Resveratrol attenuates acute kidney injury by inhibiting death receptor-mediated apoptotic pathways in a cisplatin-induced apoptotic rat model

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Abstract. Acute kidney injury is a clinical syndrome characterized by a loss of renal function and acute tubular necrosis. Resveratrol exerts a wide range of pharmacological effects based on its anti-inflammatory, antioxidant and cytoprotective properties. The present study aimed to evaluate whether resveratrol attenuates acute kidney injury in a cisplatin-induced rat model and to investigate the potential mechanisms involved. Rats were randomly divided into four treatment groups: Control, cisplatin, resveratrol, and cisplatin plus resveratrol. Rats exposed to cisplatin displayed acute kidney injury, identified by analysis of renal function and histopathological observation. Resveratrol significantly ameliorated the increased serum creatinine, blood urea nitrogen, renal index and histopathological damage induced by cisplatin. Furthermore, compared with untreated control animals, cisplatin lead to significantly increased expression of Fas ligand, tumor necrosis factor-α (TNF-α), caspase-8 and Bcl-2 associated protein X apoptosis regulator (Bax), and decreased expression of anti-apoptosis (TNF-α) receptors 5 and 11 (7). Following the interaction between TNF family ligands and receptors, the conserved death domains located in the cytoplasmic tails allow recruitment of downstream adaptors, such as TNFR1-associated death domain protein and FAS-associated death domain protein (FADD). The subsequent interaction of FADD with Fas or TNFR1 activates the recruitment of caspase-8 (6,12,13). Caspase-8 directly activates the downstream effector, caspase-3, or cleaves BH3 interacting domain death agonist (BID). A death-inducing member of the B cell lymphoma 2 (Bcl-2) family 14 (15). BID is cleaved to form truncated BID (tBID), which is translocated to the mitochondria and promotes a mitochondrial-dependent apoptotic pathway involving Bcl-2 associated X (Bax) and Bcl-2 (14,16)

Introduction

Acute kidney injury (AKI) is a multifactorial and multiphasic clinical syndrome, characterized by an abrupt (hours to days) reduction in renal function, together with an accumulation of metabolic waste and toxins, such as serum creatinine (Scr) and blood urea nitrogen (BUN), and/or decreased urine output (1,2). It is estimated that AKI affects 1.9% of all hospital inpatients, including >60% of patients in the intensive care unit (2,3). The physiopathological mechanism of AKI is characterized by renal tubular damage, vascular injury and inflammation (1,4). Injury and death of tubular cells contributes to the pathogenesis of AKI and apoptosis appears to be crucial during this process (1). Cisplatin (CP), an effective antineoplastic drug, induces a loss of renal function in 25-35% of patients following a single administration (5). Acute tubular damage caused by CP occurs primarily in the renal proximal tubular cells, particularly in the S3 segment, due to CP accumulation in the area (5,6). The pathophysiology of CP-induced acute renal tubular injury is associated with inflammation, oxidative stress and apoptosis (5-7). Via these mechanisms, apoptosis of the renal tubular cells is a key mode of cell death (8).

The extrinsic apoptotic pathway may contribute to tubular cell loss in AKI (1). TNF receptor 1 (TNFR1) and Fas (also known as CD95 or APO-1) are important transmembrane components of the tumor necrosis factor (TNF) family of receptors (9-11), whose ligands are TNF-α and Fas-ligand (Fas-L), respectively (5,11). Following the interaction between TNF family ligands and receptors, the conserved death domains located in the cytoplasmic tails allow recruitment of downstream adaptors such as TNFR1-associated death domain protein and FAS-associated death domain protein (FADD). The subsequent interaction of FADD with Fas or TNFR1 activates the recruitment of caspase-8 (6,12,13). Caspase-8 directly activates the downstream effector, caspase-3, or cleaves BH3 interacting domain death agonist (BID), a death-inducing member of the B cell lymphoma 2 (Bcl-2) family (14,15). BID is cleaved to form truncated BID (tBID), which is translocated to the mitochondria and promotes a mitochondrial-dependent apoptotic pathway involving Bcl-2 associated X (Bax) and Bcl-2 (14,16)

Previous studies have demonstrated that TNFR1 knockout mice are resistant to CP-induced AKI (6,12).
However, studies that have investigated the role of TNFR1 in apoptosis in renal tubular cells are limited and preliminary (13). In addition, whether Fas/Fas-L induces apoptosis in renal tubular cells still remains controversial (10). However, high Fas expression levels have been observed in renal tubular cells following acute and chronic renal failure (17,18).

Resveratrol (trans-3,4',5'-trihydroxystilbene; RSV) is a polyphenolic phytoalexin present in numerous edible plants, including mulberries, peanuts and grapes (19-21). RSV has been studied in vivo and in vitro (19,21) and has been demonstrated to possess a wide range of pharmacological effects, including cardioprotective (22), neuroprotective (23), nephroprotective (24), antineoplastic (25) and antiatherosclerotic (26) effects, as a result of its anti-inflammatory, antioxidative and cytoprotective properties (19). Previous studies have demonstrated the benefits of RSV towards several types of kidney disease, including diabetic nephropathy (27), drug-induced renal injury (28,24), and ischemia-reperfusion and sepsis-induced kidney injuries (29,30). The present study, therefore, aimed to determine whether RSV attenuates CP-induced AKI in a rat model and to investigate the potential mechanisms of attenuation.

Materials and methods

Reagents. CP (CAS no. 15663-27-1) and RSV (CAS no. 501-36-0) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Primary antibodies were supplied as follows: Mouse anti-Fas-L (cat. no. sc-19988), mouse anti-Bcl-2 (cat. no. sc-7382), rabbit-anti-Bax (cat. no. sc-6236), rabbit anti-BID (cat. no. sc-11423) from Santa Cruz Biotechnology, Inc. (Santa Cruz, Dallas, TX, USA); rabbit anti-TNF-α (cat. no. ab9755) and rabbit anti-caspase-8 (cat. no. ab181580) from Abcam (Cambridge, UK); and rabbit anti-β-actin from Merck Millipore (Darmstadt, Germany). Horseradish peroxidase (HRP)-conjugated anti-mouse IgG (cat. no. 12-349) and anti-rabbit IgG secondary antibodies (cat. no. 12-348) were obtained from Merck Millipore. The terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) in situ cell death detection kit was purchased from Roche Diagnostics GmbH (Mannheim, Germany).

Animals. A total of 28 adult male Wistar rats (weighing 180-200 g; 6-8 weeks old) were obtained from Shandong University Laboratory Animal Center (Jinan, China). Rats were acclimated to laboratory conditions for one week prior to experiments, and were consistently maintained in polycarbonate cages under standard conditions of temperature (20-23°C) and humidity (50-70%) with 12 h light-dark cycles. All rats had unrestricted access to food and water. All experiments involving rats were performed in accordance with the Guidelines for Animal Experiments of Qilu Hospital, Shandong University (Jinan, China) and all experimental procedures were approved by the Institutional Ethics Committee for Laboratory Animal Care of Qilu Hospital, Shandong University.

Animal treatment. Rats were randomly divided into four treatment groups, with seven animals per group: i) Control group (NS) received intraperitoneal (ip) injections of 0.9% saline (10 ml/kg) on day 1 and day 3; ii) RSV group received ip injections of 10 mg/kg RSV (2 mg/ml, dissolved in 0.9% saline) on day 1 and day 3; iii) CP group received an ip injection of 8 mg/kg CP (1 mg/ml, dissolved in 0.9% saline) on day 1 and an ip injection of 0.9% saline (10 ml/kg) on day 3; iv) CP+RSV group received ip injections of 8 mg/kg CP (1 mg/ml, dissolved in 0.9% saline) followed 30 min later by 10 mg/kg RSV (2 mg/ml, dissolved in 0.9% saline) on day 1, and an ip injection of 10 mg/kg RSV (2 mg/ml, dissolved in 0.9% saline) on day 3.

On day 5 of treatment, rats were first weighed before they were anesthetized by intraperitoneal injection of 10% chloral hydrate (0.4 ml/100 g body weight; CAS no. 302-17-0; Damaro Chemical Reagent Factory, Tianjin, China), and sacrificed by bloodletting from the left ventricle. Serum was separated from the blood by centrifugation (1,500 x g at 4°C for 15 min) and immediately stored at -20°C prior to analysis. Rat kidneys were perfused in situ through the left ventricle with 0.9% saline, then excised, weighed and cut in half by coronal position. Half of each kidney was immediately stored at -80°C, and half immersed in 4% paraformaldehyde buffered with phosphate-buffered saline (PBS) at 4°C, then fixed for 24 h and embedded in paraffin.

Assessment of renal function. Measurements of Scr and BUN were conducted in Qilu Hospital of Shandong University by a Cobas® 8000 modular analyzer (Roche Diagnostics GmbH). The renal index (RI) was calculated as follows: Both kidney weights (g) / animal weight (g) x 1,000.

Histopathological observation. Paraffinized kidneys were cut into 3-5 µm-thick sections, before they were deparaffinized and stained with hematoxylin and eosin (H&E; Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Sections were immersed in 0.5% eosin for 1 min and 0.1% hematoxylin for 5 min. The tubular damage score assessment was performed in 10 fields of 5 sections per group using the following index of renal tubular necrosis: Score of 0 (absence of damage); score of 1 (<25% damage); score of 2 (25-50% damage); score of 3 (50-75% damage); and score of 4 (>75% damage).

Immunohistochemistry. Tissue sections underwent deparafinization and rehydration with xylene and 100, 95, 90 and 80% ethanol gradients. Following 3 washes with PBS, slices were placed in 0.01% sodium citrate buffer (pH 6.0), and heated by microwave (10 min at 93-95°C) for antigen retrieval. Tissue sections were then cooled, washed with PBS 3 times and immersed in 0.1% Triton X-100 for 15 min. Sections were incubated with 3% hydrogen peroxide for 10 min at 15-25°C in the dark, to block endogenous peroxidase activity, followed by incubation with 10% goat serum (Nanjing Jiancheng Bioengineering Institute) for 45 min at 37°C, and then with mouse anti-Fas-L (dilution, 1:200) rabbit anti-Bax (dilution, 1:200) and mouse anti-Bcl-2 (dilution, 1:200) primary antibodies at 4°C overnight. The negative control sections were treated with PBS. Sections were subsequently washed and incubated with polymer helper for 20 min at 37°C, together with HRP-labeled anti-rabbit IgG polymer (cat. no. PV-9001) or HRP-labeled anti-mouse IgG polymer (cat. no. PV-9002) from the Polink-2 plus® Polymer HRP Detection System (Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd., Beijing, China). After washing 3 times with PBS, tissue slices
were stained with 3,3′-diaminobenzidine solution (DAB; cat. no. ZLI-9017; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd). Tissue slices were subsequently stained with 0.1% hematoxylin for 5 min. The stained slides were observed under a light microscope, and brown areas were deemed as positively stained. High power fields (n=10 per section) were randomly selected and 2 sections/group were scored. The intensity of dye color was graded as follows: Score 0, no color; score 1 light yellow; score 2, light brown; and score 3, brown. The percentage of positive areas was graded as follows: Score 0, <5%; score 1, 5-25%; score 2, 25-50%; score 3, 50-75%; and score 4, >75%. The two parameters were added to produce a final score.

**TUNEL assay.** The *in situ* cell death detection kit was used to detect cell apoptosis. TUNEL assay was performed according to the manufacturer's instructions. Briefly, deparaffinized tissue sections were incubated with 3% hydrogen peroxide in methanol (10 min at 15-25°C in the dark), washed 3 times with PBS, then incubated with 0.1% Triton X-100 in freshly prepared 0.01% sodium citrate (8 min at 25°C). Tissue sections were incubated with enzyme and labeling solutions (1:9; 60 min at 37°C). Following 3 washes in PBS, slices were stained with DAB and hematoxylin. Negative controls were incubated with labeling solution only. TUNEL positive nuclei were counted in 10 random, non-overlapping high power fields of 2 tissue sections.

**Western blot.** Perfused kidney tissue was snap frozen in liquid nitrogen, and 30 mg of kidney tissue was homogenized with radioimmunoprecipitation assay buffer. The supernatant was collected for protein quantification following centrifugation at 15,000 x g for 30 min at 4°C. The concentration of protein extracted from rat kidney tissue samples was quantified using a Bicinchoninic Acid Protein assay kit (Beyotime Institute of Biotechnology, Jiangsu, China). A total of 30 µg protein from each sample was separated on 12% gels by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and subsequently electroblotted onto polyvinylidene difluoride membranes. Membranes were incubated with blocking buffer (5% skimmed milk) at room temperature for 60 min and then incubated with primary antibodies (mouse anti-Fas-L, 1:200; rabbit anti-BID, 1:200; rabbit anti-Bax, 1:200; mouse anti-Bcl-2, 1:200; rabbit anti-TNF-α, 1:1,000; rabbit anti-caspase-8, 1:1,000; and rabbit anti-β-actin, 1:500) at 4°C overnight. Following washing in Tris-buffered saline with 0.1% Tween 20 (TBST), membranes were incubated with anti-mouse or anti-rabbit secondary antibodies (dilution, 1:5,000) at room temperature for 60 min. Membranes were then washed in TBST and the blots were detected using the Immobilon™ Western Chemiluminescent HRP Substrate (EMD Millipore, Billerica, MA, USA) followed by autoradiography. Protein density for quantification was determined using Image J software (version 1.45; National Institutes of Health, Bethesda, MD, USA). β-actin was used as a loading control and relative quantities of all proteins were expressed as a ratio to that of the NS group.

**Statistical analysis.** Data are expressed as the mean ± standard deviation. Analyses were performed using one-way analysis of variance with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The least-significant difference post-hoc test was used to assess differences between two groups. P<0.05 was considered to indicate a statistically significant difference.

**Results**

**Effects of RSV on renal function in CP-induced AKI.** It is known that typical AKI is characterized by a significant increase in Scr levels (2). As presented in Table I, CP led to significant increases in the levels of Scr, BUN and RI compared with the control group (P<0.001). However, co-treatment of RSV and CP attenuated the increase of Scr, BUN and RI compared with the CP group (P<0.001).

| Group    | n | Scr (µmol/l) | BUN (mmol/l) | RI         |
|----------|---|--------------|--------------|------------|
| NS       | 7 | 31.14±6.26   | 7.42±1.21    | 7.99±0.12  |
| RSV      | 7 | 28.71±5.28   | 6.13±0.61    | 8.00±0.16  |
| CP       | 7 | 192.29±11.44 | 43.39±2.20   | 9.36±0.11  |
| CP+RSV   | 7 | 63.86±8.71   | 19.04±1.94   | 8.81±0.17  |

Values are presented as the mean ± standard deviation. *P<0.05 vs. NS group; *P<0.05 vs. CP group. RSV, resveratrol group; Scr, serum creatinine; BUN, blood urea nitrogen; RI, renal index; n, number of rats per group; NS, control group; CP, cisplatin group.

**Renoprotective and anti-apoptotic effects of RSV in CP-induced AKI.** H&E staining of kidney tissues was used to evaluate the histological changes in renal tubular epithelium. As presented in Fig. 1A, histological examination revealed that the kidneys from the control and RSV groups maintained normal tubular morphology, whereas the kidneys from the CP group displayed significant features of AKI, including brush border loss, epithelial cell vacuolation and cast formation. Semi-quantitative analysis of the extent of the histological damage in the CP group was scored as 3.04, in comparison with no damage in the control group (P<0.001; Fig. 1B). By contrast, the extent of tubular damage was significantly reduced in the CP+RSV group compared with the CP group, with a histological damage score of 1.9 (P<0.001; Fig. 1A and B).

Tubular cell apoptosis was detected in the CP-induced AKI model by TUNEL assay, as presented in Fig. 1C. The NS and RSV groups exhibited limited apoptosis (Fig. 1D), whereas...
the number of TUNEL-positive nuclei, indicating apoptosed cells, was significantly increased in the CP group compared with the NS group (P<0.001; Fig. 1D). However, the number of TUNEL-positive cells in the CP+RSV group was significantly reduced compared with the CP group (P<0.001), indicating reduced apoptosis in this group.

**Effect of RSV on vital protein expressions in the process of CP-induced AKI.** Death receptor-mediated apoptotic pathways have been implicated in CP-induced AKI. Thus, the expression of certain vital proteins in this signaling pathway, including Fas-L, TNF-α and caspase-8, were examined. The function of caspase-8 in the intrinsic mitochondrial apoptotic pathway was also investigated by examining the expression levels of BID, Bax and Bcl-2.

As presented in Fig. 2A and B, Fas-L staining score in the damaged tubules was significantly higher in the CP group compared with the NS group (P<0.001), and significantly reduced in the CP+RSV group compared with the CP group (P<0.001). Western blot analysis of Fas-L protein expression was consistent with the immunohistochemical observations (NS vs. CP, P<0.001; CP vs. CP+RSV, P=0.004; Fig. 2C). Similarly, TNF-α expression was significantly higher in the CP group compared with the NS group (P<0.001), whereas the CP+RSV group demonstrated significantly less expression of TNF-α compared with the CP group (P<0.001; Fig. 2D).

In addition, the expression of caspase-8 significantly increased in the CP group compared with the NS group (P<0.001; Fig. 3A), while the CP+RSV group exhibited significantly less expression than the CP group (P<0.001). Activated caspase-8 is known to cleave BID, and thus, may cause the significantly reduced level of BID detected by western blot analysis in the CP group compared with the NS group (P<0.001; Fig. 3B). By contrast, treatment with RSV suppressed this downregulation of BID protein levels in the CP+RSV group compared with the CP group (P=0.005; Fig. 3B).
Furthermore, expression of the Bax apoptosis regulator was measured by immunohistochemistry and western blotting (Fig. 4). Significantly increased levels of Bax protein expression were observed in the CP group compared with the NS group by immunohistochemistry (P<0.001; Fig. 4A and B) and western blot (P<0.001; Fig. 4C), while Bax expression was significantly lower in the CP+RSV group than in the CP group as demonstrated by both immunohistochemistry (P<0.001; Fig. 4A and B) and western blot (P=0.002; Fig 4C). Expression of the anti-apoptosis regulator Bcl-2 was significantly reduced in the CP group compared with the NS group as demonstrated by immunohistochemistry (P<0.001; Fig. 4D and E) and western blot analysis (P=0.004; Fig. 4F). Expression of Bcl-2 detected in kidneys from the CP+RSV group was significantly increased compared with the CP group as demonstrated by immunohistochemistry (P<0.001; Fig. 4D and E) and western blot analysis (P<0.001; Fig. 4F).

Discussion

The present study sought to investigate whether RSV exerted a renoprotective effect on CP-induced AKI in a rat model by inhibiting death receptor-mediated apoptotic pathways. RSV was revealed to facilitate a significant reduction in Scr, BUN and RI levels, indicating significantly reduced renal injury and dysfunction which was further verified by H&E staining and apoptosis analysis of renal histology. In addition, RSV was demonstrated to suppress the upregulation of Fas-L and TNF-α, and to modulate the expression levels of the downstream signaling effectors, caspase-8, BID, Bax and Bcl-2, to accomplish its protective effect.

As a polyphenolic phytoalexin, RSV has been reported to be beneficial for the prevention of numerous types of kidney disease, including diabetic nephropathy (27), drug-induced renal injury (28,24), and ischemia-reperfusion and sepsis-induced kidney injuries (29,30). Consistent with these observations, the results of the present study demonstrate the beneficial effects of RSV in the prevention of renal tubular damage and dysfunction. The protective effects of RSV were confirmed to be associated with a reduction in Fas-L, TNF-α and caspase-8 expression levels, which were augmented by CP. Previous studies have reported that RSV is involved in mediating numerous signaling pathways in AKI (20,28,24), however, no study conducted to date has demonstrated the role of RSV in regulating extrinsic apoptotic signaling pathways.

In the present study, it remains unclear whether the positive effects of RSV in preventing damage to renal tubular cells, is directly associated with a reduction in the expression levels of Fas-L, TNF-α and caspase-8. CP-induced tubular apoptosis was initiated by Fas-L, which is expressed on renal tubular cells and immune cells, and is capable of inducing adjacent tubule cell death. Therefore, inhibiting Fas-L may reduce CP-induced tubular apoptosis and completely restore the survival of mice treated with a lethal CP dose (11). TNF-α knockout mice exhibit reduced renal dysfunction, renal histological injury and serum TNF-α levels (31). TNF-α receptor knockout mice also consistently present less renal tubular cell death, further supporting the involvement of death receptor-mediated pathways in the pathogenesis of AKI induced by CP (11). And the present study demonstrated that CP increased Fas-L, TNF-α and caspase-8 expression in an AKI model, and that RSV suppressed the upregulation of these effectors. High expression of Fas-L and TNF-α indicates the activation of the extrinsic apoptotic pathway that can be caused by CP. With the interaction between TNF family ligands and their receptors, the downstream signaling molecule, caspase-8 is also activated, which is a marker of the extrinsic apoptotic pathways (32). It has been demonstrated that RSV can serve a protective role in CP-induced renal injury by reducing free radicals (28) and activating sirtuin 1 (24). The results of the present study demonstrate that RSV can decrease Fas-L, TNF-α and caspase-8 expression, which is similar to the effect of other antioxidants on CP-induced renal injury, such as epigallocatechin-3-gallate (10) and dimethylthiourea (13). Therefore, these findings indicate that the potential mechanism of RSV in the prevention of CP-induced AKI involves extrinsic apoptotic pathways.

The implementation of programmed cell death is enforced by caspase-8 through two different pathways (14,33). In pathway 1, the high caspase-8 concentration directly activates the downstream effector, caspase-3. Caspase-3 is then cleaved and stimulates apoptosis. In pathway 2, the low caspase-8 concentration can cleave BID, a death-inducing member of the Bcl-2 family (14,15), rather than directly activating caspase-3.

Figure 3. Protein expression levels of caspase-8 and BID. Western blot analysis and quantification protein expression levels of (A) caspase-8 and (B) BID, relative to β-actin control. Values are presented as the mean ± standard deviation of three independent experiments. *P<0.05 vs. NS group; #P<0.05 vs. CP group. NS, untreated control; RSV, resveratrol; CP, cisplatin; BID, BH3 interacting domain death agonist.
to execute programmed cell death. tBID translocates to the mitochondria membrane (16,32,34). Additionally, previous studies have demonstrated that tBID promotes Bax activation and facilitates the insertion/oligomerization of Bax into the mitochondrial outer membrane (35,36). As a result, pores of the mitochondrial membranes are formed, and apoptotic proteins residing in the intermembrane space are released (36). As a member of the anti-apoptotic Bcl-2 family, Bcl-2 can prevent mitochondrial permeability transition of tBID and Bax, and is pivotal for the inhibition of apoptosis (1,15). Overexpression of Bcl-2 suppresses apoptosis (1,15), thus, the cross talk between the mitochondrial and death receptor-mediated apoptotic pathways occurs through caspase-8. In the present study, CP has been suggested to increase the cleavage of BID as the expression of BID in the CP group was significantly lower than in the NS group, whereas compared with the CP group the expression of BID increased upon treatment with RSV. Meanwhile, the activation of the intrinsic mitochondrial pathway was examined through examination of Bax and Bcl-2 expression. High level expression of Bax and low level expression of Bcl-2 were observed in the CP group, and the reverse phenomenon in the CP+RSV group. Previous studies have demonstrated that caspase-8 (following activation in the extrinsic pathway) can activate the intrinsic apoptosis pathway through Bcl-2 family proteins, such as Bid (16,32,34). In the present study, CP is demonstrated to induce the apoptosis pathway mediated by death receptors, which is similar to the effects observed from dimethylthiourea on CP-induced renal injury (13) and the loss of α(E)-catenin on CP-challenged renal tubular epithelial cells (15). Finally, the expression of these signal pathways leads to renal tubular cell apoptosis. Therefore, RSV treatment may reduce Bax expression and upregulate BID and Bcl-2 expression via the interaction between the extrinsic and intrinsic signaling pathways through caspase-8, which could exert an important protective role in the process of CP-induced AKI.

In conclusion, the present study indicated that RSV may protect against CP-induced AKI, and the underlying mechanism is associated with the suppression of apoptosis via death receptor-mediated pathways. RSV may, therefore, have potential value in the treatment of patients suffering from AKI and warrants further investigation of its therapeutic activity in the clinic.
Resveratrol reverses remodeling in hearts

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