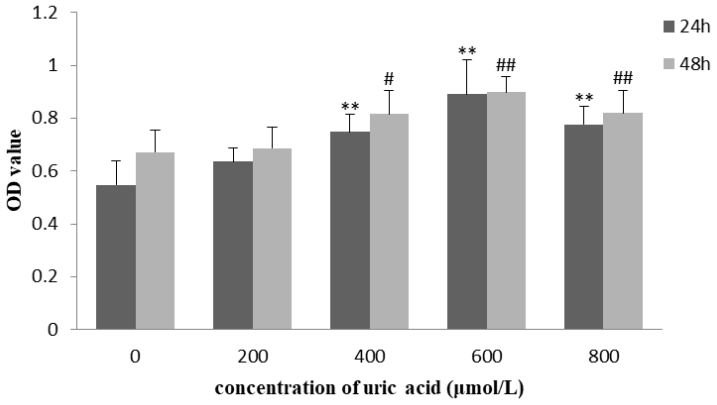


Fig 1. Effect of uric acid on the proliferation of cardiac fibroblasts. Cells were incubated with various concentrations of uric acid for 24h and 48h, and cell viability was determined by MTT assay. Data were shown as the mean ± SD (n = 3).* $P < 0.05$, *vs*. control group (24h); ** $P < 0.01$, *vs*. control group (24h); # $P < 0.05$, *vs*. control group (48h); ## $P < 0.01$, *vs*. control group (48h).



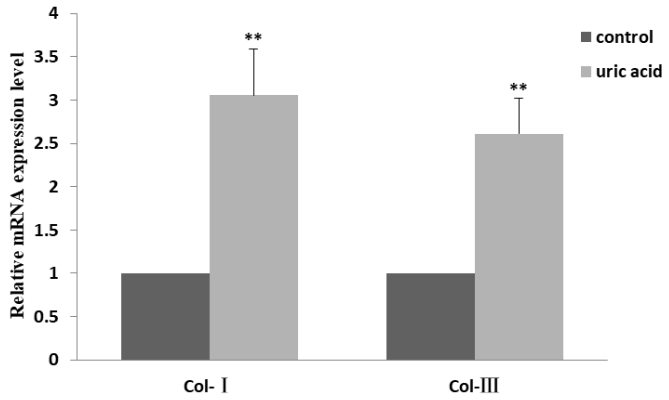
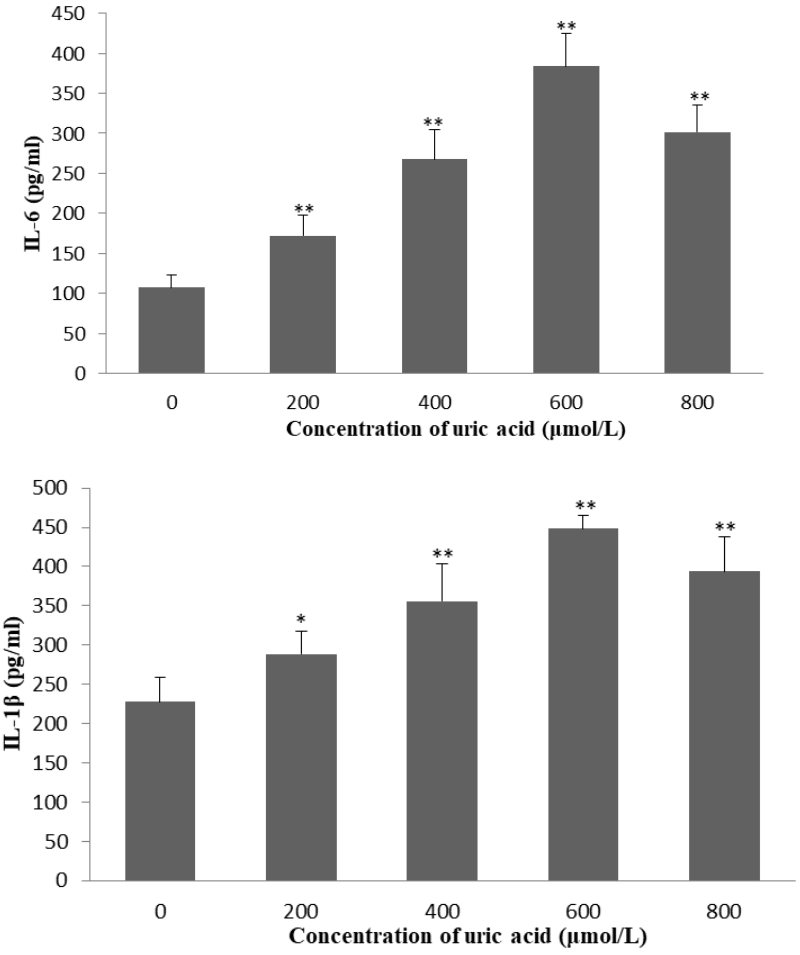


Fig. 2. Effect of uric acid on the synthesis of collagen in cardiac fibroblasts. A Cells were pretreated with various concentrations of uric acid for 24h and 48h, the synthesis of collagen was measured by hydroxyproline assay. B The relative mRNA levels of Col-Ⅰ and Col-Ⅲ in uric acid (600μmol/L, 24h) group were higher than those in control group. Data were shown as the mean ± SD (n = 3). ** $P < 0.01$, *vs*. control group (24h); # $P < 0.05$, *vs*. control group (48h); ## $P < 0.01$, *vs*. control group (48h).



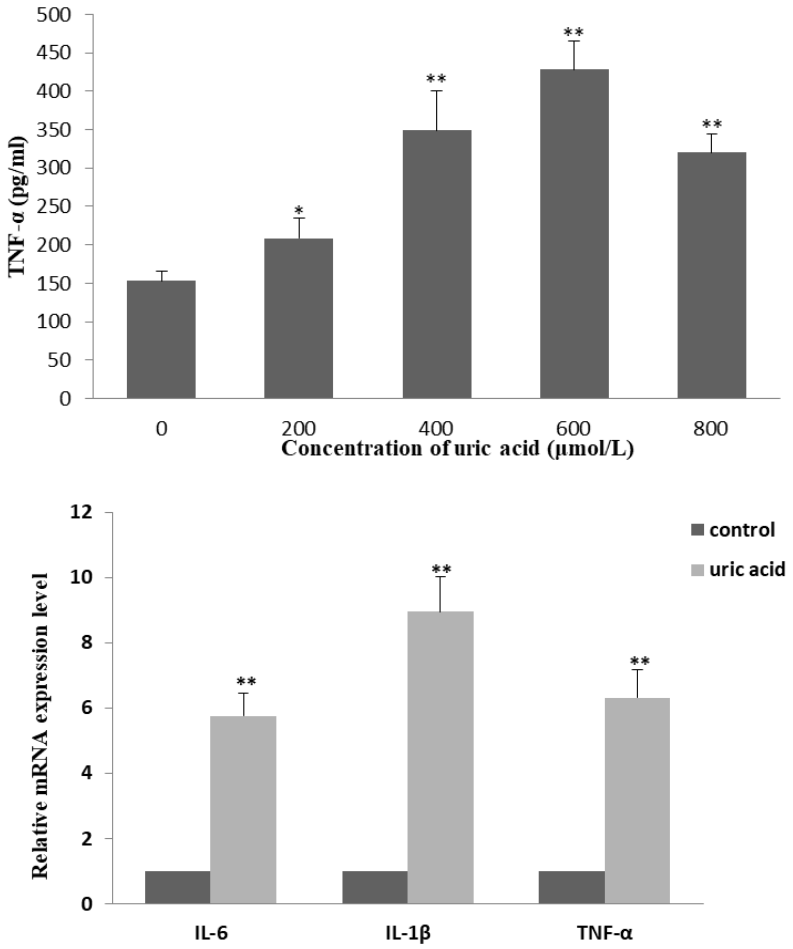


Fig. 3. Effect of uric acid on the production of inflammatory cytokines in cardiac fibroblasts. Cells were exposed to various concentrations of uric acid for 24h, the levels of IL-6 (A), IL-1β (B), and TNF-α (C) were measured by ELISA assay. D The relative mRNA levels of IL-6, IL-1β, and TNF-α in uric acid (600μmol/L, 24h) group were higher than those in control group. Data were shown as the mean ± SD (n = 3). * $P < 0.05$, *vs*. control group; ** $P < 0.01$, *vs*. control group.

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