Expression of NAD(P)H:Quinone Oxidoreductase 1 and Its Significance in Human Abdominal Aortic Aneurysmal Tissues

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Research article

Keywords: abdominal aortic aneurysm, tandem mass tag, proteomics, oxidative stress, NQO1, aging

Posted Date: September 15th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-72838/v1

Abstract

Background NAD(P)H:quinone oxidoreductase 1 (NQO1) protein protects cells against redox cycling of quinones and oxidative stress. Oxidative stress represents key mechanisms leading to abdominal aortic aneurysm (AAA) formation. However, a role of NQO1 in AAA formation has not been investigated previously.

Methods The Tandem Mass Tag (TMT) labeling quantitative proteomics technique was utilized to detect 3 AAA tissues and 3 corresponding adjacent normal abdominal aorta tissue specimens. Immunohistochemistry was used to detect NQO1 expression in 8 AAA tissues, and the correlation with AAA size, MDA and SOD levels was analyzed. The senescence model of human vascular smooth muscle cell (VSMCs) induced by Angiotensin II (AngII) was established in vitro. The effect of AngII on the level of reactive oxygen species (ROS) and β-galactosidase activity of VSMCs were observed after NQO1 expression was inhibited by specific interfering RNA (si-NQO1) technique.

Results NQO1 expression was the highest up-regulation (3.1fold) among 11 differentially expressed oxidative stress-related proteins (> 1.2 or<0.83 and P<0.05), and the expression of NQO1 was positively correlated with the AAA size (R^2=0.517, P<0.05) and MDA level (R^2=0.659, P<0.05). AngII treatment of human VSMCs increased ROS expression and β-galactosidase activity, while knocking down NQO1 expression promoted AngII-induced ROS production and cell aging.

Conclusion Up-regulation of NQO1expression plays an antioxidant role in AAA, and it is expected to be a biomarker for early diagnosis and prognosis assessment of AAA.

Background

Abdominal aortic aneurysm (AAA) is a vascular wall degenerative disease characterized by immune response, degradation of extracellular matrix, apoptosis of vascular smooth muscle cell and oxidative stress, because the growth and rupture of the aneurysm was uncertained that makes it high potentially lethal[1]. At present, surgical treatment of AAA only includes open surgical repair (OSR) and endovascular aneurysm repair (EVAR), the survival rate of patients treated with AAA is low and most of them would choose to undergo acute AAA repair again [2]. Small aneurysms and AAA in the early stage have no clinical symptoms and can't be treated by surgery, and there are still no effective therapy targets to intervene the evolution of AAA [3]. Therefore, it is very important to study its pathogenesis and targets of the diagnosis and treatment. Oxidative stress is considered to be the initial factor of vascular wall injury, which further leads to the accumulation of inflammatory cells, and the excessive production of reactive oxygen species (ROS) leads to degradation of extracellular matrix and apoptosis of VSMCs [4], which promotes the progression of AAA disease. Yang et al used gene chip to analyze 3 AAA samples in 2016 and found that most of the significantly different genes were related to energy metabolism and oxidative stress [5]. In an experimental animal AAA model, it was also found that the differentially expressed genes

were mainly enriched in oxidative stress [6], suggesting that oxidative stress is expected to become the therapeutic target of AAA [7].

In this study, Tandem mass tag (TMT) quantitative proteomics technique was used to detect the differentially expressed proteins(DEPs) related to oxidative stress in human AAA tissue samples and corresponding para-tumor vascular tissue samples. To explore the role of NQO1 expression in oxidative stress injury and aging induced by Angiotensin II (AngII) in human VSMCs in vitro, and to clarify the protective effect of NQO1 on oxidative stress damage in VSMCs, which is a potential molecular target for early diagnosis, treatment and prognosis evaluation of AAA.

Materials And Methods

Collection of tissue samples of AAA patients and healthy control group

8 cases of AAA tissue samples and 8 cases of paratumoral vascular tissue samples from September 2019 to November 2019 were collected from the Department of Cardiac surgery of the fourth Hospital of Hebei Medical University. The program and implementation of specimen collection have been approved by the Ethics Committee of Hebei Medical University, and all patients or their families have signed informed consent forms. Each vascular tissue sample was divided into two parts, one preserved in liquid nitrogen and the other embedded in paraffin.

TMT quantitative proteomics technique

Protein preparation, Peptide enzymatic hydrolysis and TMT labeling

Vascular tissue samples from 3 cases of AAA and 3 cases of Control were selected and the total protein was extracted by SDT (4% (w / v) SDS, 100mM Tris/HCl pH7.6, 0.1M DTT) cleavage method. The protein was quantified by BCA method, and the protein degradation of vascular tissue was observed by SDS-PAGE electrophoresis. An appropriate amount of protein was taken from each sample and trypsin was hydrolyzed into peptides by Filter aided proteome preparation (FASP) method. 100ug peptides were taken from each sample and labeled according to the (Thermo) instructions of TMT labeling kit, and the labeled peptides of each group were mixed in the same amount and classified by High pH Reversed-Phase Peptide Fractionation Kit.

LC-MS/MS data acquisition, Protein identification and Quantitative analysis

The fractionated samples were separated by HPLC and the chromatographic peaks were analyzed by Q-Exactive mass spectrometer. The original data of MS analysis was RAW file, and the database identification and quantitative analysis were performed by software Mascot2.2 and Proteome Discoverer1.4. The DEPs were screened according to the standard that the expression multiple changed up-regulated >1.2 or down-regulated< 0.83 with P value <0.05

Immunohistochemical Staining

4 μm tissue sections were dewaxed and immersed in PBS for high-pressure repair. Immunohistochemistry was performed using SP method according to the instructions. Five visual fields were randomly selected, and the percentage of brown particles in the whole visual field was analyzed by Image-Pro Plus 6.0software (American MEDIA CYBERNETIC Image Technology Company). The first antibody was rabbit anti-human antibody NQO1 (11451-1- AP, Proteintech).

Determination of MDA level and SOD activity in AAA tissue

Take 50 mg of human AAA tissue and Control tissue (8 cases each), add normal saline according to the volume (V) ：bimass (W) = 9:1, cut the vascular tissue, homogenate on ice, centrifuge for 4000 rpm/min and collect the supernatant, use SOD and MDA kit (Beijing Solarbio Science & Technology Co., Ltd.) to detect SOD activity and MDA level according to the instructions.

Detection of ROS level and β-galactosidase activity in VSMCs

Human VSMCs (ScienCell, no. 6110) was cultured with low glucose DMEM in vitro. The expression of NQO1 was inhibited by small RNA interference transfection technique and oxidative stress and aging were induced by AngII (100nmol/L, 5 d). The VSMCs of different treatment groups were divided into control group：Ang： group, Ang： + si-NC group and Ang： + siNQO1 group. Reactive oxygen species ROS detection kit (Biyuntian) and β-galactosidase staining kit (Cell signaling) were used to detect the level of ROS and the degree of cell aging in each group, and to clarify the relationship between NQO1 expression and oxidative stress damage and aging of VSMCs.

Statistical analysis

Graphpad Prism 8.0 and SPSS 23.0 statistical software were used for data analysis. Measurement results were expressed as mean ± standard deviation. T-test was used to compare the mean between the two groups, differences with $P < 0.05$ were reviewed statistically significant.

Results

Detection of protein expression in human AAA tissues by TMT

According to the results of TMT labeling mass spectrometry to detect the DEPs related to oxidative stress, a total of 11 proteins (NQO1, EPHX2, ALDH18A1, Ndufs2, PNPO, CST3, AXL, NDUFA4L2, NDUFS6, MFGE8 and SUMO3) were screened, of which the most significantly up-regulated protein was NQO1 (3.1fold). The cluster analysis was shown in figure 1, and the specific expression changes were shown in Table 1.

Table1. Oxidative stress related DEPs		
Protein	Fold	P
NQO1	3.124365	0.004852374
EPHX2	1.882234	0.033397493
ALDH18A1	1.477494	0.038565105
NDUFS2	0.812414	0.016298336
PNPO	0.787561	0.049461475
CST3	0.742132	0.013198098
AXL	0.721082	0.045381332
NDUFA4L2	0.68605	0.033294165
NDUFS6	0.664919	0.033121857
MFGE8	0.660409	0.042436533
SUMO3	0.655326	0.037141936

Immunohistochemical detection of NQO1 expression in AAA tissues

In order to determine the specific expression of NQO1 in AAA tissue and verify the results of TMT quantitative proteomics, we detected the media tissue of 8 cases of human AAA and corresponding adjacent control (Control) by immunohistochemistry. The results further confirmed that the expression of NQO1 protein in AAA tissue was significantly up-regulated (57.9 ± 4.9 vs 11.5 ±2.1%, $P < 0.001$), as shown in figure 2.

Relationship between NQO1 expression and AAA swelling size, MDA level and SOD activity

Taking the expression of NQO1 in AAA tissue as the dependent variable, the correlation between NQO1 expression and AAA expansion size, MDA evel and SOD activity was analyzed. The correlation between each index and NQO1 expression was statistically significant by using SPSS 23.0 analysis software. NQO1 was positively correlated with the swelling size of AAA($P=0.044$) and the level of MDA in tissue($P=0.015$), and negatively correlated with the activity of SOD, but there was no statistical difference ($P > 0.05$), as shown in figure 3.

Inhibition of NQO1 expression in human VSMCs promotes AngII-induced oxidative stress damage and cell aging

In order to explore the relationship between NQO1 expression and oxidative stress injury and cell aging induced by AngII, AngII (100 nmol/L, 5 d) was used to treat the specific knockdown of NQO1 expression (si-NQO1) in transfected siRNA or human VSMCs transfected with si-NC control. Results as shown in

figure 4, ROS level andβ-galactosidase staining increased in VSMCs treated with Ang (***P < 0.001), while the oxidative stress damage and cell aging of VSMCs in Ang + si-NQO1 were further aggravated (#P < 0.001). It is therefore suggested that NQO1 may play a certain role in vascular protection by antagonizing oxidative stress injury and cell aging in AAA tissue.

Discussion

In this study, we compared with the control group by using TMT-labeled proteomic method, which was found that there were 11 DEPs related to oxidative stress in human AAA tissues, the expression of NQO1was the most significantly up-regulated(3.1 fold). The expression of NQO1 was positively correlated with the swelling size of AAA and the level of ROS. In the senescence model of human VSMCs induced by AngII, it was found that inhibiting the expression of NQO1 promoted the accumulation of ROS and cell aging, suggesting that the increased expression of NQO1 could antagonize the cell injury induced by ROS accumulation.

NQO1 is a kind of luteinase located in the cytoplasm, which can catalyze the production of stable hydroquinone and protect cells against redox cycling of quinones and oxidative stress [8, 9]. However, NQO1 can also be directly reduced to unstable hydroquinone in some cases, leading to DNA alkylation or a large amount of ROS rapid production through via redox cycling [9, 10]. It has been reported that NQO1 can mitigate the oxidative DNA damage arising from the interplay intracellular ROS in post-mitotic ocular tissue [11]. ROS is overproduced in the progression of AAA disease, which leads to the degradation of extracellular matrix and the change of VSMCs phenotype [12]. It is found that the overexpression of NQO1 in AAA tissue antagonizes the oxidative stress damage caused by excessive ROS. Meanwhile, the high expression of NQO1 may be accompanied by the production of unstable hydroquinone, which promotes the production of a large number of ROS and aggravates the oxidative stress damage of blood vessels, suggesting that oxidative stress is expected to become a potential target for the treatment of AAA [4]. It is of great significance to explore the role of NQO1 in AAA.

The overexpression of NQO1 in lung, gastric, colon, cervical, pancreatic and breast cancer is closely associated with poor patient prognosis [13]. As a regulator of transcription factor NRF2, the increased expression of NQO1 in cancer cells contributes to tolerance to oxidative stress [9]. The overexpression of NRF2/NQO1 in hepatocellular carcinoma was associated with tumor size, high α-fetoprotein, DES-γ-carboxy-prothrombin levels and multiple intrahepatic recurrences, could as an independent risk factor [14]. It has been found that the potential mechanism of NQO1 promoting cancer cell proliferation is mainly through the activation of SIRT6/AKT/XIAP signal pathway [15] or by regulating the activity of STRI2 to regulate the process of mitosis [16]. In this study, it was found that NQO1 expression was positively correlated with AAA size and ROS level. Silencing NQO1 expression promoted the oxidative stress damage and aging of VSMCs induced by AngII, which indicated that NQO1 played the role of antioxidant stress damage in AAA, but also showed that NQO1 expression could not balance the oxidative stress level of AAA, which led to the increase of NQO1 expression related to the histopathological severity of AAA, suggesting that it may become a biomarker of AAA. In addition, the up-

regulated expression of NQO1 can slow down cell aging and play the anti-apoptosis role of VSMCs; furthermore, NQO1 promotes VSMCs proliferation by promoting mitosis and participates in intimal hyperplasia and pathological remodeling, the specific mechanism still needs to be further studied.

In this study, we found that among the 11 oxidative stress-related DEPs in AAA, the up-regulated proteins included NQO1, EPHX2 and ALDH18A1. Among them, the up-regulation of EPHX2 is related to endoplasmic reticulum stress in obesity, physical activity may reduce metabolic stress by inhibiting EPHX2 expression, and then activating PI3K/Akt/GSK3 β signal pathway to achieve the protective effect of antioxidant injury [17, 18]. Down-regulated proteins include Ndufs2, PNPO, CST3, AXL, NDUFA4L2, NDUFS6, MFGE8 and SUMO3, in which Ndufs2 is the core subunit of mitochondrial complex I, which can improve pulmonary vascular sensitivity during acute hypoxia and play an important protective role in hypoxic pulmonary vasoconstriction [19]. It has been reported that CST3 has protective effects on various oxidative stress injuries that induce neuronal apoptosis [20]. In the process of acute kidney injury (AKI) developing into chronic kidney disease (CKD), melatonin and Poricoic Acid A (PAA) in the early stage can up-regulate Gas6/AXL signal to attenuate the oxidative stress and inflammation in AKI, and in the later stage down-regulate Gas6/AXL signal to reduce renal fibrosis and CKD [21]. It is inferred that AXL expression may be up-regulated in the stage of AAA formation and contribute to antioxidant stress. However, the expression may be down-regulated due to decompensation in ruptured AAA or giant aneurysms. It has been reported that the up-regulated expression of NDUFA4L2 improves the apoptosis of nucleus pulposus (NP) cells by inhibiting mitosis induced through oxidative stress [22]. NDUFS6 is one of the important components of NADH, and NDUFS6 knockout mice can cause mitochondrial complex I deficiency specific cardiomyopathy, which reduces cardiomyocyte energy metabolism and mitochondrial function in mice, it is consistent with the clinical symptoms of patients with mitochondrial cardiomyopathy [23]. MFGE8 can attenuate oxidative stress and brain injury after subarachnoid hemorrhage through integrin β-3-related molecular pathways [24, 25]. SUMO is a small ubiquitin-related modifier that could protect cells from various stressors including ischemia-reperfusion [26], while cellular oxidative stress leads to down-regulation of SUMO3 transcription [27]. The results of this study are consistent with previous research reports, the expression of these proteins is decreased in AAA tissues, resulting in redox homeostasis imbalance. The up-regulated expression of NQO1 alone is not enough to maintain vascular homeostasis, so the oxidative stress in AAA is still at a high level.

Conclusion

In a conclusion, the up-regulated expression of NQO1 in the pathological changes of AAA is a compensatory mechanism. Under various inducing factors of AAA (AngII, serum factors, hypoxia, inflammatory factors, oxidized low density lipoprotein, etc.), excessive oxidative stress of VSMCs, compensatory increase of NQO1, imbalance the expression of multiple genes maintaining redox balance, intimal hyperplasia and remodeling, and finally lead to the formation and progression of AAA. Therefore, NQO1 may be used as a biomarker for AAA early diagnosis, and multi-target regulation of oxidative stress-related protein expression is likely to be one of the measures for the treatment of AAA.

Declarations

Authors' contributions

Q C, J Z, S J and Y X: clinical sample collection, data analysis and interpretation, manuscript writing; J Z, X B and Q L.: Experimental study design, collection and assembly of data, manuscript writing; D M.: concept and design, financial support, collection and assembly of data, data analysis and interpretation, manuscript writing. All authors have read and approved the manuscript.

Acknowledgments

Not applicable.

Availability of data and materials

All original source datasets and measurements in the study are available from the corresponding author on request.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

Project supported by the Funds of the National Natural Science Foundation of China (Grant No.81700416).

Consent for publication

Approved by the Ethics Committee of Hebei Medical University.

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Figures

Figure 1

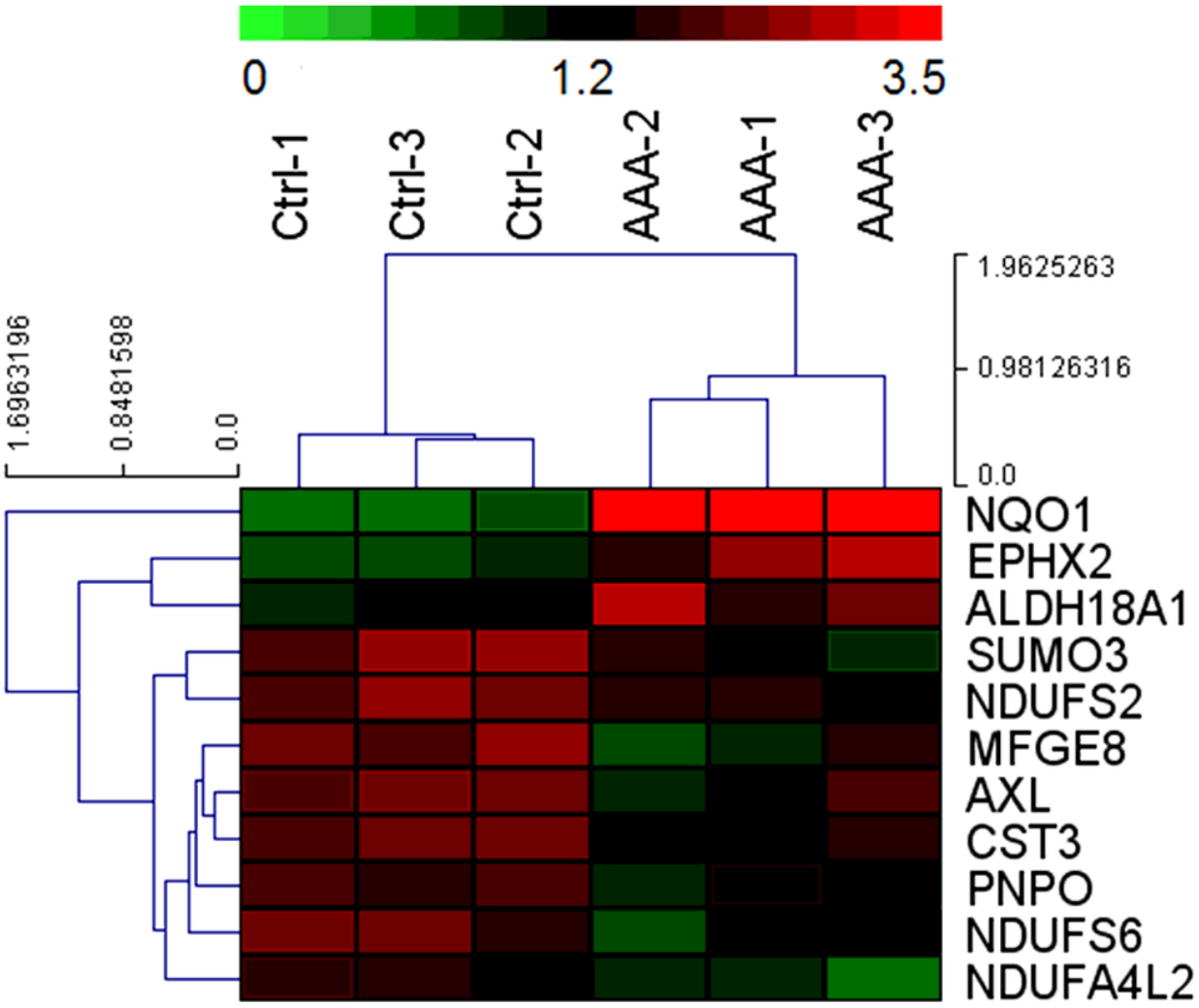

Figure 1

DEPs cluster analysis of oxidative stress in human AAA tissue detected by TMT

Figure 2

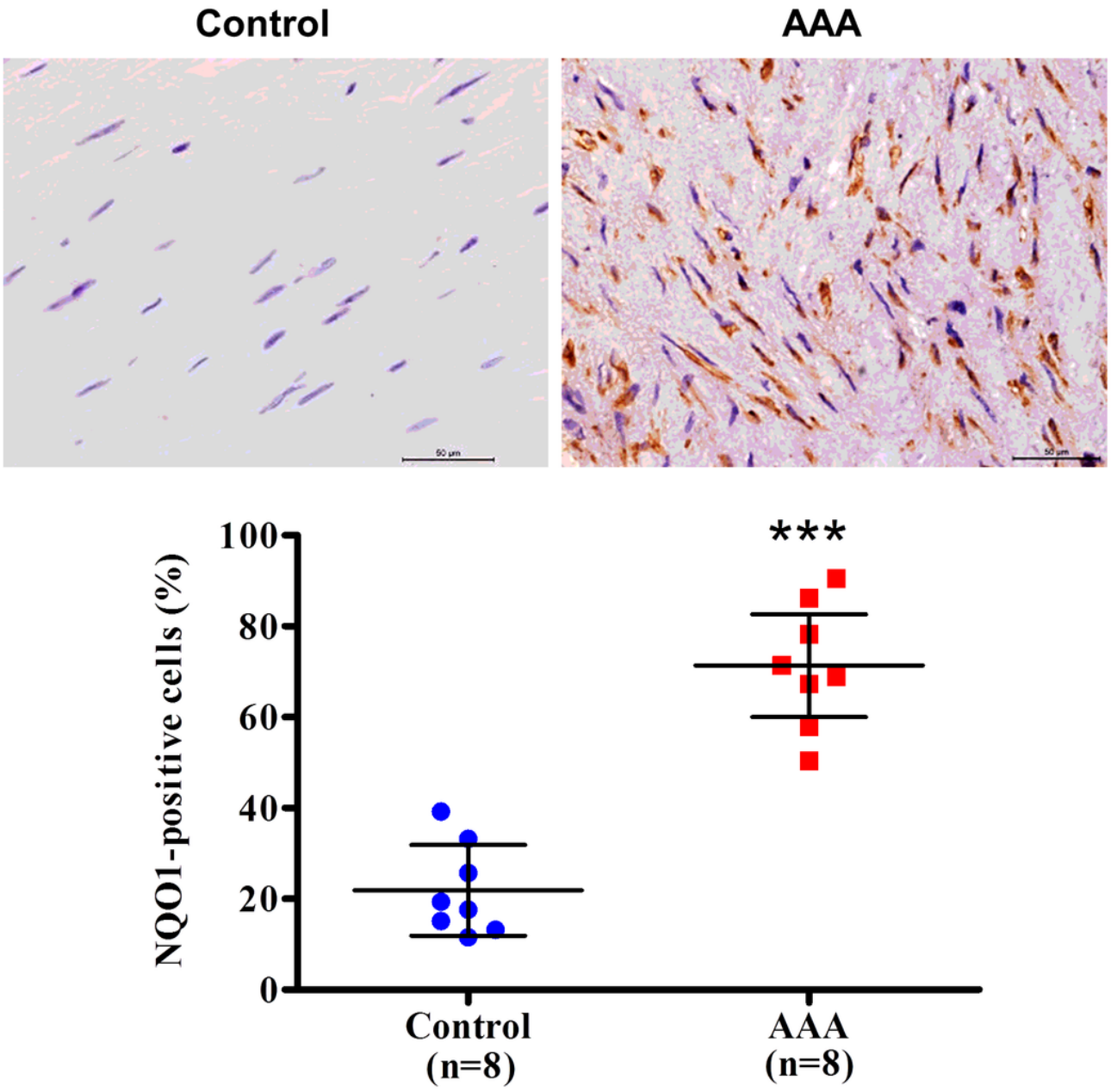

Figure 2

IHC detection of NQO1 expression in human AAA and corresponding control tissues

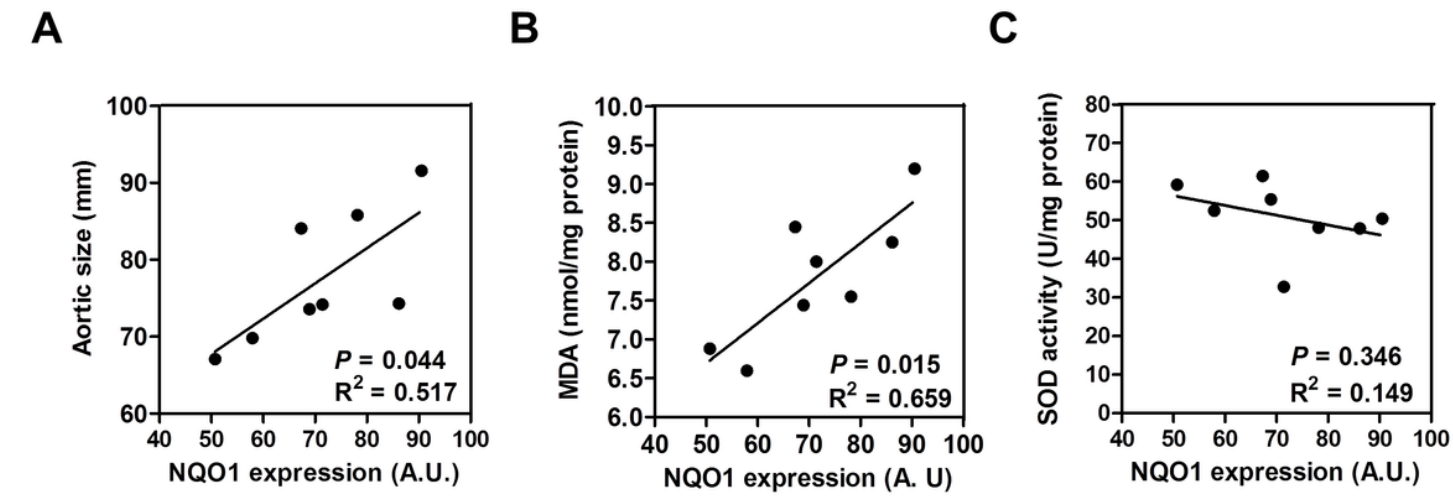

Figure 3

Correlation between NQO1 expression and AAA swelling size, MDA level and SOD activity

Figure 4

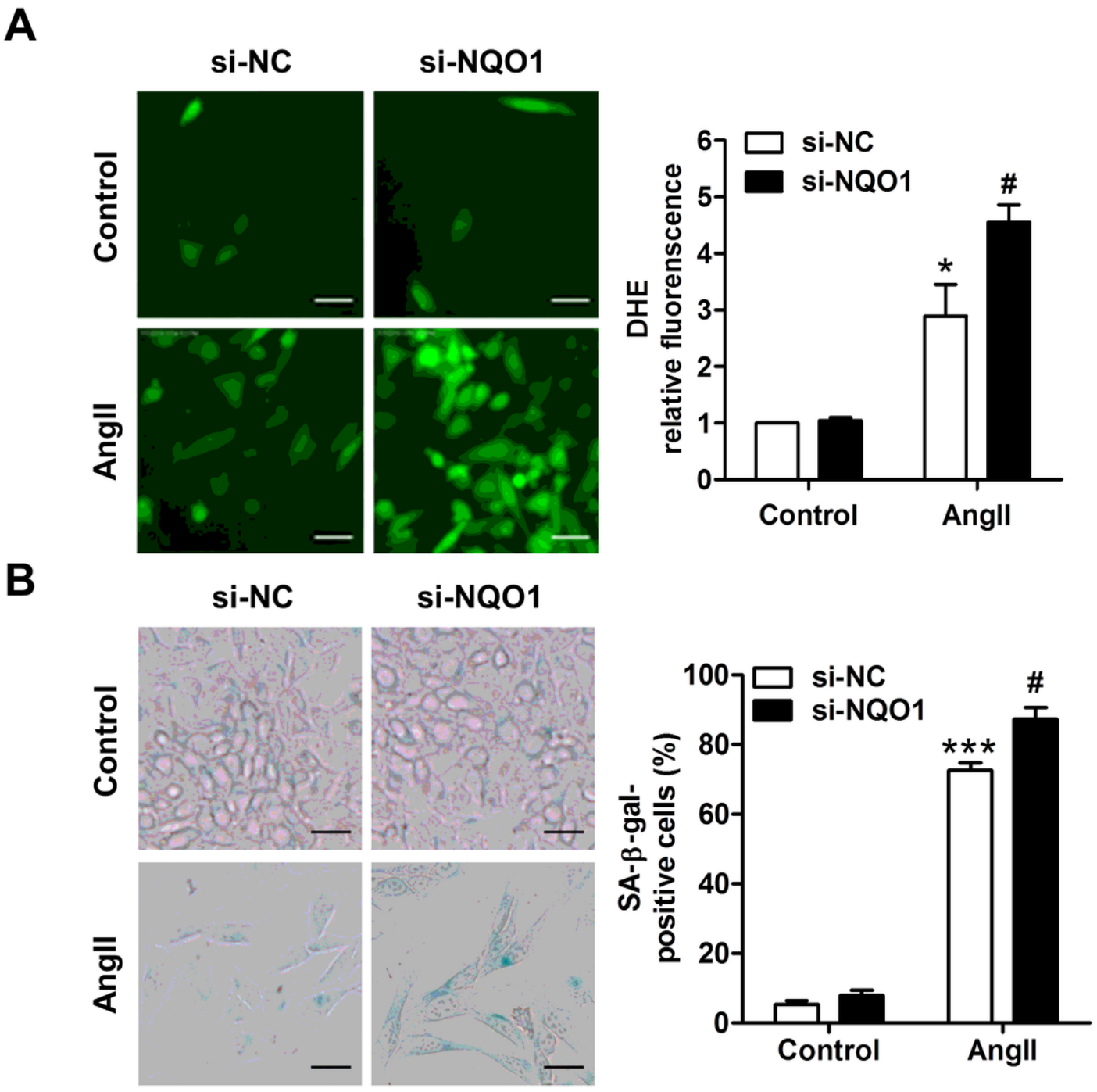

Figure 4

Silencing NQO1 expression affects AngII-induced oxidative stress damage and cell aging of human VSMCs. A. The result is to detect the level of ROS production by DHE staining. B. Staining result showed β-galactosidase activity. *P<0.05 and ***P<0.001 vs Control；#P<0.05 vs AngII.