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Original Article

Altered patterns of gene expression distinguishing unruptured abdominal aortic aneurysms from ruptured ones: comprehensive analysis of inflammatory factors

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Abstract: The purpose of this study was to profile altered patterns of gene expression that characterize abdominal aortic aneurysm and to compare these patterns between different conditions, unruptured (URA) and ruptured (RA). Full-thickness aortic wall tissues were obtained from patients during surgical repair of abdominal aortic aneurysm, including unruptured (n=29) and ruptured (n=11). RNA, protein and blood samples were prepared for each specimen, and differential levels of gene expression between unruptured and ruptured abdominal aortic tissues were assessed by immunohistochemistry, RT-qPCR and ELISA assays. Biochemical assay showed that triglyceride (TG), total cholesterol (TC) and low density lipoprotein (LDL) concentration in the peripheral blood of URA and UA patients with large size of aneurysm (>5 cm) was significantly increased compared with those with small size of aneurysm (3-5 cm). Of 7 genes examined, TRPV1, CAM, TNF-α, IL-6, MCP-1 and VCAM were significantly increased in RA patients compared with URA patients, which also showed markedly increased expression in large size of aneurysm, with TRPV1 and CAM exception in RA patients. Only PPARδ expression observed decrease in RA patients with larger size of aneurysm. Taken together, URA and RA exhibit distinct patterns of gene expression, with most alterations being unique to this disease. Abdominal aortic aneurysm arising in different sizes of aneurysm is thus characterized by a high degree of molecular heterogeneity, reflecting different pathophysiologic mechanisms.

Keywords: Abdominal aortic aneurysm, gene expression, inflammation

Introduction

Abdominal aortic aneurysm characterized by a localized dilation of the abdominal aorta that exceeds 50% of the normal diameter, the histopathological features of which are dominated by upregulation of proteolytic pathways, apoptosis, oxidative stress, inflammation, and loss of arterial wall matrix [1]. Rupture occurs when the tangential tension and stretch on the aneurysmal wall from blood pressure exceeds maximum allowable thresholds. Although the chance that aneurysm is detected has increased, with advanced improvement of imaging techniques, the decision for patients with unruptured aneurysms whether to treat is often ambiguity because of the considerably balanced the risk between treatment and rupture [2]. The most commonly used predictor of abdominal aortic aneurysm rupture is the maximum diameter of the aneurysm, and others such as biomarkers and biomechanics have also been investigated for predicting rupture [3, 4], however, it is not yet sufficiently specific to apply in general clinical practice.

Risk factors for abdominal aortic aneurysm have been described based on large scale and cross-sectional studies, including age, sex, family history, smoking, lipid levels, hypertension, obesity, alcohol intake and diabetes [5-8]. Previous studies have been reported that the rate of rupture was higher in women than in men with abdominal aortic aneurysm, suggesting the diameter threshold for elective surgical intervention might be lower for women than for men [2]. Elevation in the level of on inflammation-sensitive plasma proteins, such as fibrinogen and α1-antitrypsin, is likely to be a consequence of rupture, rather than an actual predictor of risk [9]. Numerous studies have reported on mechanical and structural properties

Table 1. Clinicopathological characteristics and follow-up data of 40 patients with abdominal aortic aneurysm

	No. of 3-5 URA (n=17)	No. of 5 URA (n=12)	No. of 3-5 RA (n=6)	No. of 5 RA (n=5)
Gender (Male/female)	15/2	11/1	5/1	4/1
Age range (median)	51-74 (64.0)	56-79 (64.5)	57-72 (61.3)	53-66 (58.0)
Hypertension (yes/no)	9/8	9/3	2/4	0/5
Diabetes (yes/no)	1/16	2/10	1/5	1/4
Coronary disease (yes/no)	2/15	5/7	1/5	1/4
Smoke (yes/no)	12/5	8/4	5/1	4/1
Pulmonary disease	2/15	4/8	0/6	0/5
Size of aneurysm (mm), range (median)	31-50 (39.0)	54-83 (64.5)	55-89 (84.3)	62-100 (99.0)

of unruptured abdominal aortic aneurysm [10, 12]. However, the cause(s) and prognostic indicator(s) of AAA rupture continue to elude our understanding largely because studies on lesions that did rupture are scarce that attributed to their rarely available for studies [9, 13]. Understanding the mechanical failure properties can be valuable in gaining insights into the phenomenon of rupture.

Further studies indicate that the cellular and molecular mechanisms underlying aneurysmal disease may be different, with unlikely to be related to a single gene mutation, but multiple genetic factors are implicated, particularly proinflammatory cytokines (e.g. TNF, IFN-γ, TGF-1β, IL-4, IL-5 and IL-10) [14, 15], chemokines (e.g. COX-2 and CCL22) [16, 17], and cell adhesion molecules (e.g. MMP8 and MMP9) [18, 19]. Despite significant progress during the past decade toward understanding the pathogenesis of aneurysmal disease, the specific factors causing abdominal aortic aneurysm in various lesions remain unresolved.

In this study, clinical patients at the hospital with unruptured and ruptured abdominal aortic aneurysm were wholly harvested, and mechanical properties and cellular content were assessed.

Materials and methods

Aortic tissues

Full-thickness aortic wall specimens were obtained from 40 patients undergoing elective surgical repair of asymptomatic abdominal aortic aneurysm. The clinicopathological characteristics and follow-up data of 40 patients with abdominal aortic aneurysm were shown in **Table 1**. All tissue specimens were snap-frozen in liquid nitrogen immediately on procurement and stored at -80°C before nucleic acid extraction. All tissues were obtained with approval by The Affiliated Hospital of Qingdao University human research subjects committee.

Biochemical measurement

Blood samples were collected after an overnight fast, and the serum was separated and analyzed for total cholesterol (TC), triglycerides (TG), and low density lipoprotein (LDL) using automated assays (Hitachi 917, Roche Diagnostics GmBH, Mannheim, Germany).

Histological analyses

Following fixation with 4% paraformaldehyde, tissues were embedded in paraffin. The paraffin blocks were sectioned into 5-μm slices, deparaffinized and hydrated in H_2O. Aortic sections were stained with hematoxylin-eosin (HE) as the manufacturer's instructions. For immunohistochemistry, tissues were boiled in 10 mmol/L sodium citrate buffer (pH 6.0) for 10 min to retrieve antigens. Each section was incubated with primary antibody overnight at room temperature or 4°C. To detect TRPV1, CAM, and PPARδ, HRP-conjugated secondary antibodies (Invitrogen) were used. Immunohistochemical signals were calculated with the positive staining cells under a microscope (Olympus Corporation) with magnification of × 200.

Reverse transcription-quantitative polymerase chain reaction

To independently confirm results obtained by immunohistochemistry analysis, the relative expression patterns of 3 out of 9 selected genes were also measured by reverse tran-

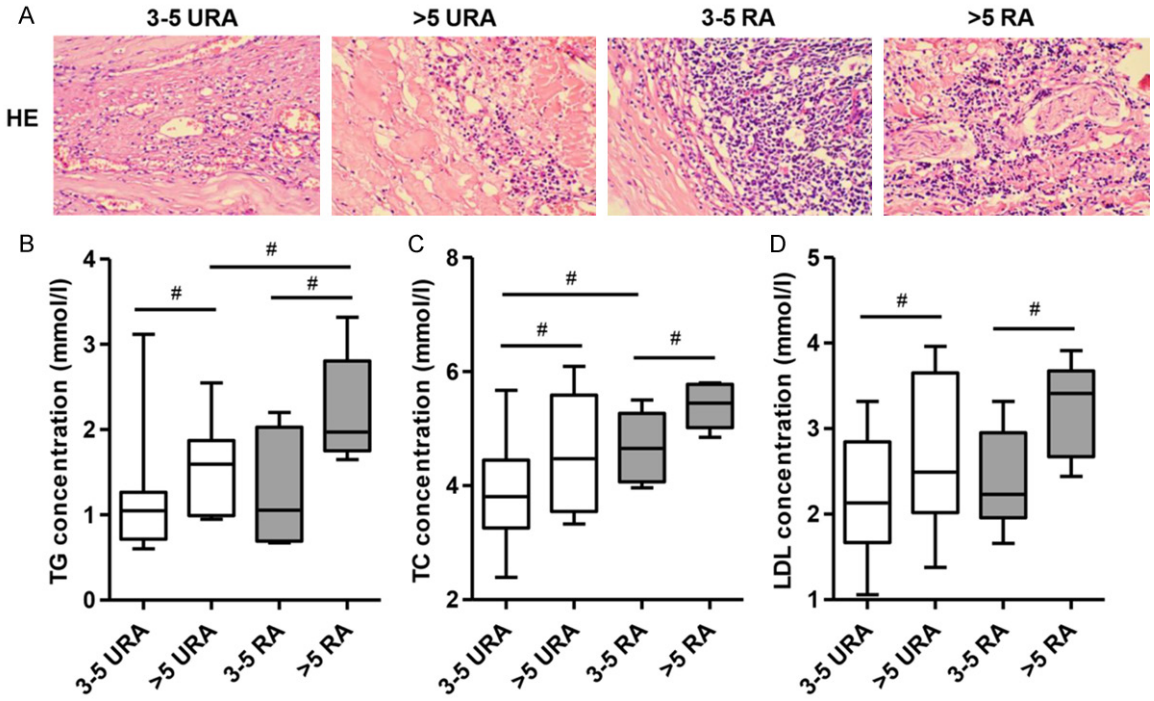

Figure 1. Histopathology of aortic aneurysms and serum lipid concentrations. (A) Representative sections of aortic wall tissue stained with HE (×200). The serum TG (B), TC (C) and LDL (D) concentrations were measured by biochemical analysis. #P<0.05.

scription-quantitative polymerase chain reaction (RT-qPCR) assays. Total RNA was extracted using TRIzol reagent, and cDNA was synthesized using SuperScript II Reverse Transcriptase. qRT-PCR was performed in a 25 μl of reaction system using SYBR® Green 10 × Supermix (Takara, Japan) on Roche Light Cycler® 480 II System (Roche Diagnostics Ltd., Switzerland). The following gene-specific primers were used in this study: TRPV1, 5'-GAAGACCCTCAGGCTCTATG-3' (forward) and 5'-CTTCAGGCTGTCCGTTTG-3' (reverse); CAM, 5'-TAGCAAGGCAGTGAGAAG-3' (forward) and 5'-AAGGACCAGTAGCAGAAG-3' (reverse); PPARδ, 5'-AGCACTGAAATCACTTTACC-3' (forward) and 5'-TATTGGGACAAATGGACATC-3' (reverse); GAPDH, 5'-CACCCACTCCTCCACCTTTG-3' (forward) and 5'-CCACCACCCTGTTGCTGTAG-3' (reverse). Relative quantification of the signals was performed by normalizing the signals of different genes with that of GAPDH. The gene expression was calculated using the $2^{-\Delta\Delta CT}$ method.

Serum cytokines

Serum TNF-α, IL-6, MCP-1 and VCAM levels were determined by commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions.

Statistical analysis

Experiments were performed with values expressed as mean ± SD. All statistical analyses were conducted using the Graphpad Prism 5.0 software (GraphPad Software, La Jolla, CA). Data were analyzed byunpaired, two-tailed Student's t-test. Differences below P<0.05 were considered statistically significant.

Results

Morphologic appearance of aneurysmal tissues

Light microscopy of abdominal aortic aneurysm tissues revealed extreme destruction of medial elastic fibers with replacement by a fibrocollagenous extracellular matrix and depletion of medial smooth muscle cells (**Figure 1A**). Abdominal aortic aneurysms also exhibited infiltration of the media and adventitia by mononuclear inflammatory cells, often in direct association with degenerating elastic fibers. Importantly, ruptured abdominal aortic aneurysm (RA)

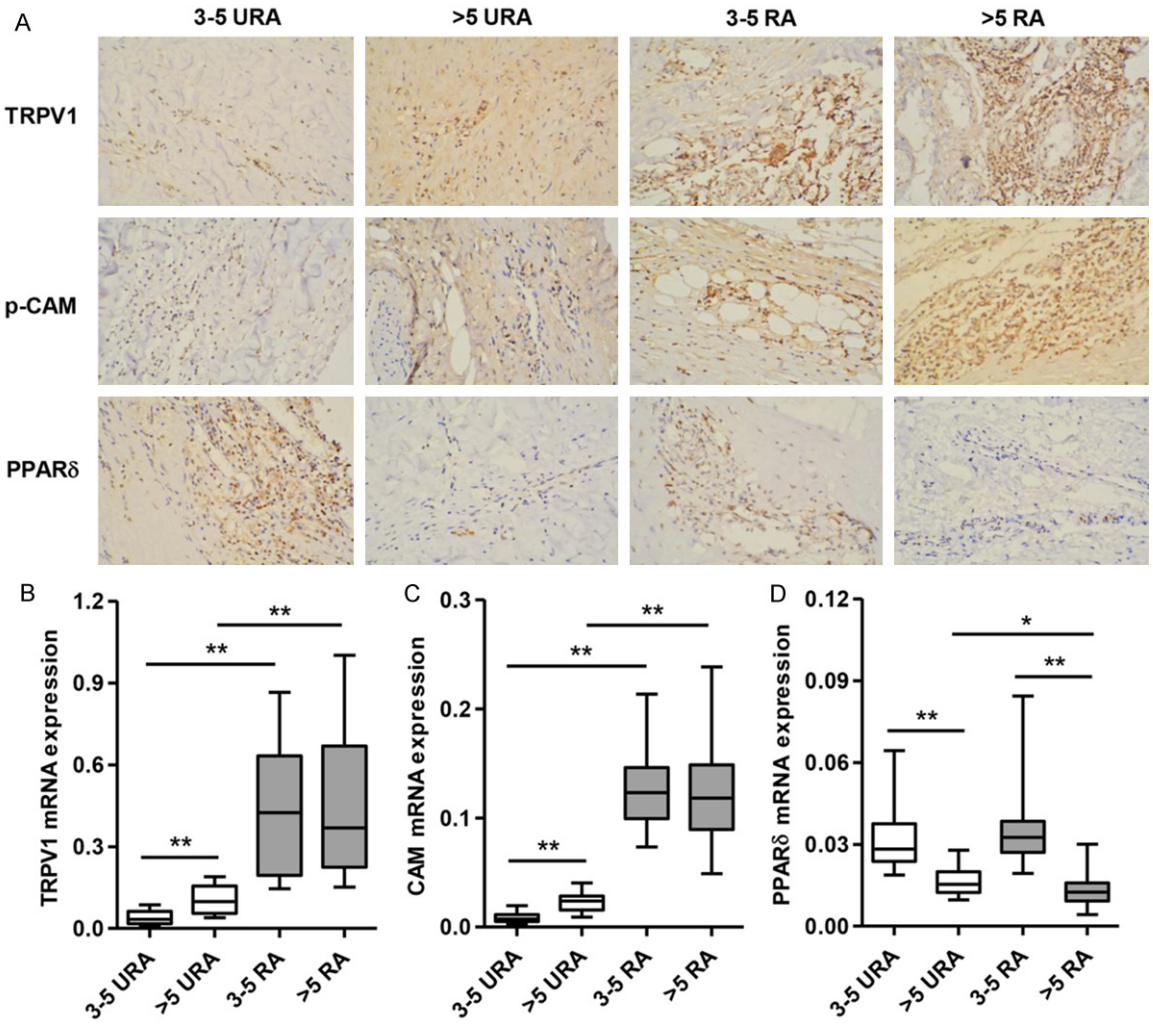

Figure 2. TRPV1, CAM and PPARδ expression in abdominal aortic aneurysm. (A) The TRPV1, p-CAM and PPARδ protein expressions were measured by immunohistochemical analysis. The TRPV1 (B), CAM (C) and PPARδ (D) mRNA expressions were measured by RT-qPCR. *P<0.01, **P<0.001.

showed serious physiological destruction compared with unruptured abdominal aortic aneurysm (URA), especially in larger size of aneurysm tissues.

Medications targeted at altering the concentrations of circulating lipids have an established role in occlusive atherosclerosis but are of unknown value in the primary prevention of abdominal aortic aneurysm. Therefore we examined the association between serum levels of TG, TC and LDL and the lesions of abdominal aortic aneurysm in a cohort of 40 patients with abdominal aortic aneurysm, including URA and RA. As shown in **Figure 1B**, **1C**, the serum TG, TC and LDL concentrations were lower in patients with small size of aneurysm, of which differential expression between URA and RA was also found.

Gene expression profiles of aneurysmal tissues

Three of genes represented on the immunohistochemical analysis were differentially expressed between aneurysmal tissues with small and large size of aneurysm, with the significantly increased expression of TRPV1 and phosphorylation of CAM (p-CAM) in large size of aneurysm in URA, and higher expression was also found in RA patients with same size of aneurysm compared with URA patients (**Figure 2A**). While, PPARδ expression was significantly decreased in patients with large size of

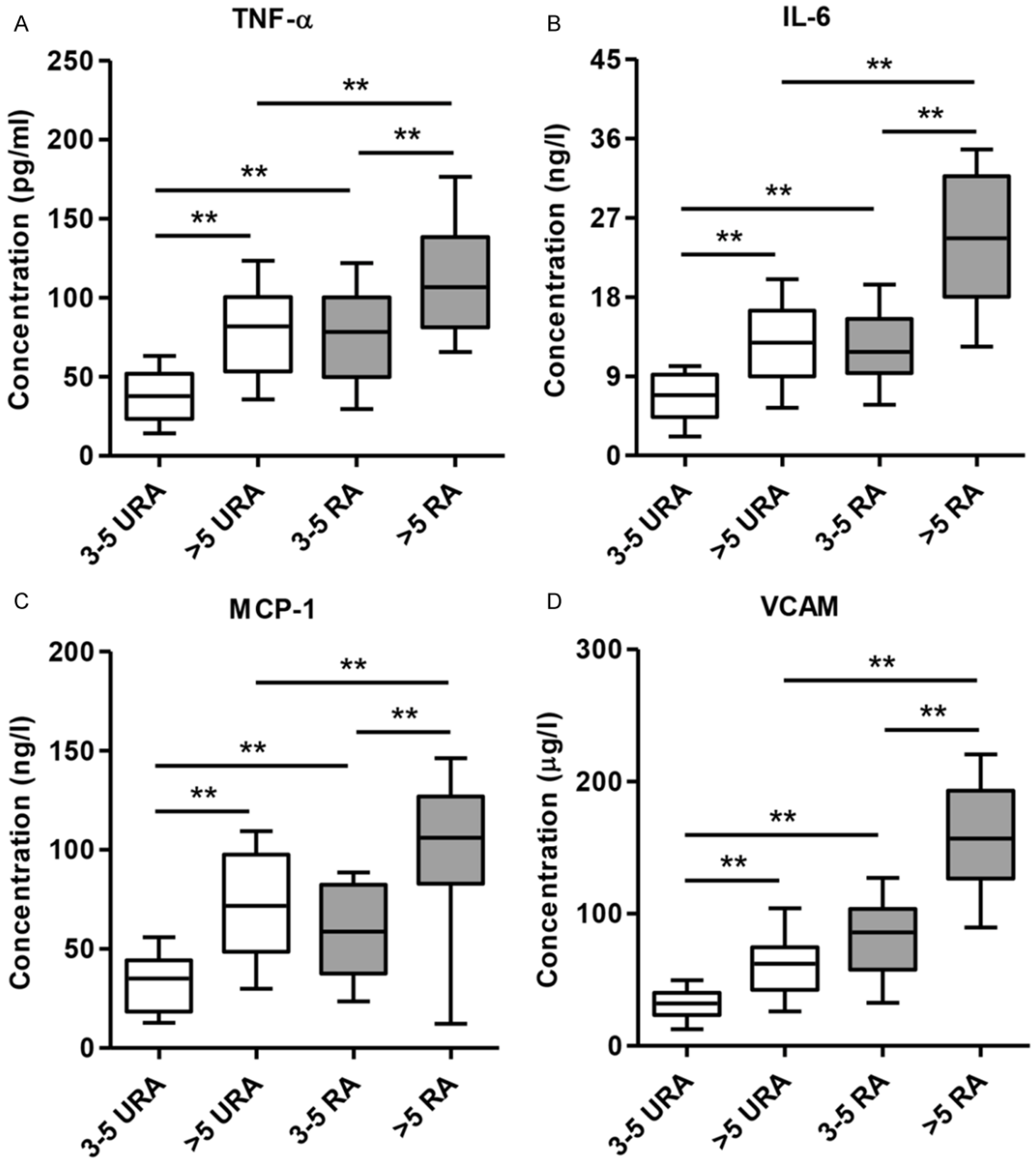

Figure 3. Serum cytokine levels in abdominal aortic aneurysm. The TNF-α (A), IL-6 (B), MCP (C) and VCAM (D) concentrations were measured by ELISA analysis. **P<0.001.

aneurysm. Moreover, TRPV1, CAM and PPARδ expression was also measured by RT-qPCR, which showed similar results as immunohistochemical analysis (**Figure 2B**, **2D**). Thus there was a high degree of consistency between the quantitative results obtained with the two independent techniques. These results suggest important role of these genes in the pathophysiologic mechanism in abdominal aortic aneurysm.

Serum cytokine levels of patients with abdominal aortic aneurysm

To assess the association of serum proinflammatory cytokine with abdominal aortic aneurysm, we compared the serum TNF-α, IL-6, MCP-1 and VCAM in patients with URA and RA using the ELISA analysis. The proinflammatory cytokine, TNF-α, IL-6, MCP-1 and VCAM, in serum was significantly increased in patients

with RA compared with URA, especially in patients with large size of aneurysm (**Figure 3A-D**). These data indicate that those cytokines associated with pathogenesis of abdominal aortic aneurysm through inflammation responses.

Discussion

To better understand cellular and molecular changes that accompany aneurysm development, biochemical, immunohistochemical, RT-qPCR and ELISA assays have been used to profile differences in gene expression and lipid level between unruptured abdominal aortic aneurysm (URA) and ruptured abdominal aortic aneurysm (RA) as well as between small and large sizes of aneurysm, thereby providing some initial insights into molecular similarities and differences that may exist between URA and RA.

Risk factors can be associatedwith abdominal aortic aneurysm development, expansion, and rupture. Initiation and promotion of the pathogenesis of abdominal aortic aneurysm may be multifactorial, combined with genetic predisposition and environmental and physiological factors leading to abdominal aortic aneurysm phenotype. Previous study showed advanced age (>65 years), male gender, smoking, and hypertension were associated with abdominal aortic aneurysm [5-8]. When the women who were found in the ruptured aneurysms appear to have a family history, which is likely to be reflective of awareness on the part of the women [20]. However, the evidence suggests that the prevalence of abdominal aortic aneurysm in women is likely to increase slowly, and now accounts for 1/3 of women who presenting with rupture [21]. In this study, we found higher number of male in patients with either URA or RA and the ages of detected patients were below 65 years that no significant differences were found between URA and RA with either small or large size of aneurysm. Hypertension is associated with abdominal aortic aneurysm risk only in women and increased experimental abdominal aortic aneurysm growth only in a rat model [22], while diabetes associated with a slower rate of experimental abdominal aortic aneurysm growth through increasing aortic wall stiffness and decreasing systemic inflammation, suggesting a protective role against the development of abdominal aortic aneurysm [23]. In contrast, our data showed that RA has a higher incidence of diabetes compared with URA with small size of aneurysm. Additionally, patients with coronary and pulmonary disease and matched for smoking have been reported to be associated with higher risk of abdominal aortic aneurysm rupture [7, 24]. In the present study, most patients with abdominal aortic aneurysm have an incidence of smoke, which is common in RA than in URA. Comparing with the number of cigarettes smoked per day, the duration of smoking is observed more important [25]. Other risk factor associated with increased risk of abdominal aortic aneurysm such as alcohol intake, not implicated in this study, was also reported in the previous study, which characteristics of the upregulation of MMPs and focal elastin degradation [26].

The association between plasma lipid levels and abdominal aortic aneurysm is complicated. Golledge et al. [27] reported that LDL and TG were not associated with the presence of abdominal aortic aneurysm, and the serum HDL concentration was independently associated with a reduced risk of having an abdominal aortic aneurysm in men not receiving current lipid-modifying therapy that in lines with other report [6]. However, contrast with the previous study, we found that serum TG, TC and LDL concentration was increased in abdominal aortic aneurysm with large size of aneurysm, which appeared to be the most important lipid in predicting the risk of abdominal aortic aneurysm development, with potential value as a therapeutic target. The reason for this trend is not fully understood. One explanation is that the small size of our experiment data (n=40) compared with data from Golledge, et al (n=2284). Thus, data are conflicting on the role of TG, TC and LDL in abdominal aortic aneurysm and indicate that further investigation of the effects of these specific lipid levels in this setting is needed.

Inflammation seems to be an important process in the formation of abdominal aortic aneurysm through involvement of extensive media and adventitial inflammatory cell infiltration. Up-regulation of immune and inflammation-associated gene expression in the aneurysms suggests that a broad range of immune and inflammatory responses may be one of the most important causes of inflammatory injury and aneurysm formation [15]. Three immune and inflammatory reaction-associated genes,

TRPV1 and CAM, were up-regulated in aneurysm tissues obtained from RA patients compared with URA, but PPARδ was down-regulated in RA than in URA in our study. Furthermore, up-regulated expression of TRPV1 and CAM was also found in URA with large size of aneurysm (>5 cm), but not in RA tissues. In each case, the significance and magnitude of the alterations in expression as detected by RT-qPCR corresponded with the results of the immunohistochemical analysis. In line with our findings that TRPV1 mRNA level showed a significant increase in aneurysm of ascending aorta as compared to the normal aorta of patients. However, Yu et al. [28] have been shown that nine immune and inflammatory reaction-associated genes, AGTR1, AOC3, COL4A6, CXCL14, PDE4C, TNC, TRPV1, AIF1L, and CYP4B1, were down-regulated in the intracranial aneurysms. The reason for this trend is not fully understood. One explanation is that the role of TRPV1 may differentially dependent on the location of aneurysms. The ubiquitous calcium-binding protein calmodulin (CAM) is a binding partner for TRE17 that as a key etiological factor in aneurysmal bone cyst through TRE17/USP6/Tre-2 signaling pathway [29]. Peroxisome proliferator-activated receptors (PPARs) are ligand activated transcriptional factors with multiple functions in energy metabolism and vascular biology. PPARδ attenuates Ang II-induced abdominal aortic aneurysm formation by regulating ECM homeostasis and inflammatory responses, suggesting a novel strategy for the treatment of abdominal aortic aneurysm [12].

Increased expression of proinflammatory cytokines is found in aneurysmal tissue and circulating levels of inflammatory cytokines are elevated in patients with abdominal aortic aneurysm. Several studies have demonstrated elevated levels of circulating IL-1, IL-6, TNF-α, MCP-1, and IFN-γ in patients with abdominal aortic aneurysm, and also specifically implicated involvement of these cytokines in abdominal aortic aneurysm pathogenesis [30]. In the present study, we found that TNF-α, IL-6, MCP-1 and VCAM concentrations were significantly increased in RA patients, as compared to URA patients especially who with large size of aneurysm, suggesting these cytokines were associated with abdominal aortic aneurysm pathogenesis. Other showed that the magnitude of TNF-α and VCAM increased expression was at least 7-fold greater in thoracic aortic aneurysms than in normal ascending aorta [31]. These data suggested that TNF-α and VCAM play important role in the aneurysms, regardless of their location.

Although the clinical significance of this work is yet unknown, the altered patterns of gene expression identified here will provide a valuable foundation for further investigations into the pathobiology of aortic aneurysmal disease. This study also demonstrates that significant heterogeneity exists between URA and RA at the molecular level. Further applications of gene expression profiling using of high-throughput cDNA microarrays or RNA sequencing analysis can be expected to substantially enhance our understanding of the diverse processes involved in aneurysmal degeneration.

Disclosure of conflict of interest

None.

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