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Original Article

Research of resveratrol regulating JAK/STAT signaling pathway in the treatment of atherosclerotic rats

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Abstract: Objective: To elucidate the mechanism of resveratrol on atherosclerotic (AS) rats by detecting the effect of resveratrol on JAK/STAT signaling pathway related proteins. Methods: Wistar rats were used as a model system. Ten rats were selected for each of the AS group, A group, and B group, respectively. Rats in A group and B group were given resveratrol by intragastric administration daily (20 mg/kg and 40 mg/kg, respectively). Ten healthy rats were randomly selected as the control group. AS group and the control group were given the same amount of normal saline. All rats were continuously fed for 6 weeks. At the end of the experiment, the levels of serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) were detected; the pathological changes of blood vessels in rats were detected by HE staining method; the JAK1 and STAT5 proteins in the arterial tissues of rats were detected by immunohistochemistry. The transcription and translation of JAK1 and STAT5 genes in rat arterial tissues were detected by RT-PCR and Western-blotting methods. Results: Compared with AS group, the changes of vascular structure in A group and B group were lighter, and a small number of foam cells infiltrated the intima. Compared with A group, after administration of resveratrol in B group, serum TC, TG, and LDL-C levels were significantly decreased (P=0.027, P=0.021, P=0.034), HDL-C levels were increased (P=0.018); tumor necrosis factor-α and interleukin-6 were significantly decreased (P=0.024, P=0.029); JAK1 and STAT5 positive staining in the rat artery was significantly less, and there was a certain decrease in the mRNA (P=0.033, P=0.027) and protein levels of JAK1 and STAT5 genes (P=0.026, P=0.032). Conclusion: Resveratrol can improve blood lipids in AS rats, reduce inflammatory response *in vivo*, and inhibit JAK/STAT signaling pathway related proteins, thus exerting anti-AS effect.

Keywords: Atherosclerosis, JAK/STAT signaling pathway, resveratrol

Introduction

Atherosclerosis (AS) is a common chronic inflammatory disease, which is an important pathological basis of cardiovascular diseases such as coronary heart disease and hypertension [1]. The JAK/STAT signaling pathway is an important signal transduction pathway in cells, which is closely related to cellular oxidative stress, inflammatory cytokine secretion, and other functions It can promote the expression of inflammatory mediator genes and is the key pathway for the body to control the inflammatory response [2]. Guo et al. found that under the action of the JAK2-specific inhibitor AG490, the vascular endothelial cells secrete less inflammatory cytokines of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which can cause dysfunction of vascular endothelial cells [3].

Resveratrol is a non-flavonoid polyphenol compound. It has been found that resveratrol can effectively inhibit the inflammatory response in rats, reduce the level of oxidative stress, and alleviate the symptoms of AS [4]. As the pathogenesis of AS is complicated, clinical use of drugs produces effect mainly through the inhibition of the important aspects of the pathogenesis of AS, thus achieving the effect of treatment. Nicotinic acids and fibrates can control lipid synthesis, but they can induce chronic inflammation in patients with AS [5]. Statins are mainly used in hypercholesterolemia patients, while long-term use may induce liver dysfunction. There is a lack of ideal drugs for the treatment of AS [6].

In this study, we provide an experimental basis for the clinical treatment of AS by observing the

Table 1. Gene primer sequence

Gene		Sequence
JAK1	Forward primer	5'-CGACTGACTGCTGGCAACTC-3'
	Reverse primer	5'-GACTTGCACTGGCATCACTCG-3'
STAT5	Forward primer	5'-GTCCACTGTGCCATGACGTCAC-3'
	Reverse primer	5'-GTCCGACTGACTTGACTACCAG-3'
GAPDH	Forward primer	5'-CTGACGTGACGTCATGACTGAC-3'
	Reverse primer	5'-GTCACTGACTGCCATGCATGC-3'

regulation of resveratrol on the JAK/STAT signaling pathway of AS rats.

Materials and methods

Materials

This study was approved by the Animal Welfare Committee of The Affiliated Hospital of Inner Mongolia Medical University. Fifty Wistar rats were purchased from Shanghai Shrek Experimental Animal Co., Ltd. The qualification certificate number was SCXK (HU) 2007-0005. The rats were 20 weeks old and weighed 180-200 g. After 3 days of adaptive feeding, 10 of them were given common diet as control group (n=10). The other 40 rats were injected with vitamin D3 (70 U/kg) for 5 consecutive days. At the same time, high fat diet was given to model the rats. Then, ten rats were selected as: AS group (n=10), A group (n=10) and B group (n=10), respectively. Rats in A group and B group were given resveratrol (20 mg/kg and 40 mg/kg, respectively) and were given intragastric administration once daily. After 6 weeks of continuous feeding, the rats of each group were anesthetized and the blood was collected from the eyeballs. The serum was collected and stored at -20°C. At the same time, the rat's thoracic aorta was dissected and cut into 2 parts, one of which was soaked in 10% formalin, and the other was stored at -20°C until use.

Detection of vascular pathological changes in rats by HE staining

The thoracic aorta samples fixed with 4% paraformaldehyde were dehydrated in an ethanol solution of gradient concentration, and paraffin specimens were prepared by vitrification and paraffin immersion steps. The paraffin sample was made into 4 μm slices by the slicing machine. The slices were roasted at 60°C, so that the thoracic arterial tissue samples were deparaffinized. Then, the samples were rehydrated in ethanol solution of gradient concentration. After washing with running water for 3 min, hematoxylin staining was performed for 6 min. After washing with running water for 3 min again, 1% hydrochloric acid ethanol was used to differentiate the sample for 10 s. After washing with running water for 3 min again, it was stained with eosin for 5 min. After washing with running water for 3 min again, it was dehydrated with an ethanol solution of gradient concentration, placed in xylene for vitrification for 15 min, and then drops of resinene were used to seal the slice. The pathological structure of the sample was observed under microscope.

Detection of serum indexes in rats

The frozen rat serum samples were taken and examined. Phosphoglycerol oxidase cholesterol method was used to measure total cholesterol (TC) [5]; dichloromethane-silicic acid method was used to measure triglyceride (TG) [6]; immunochemical precipitation was used to measure high-density lipoprotein-cholesterol (HDL-C); polyvinyl sulfate chemical precipitation method was used to measure low-density lipoprotein-cholesterol (LDL-C) [7]. The serum levels of TNF-α and IL-6 were measured by ELISA. Blank control wells, standard wells, and sample wells were set, all with 3 replicates. After adding 20 μL samples and standards to each well, the plate was incubated at 37°C for 1 h. After washing, diluted primary antibody was added and the plate was incubated at 37°C for 1 h. After washing, the secondary antibody conjugated with HRP was added and the plate was incubated at 37°C for 1 h. After washing, 10 μL color developing agent was added, and the reaction was terminated after 6 min. The OD values of each well were measured at 450 nm wavelength. The standard curve was plotted according to the OD value of the relevant standards.

Immunohistochemical experiments

Paraffin sections were placed in 70°C oven for 2 h and then dewaxed with xylene. Then it was dehydrated in ethanol solution of gradient concentration and washed 3 times with PBS (5 min/time). The slices were placed in a 0.01 mol/L citrate buffer and boiled for 0.5 h and

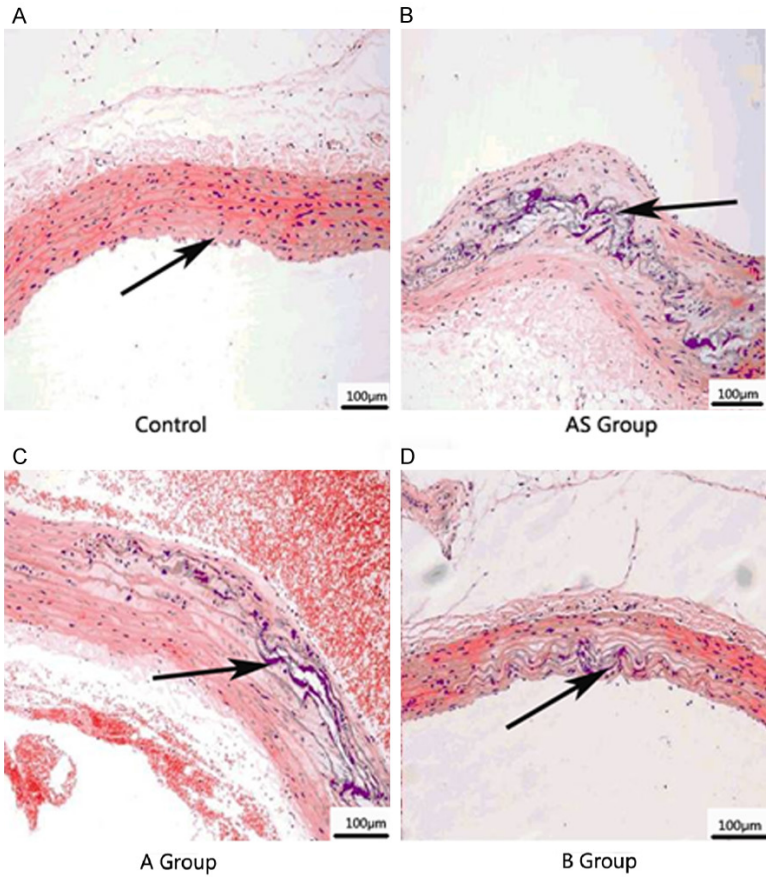

Figure 1. HE staining of vascular lesions in rats of each group (200×). A: HE staining results of blood vessels in rats of control group show that the basic structure of the blood vessel is normal; B: HE staining results of blood vessels in rats of AS group show that local thickening of the intima, more foam-like cells infiltrating the intima and atrophy of the medial membrane; C: HE staining results of blood vessels in rats of A group show that the intima has a certain degree of thinning, and the degree of atrophy in the medial membrane has been reduced; D: HE staining results of blood vessels in rats of B group show that foam-like cells decreased and pathological changes were significantly alleviated.

washed 3 times with PBS (5 min/time). A proper amount of goat serum was added dropwise to block the slice. Rabbit anti-mouse JAK1 and STAT5 primary antibodies (diluted according to 1:600 and 1:1,000, respectively) were then added dropwise, and the slice was incubated overnight at 4°C and washed 3 times with PBS (5 min/time). Then, biotin-labeled goat anti-rabbit secondary antibody was added dropwise and washed 3 times with PBS (5 min/time). DAB colorimetric solution was added to the slice and incubated for 10 min. After rinsing with clear water, it was restained with hematoxylin for 20 s and differentiated by 0.1% hydrochloric acid alcohol. The slices were dehydrated in a gradient concentration of ethanol, vitrificated by xylenes and sealed with resinene.

Real-time PCR detection of resveratrol's effect on gene expression

Cryopreserved rat thoracic aorta tissues were weighed in an amount of 0.2 g and homogenized by adding 1 mL of Trizol reagent. The total RNA was extracted by centrifugation at 4°C for 8 min at 10,000 rpm. The quality of the RNA was tested using a Nanodrop spectrophotometer. The A260/A280 value of 1.8-2.0 suggested good RNA purity. The cDNA was synthesized by reverse transcription kit and the reaction conditions were: 42°C for 30 min, 70°C for 5 min. After the reaction, the product was stored at -20°C. Primer 6.0 was used to design gene primers. The reaction conditions were: 95°C for 2 min, 62°C for 30 s, 72°C for 45 s, 32 cycles, and 72°C for 6 min. The relative expression levels of the target gene were detected by $2^{-\Delta\Delta Ct}$ method with GAPDH as the reference gene. The primer sequence was synthesized by Shanghai Generay Biotech Co., Ltd. See **Table 1**.

Detection of related proteins by Western blotting

The cut samples of rat thoracic aorta were weighed 0.5 g. After crushing, 4 mL of lysate containing 1 mmol/L PMSF was added and homogenized. After centrifugation at 10,000 rpm for 10 min at 4°C, the supernatant was collected and assayed for protein concentration using the BCA method. After mixing the protein sample solution with the loading buffer (volume ratio 1:5), the mixture was bathed in water at 100°C for 5 min. After cooling, the samples were loaded and separated by 10% gel electrophoresis. Then, the separated protein was transferred to a PVDF membrane

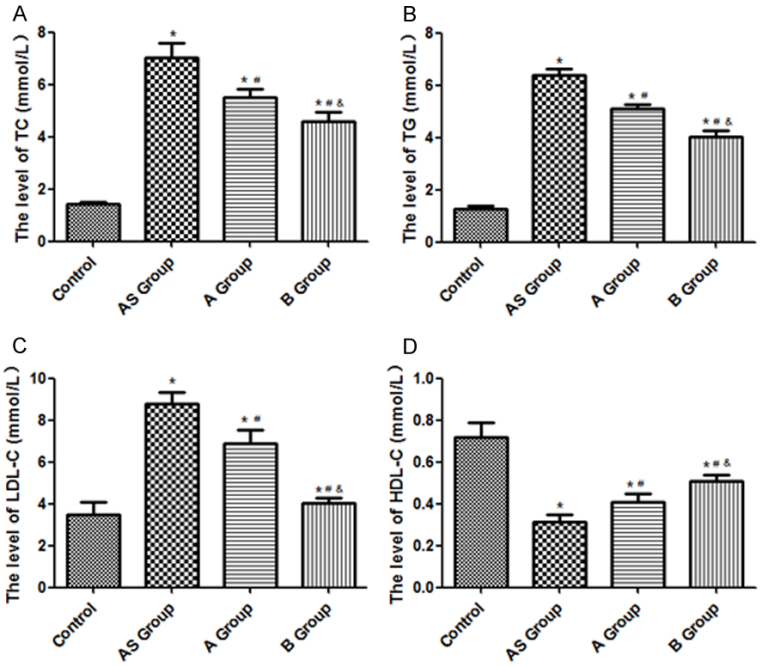

Figure 2. Comparison of blood lipids levels in rats. A: Serum TC level of rats in each group; B: Serum TG level of rats in each group; C: Serum LDL-C level of rats in each group; D: Serum HDL-C level of rats in each group. Compared with control group, *P<0.05; compared with AS group, #P<0.05; compared with A group, &P<0.05. TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

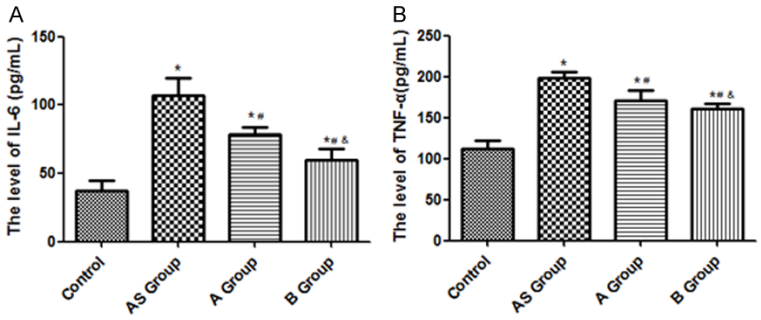

Figure 3. Comparison of blood lipids levels in rats in each group. A: Serum IL-6 level of rats in each group; B: Serum TNF-α level of rats in each group. Compared with control group, *P<0.05; compared with AS group, #P<0.05; compared with A group, &P<0.05. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

using wet method. The PVDF membrane was washed with TBST and placed in a TBST solution containing 5% skimmed milk powder. After blocking for 2 h, rabbit anti-mouse JAK1 and STAT5 primary antibodies (diluted according to 1:500 and 1:1,200, respectively) were added and incubated on a shaker overnight at 4°C. The PVDF membrane was washed with TBST solution and then incubated with HRP-labeled secondary antibody for 1 h at room temperature. After washing with the TBST wash solution again, the image was visualized using ECL reagents and ImageJ software was used to analyze the protein band gray values.

Statistical analysis

SPSS 21.0 software was used to analyze data and data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). The data in accordance with normal distribution were tested by t test. Analysis of variance was used to compare multiple sets of data. P<0.05 means there is a statistical difference.

Results

Effects of resveratrol on blood vessels of AS rats

In the control group, the vascular intimal morphology was normal, and the structure of vascular smooth muscle cells and endothelial cells was clear. In AS group, the intima of the artery was thickened, and more foam-like cells infiltrated the vascular intima. Compared with AS group, the changes of vascular structure in the rats of A group and B group were lighter, and a small amount of foam cells infiltrated in the intima of the blood vessels. See **Figure 1**.

Effect of resveratrol on blood lipids in AS rats

Compared with control group, the serum levels of TC, TG and LDL-C in the rats of control group were all increased (P=0.023, P=0.036, P=0.032). Compared with AS group, the levels of TC, TG and LDL-C in the rats of A group and B group, after administration of resveratrol, were decreased significantly (P=0.015, P=0.032,

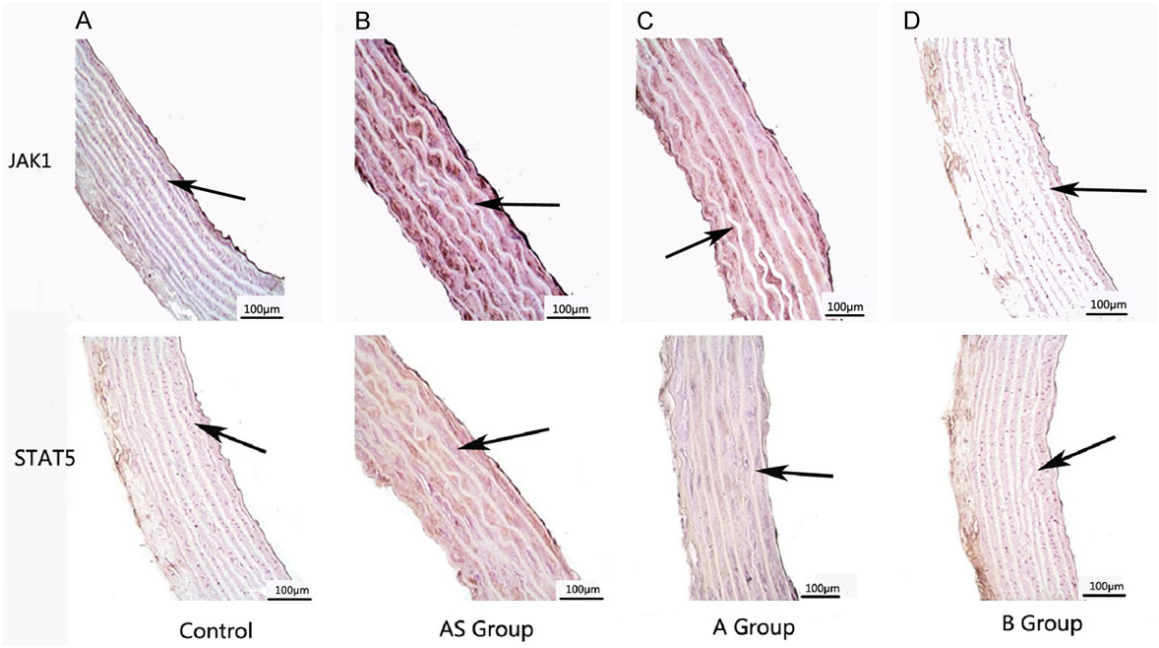

Figure 4. Immunohistochemical results of arterial vessels of rats in each group (200×). A: The staining of JAK1 and STAT5 in the arterial tissue of rats in control group; B: The staining of JAK1 and STAT5 in the arterial tissue of rats in AS group; C: The staining of JAK1 and STAT5 in the arterial tissue of rats in A group; D: The staining of JAK1 and STAT5 in the arterial tissue of rats in B group.

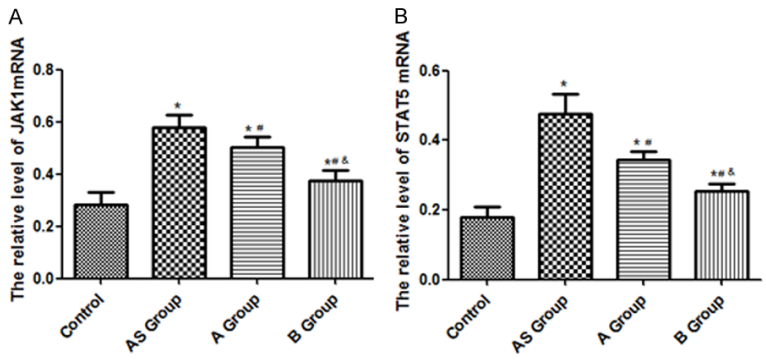

Figure 5. Comparison of JAK1 and STAT5 mRNA levels in arterial tissue of rats in each group. A: JAK1 mRNA levels in arterial tissues of rats in each group; B: STAT5 mRNA levels in arterial tissues of rats in each group. Compared with control group, $^{*}P<0.05$; compared with AS group, $^{\#}P<0.05$; compared with A group, $^{\&}P<0.05$.

P=0.036, P=0.029, P=0.024, P=0.017). Compared with control group, serum HDL-C levels in AS group rats were significantly decreased (P=0.028). Compared with AS group, the HDL-C levels in the rats of A group and B group both increased after taking resveratrol (P=0.024, P=0.037). Compared with A group, TC, TG and LDL-C levels in B group rats were significantly decreased after taking resveratrol (P=0.027, P=0.021, P=0.034). Compared with A group, HDL-C levels in B group increased significantly (P=0.018). See **Figure 2**.

Effect of resveratrol on serum inflammatory cytokines in rats with AS

Compared with control group, the serum levels of TNF-α and IL-6 in AS group were both increased (P=0.024, P=0.022). Compared with AS group, TNF-α and IL-6 in A group and B group were both significantly decreased after taking resveratrol (P=0.026, P=0.018, P=0.019, P=0.032). Compared with A group, TNF-α and IL-6 in B group rats were significantly decreased after taking resveratrol (P=0.024, P=0.029). See **Figure 3**.

Immunohistochemical detection of JAK1 and STAT5 proteins in artery tissue of AS rats

Compared with the control group, the positive staining of JAK1 and STAT5 in arterial tissue of rats in AS group was significantly more than that in the control group, suggesting that the expression of JAK1 and STAT5 in the arterial tissue of the rats in AS group was higher than that

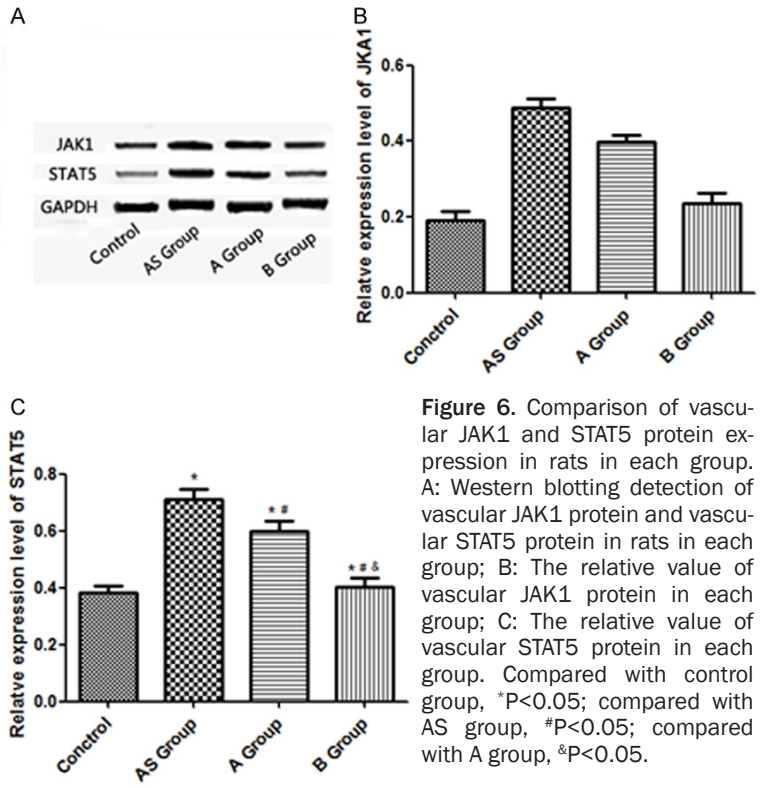

Figure 6. Comparison of vascular JAK1 and STAT5 protein expression in rats in each group. A: Western blotting detection of vascular JAK1 protein and vascular STAT5 protein in rats in each group; B: The relative value of vascular JAK1 protein in each group; C: The relative value of vascular STAT5 protein in each group. Compared with control group, *P<0.05; compared with AS group, #P<0.05; compared with A group, &P<0.05.

in the control group. Compared with AS group, the positive staining of JAK1 and STAT5 in arterial tissue of rats in A group and B group was significantly less than that in AS group, suggesting that the expression of JAK1 and STAT5 in arterial tissue of rats in AS group was lower than that in AS group. See **Figure 4**.

RT-PCR detection of mRNA levels of JAK1 and STAT5 in arterial tissue of AS rats

Compared with control group, mRNA levels of JAK1 and STAT5 in rats of AS group were increased (P=0.032, P=0.027). Compared with AS group, the mRNA levels of JAK1 and STAT5 were both decreased to some extent in A group and B group after administration of resveratrol (P=0.042, P=0.036, P=0.031, P=0.019). Compared with A group, the mRNA levels of JAK1 and STAT5 in B group was decreased to some extent after administration of resveratrol (P=0.033, P=0.027). See **Figure 5**.

Western blotting detection of JAK1 and STAT5 protein expression in arterial tissue of AS rats

Compared with control group, the protein levels of JAK1 and STAT5 in AS group were both increased (P=0.023, P=0.026). Compared with AS group, the protein levels of JAK1 and STAT5 in A group and B group were both decreased to some extent after resveratrol administration (P=0.031, P=0.025, P=0.016, P=0.029). Compared with A group, the protein levels of JAK1 and STAT5 in B group both decreased to some extent after administration of resveratrol (P=0.026, P=0.032). See **Figure 6**.

Discussion

AS is an important pathological basis for cardiovascular disease. Abnormal metabolism of glucose and lipids, aggravation of inflammatory reactions, and bacterial infection all can induce abnormal function of vascular endothelial cells, result in excessive secretion of inflammatory factors and adhesion molecules, and eventually leading to the occurrence and development of AS [8, 9]. Resveratrol is a plant polyphenol that provides cardiovascular protection. A study has found that resveratrol could regulate glucose and lipid metabolism, inhibit platelet aggregation, and improve immune function [10]. Ikeda et al. found that resveratrol could significantly reduce serum TG and TC levels in AS rats and enhance arterial wall elasticity [11]. Zhang et al. found that resveratrol can reduce the area of AS plaques in vascular and improve hemorheology factors through animal experiments [12]. In this study, it was found that the levels of serum TG, TC, and LDL-C were decreased significantly after resveratrol administration in AS rats, which indicated that resveratrol could reduce the level of exogenous lipid metabolism, thusly reducing the synthesis of cholesterol and inhibiting the damage of hyperlipidemia to the intima of the blood vessel. This is consistent with previous studies [13]. HE staining showed that the area of atherosclerotic plaques in the aorta and the number of foam cells in the intima were decreased, which suggested resveratrol had a better preventive effect on AS.

TNF-α is a polypeptide inflammatory factor secreted by neutrophils, lymphocytes, and other cells. It can stimulate vascular endothelial cells to secrete platelet active factors and pro-

mote thrombosis [14]. IL-6 is an inflammatry factor secreted by immune cells and plays an important role in regulating the secretion of other inflammatory factors *in vivo* [15]. Wang et al. found that serum levels of TNF-α and IL-6 in AS rats were significantly higher than those in healthy rats, suggesting that inflammatory factors are closely related to the development of AS [16]. In this study, we found that the serum levels of TNF-α and IL-6 were increased significantly in AS model rats, and the levels of serum TNF-α and IL-6 in A group and B group were decreased significantly after resveratrol administration, which is consistent with existing study [17]. Through higher levels of resveratrol, Lerchenmuller et al. stimulated the activation of JAK/STAT signaling pathways in vascular endothelial cells, regulated the synthesis of TG, TC, LDL-C and other blood lipid metabolic indicators, reduce the secretion levels of serum TNF-α and IL-6, promoted the migration of vascular smooth muscle cells, which led to thickening of the arterial wall [18]. One study has suggested that, after binding to the corresponding specific receptors, active substances could increase the tyrosine kinase gene transcription factor in the nucleus and promote the expression of JAK1 gene. At the same time, STAT5 protein binding to JAK1 could promote the transcription of genes related to cell metabolism and proliferation, and has a greater effect on the function of vascular endothelial cells [19]. In this study, the positive staining of JAK1 and STAT5 in the arterial tissue of AS model rats by immunohistochemistry increased significantly. After administration of resveratrol in rats of A group and B group, the positive staining of JAK1 and STAT5 decreased significantly. The results of RT-PCR and western blotting showed that the expression level of JAK/STAT was decreased, which is consistent with the results of immunohistochemistry. This suggests that resveratrol can effectively inhibit the expression of JAK/STAT. Zopfs et al. found that the proliferation ability of vascular endothelial cells was decreased after protein phosphorylation inhibitors block JAK/STAT3 signaling [19]. Wincewicz et al. found that TNF-α could increase the expression of JAK1 protein in vascular tissues, thereby activating the JAK/STAT signaling pathway and promoting the occurrence of AS [20]. The biological function of resveratrol is relatively complicated. The specific pathway of resveratrol affecting JAK/STAT signaling pathway was not studied in this paper. At the same time, the effect of resveratrol on the biological activity of vascular endothelial cells in rats can be further studied to explore the mechanism of resveratrol on the treatment of AS at the cellular level.

In conclusion, resveratrol can improve the blood lipid indexes of AS rats, reduce the level of inflammatory factors *in vivo*, down-regulate the expression of JAK1 and STAT5 proteins, suggesting resveratrol may inhibit the development of AS through the JAK/STAT signaling pathway.

Disclosure of conflict of interest

None.

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