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Increased levels of interleukin-22 in thoracic aorta and plasma from patients with acute thoracic aortic dissection☆

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ABSTRACT

Background: Interleukin (IL)-22 plays important roles in the development of arterial disease, including atherosclerosis and hypertension. However, the relationship between IL-22 and acute thoracic aortic dissection (TAD) remains unknown.

Methods: Blood samples were collected from patients with chest pain who underwent computed tomography angiography of the thoracic aorta but had no known preoperative diagnosis of coronary artery disease, peripheral artery disease, arthritis, and/or membranous nephropathy. Patients were divided into non-AD (NAD) and TAD groups, and the plasma concentrations of IL-22, IL-6 and tumor necrosis factor (TNF)-α were measured. In addition, aortic tissue samples from acute TAD patients and normal donors were collected, and the expression levels of IL-22 and IL-22 receptor 1 (IL-22R1) were measured.

Results: IL-22, IL-6 and TNF-α levels were significantly higher in acute TAD patients than in NAD patients (IL-22, NAD group: 27.0 (19.1, 38.6) pg/ml vs. TAD group: 32.9 (20.6, 58.3) pg/ml, $p < 0.0001$). The correlation analysis showed that IL-22 levels were positively correlated with levels of IL-6, TNF-α, fasting glucose, blood pressure, white blood cells, C-reactive proteins and D-dimers. Binary logistic regression analyses showed that IL-22 was independently associated with the presence of acute TAD (OR 1.169, 95% CI 1.069 to 1.277; $p = 0.001$). In addition, compared with aortic tissue of normal controls, TAD aortas showed increased expression of IL-22 and IL-22R1, especially in the torn section (IL-22, non-torn section: 2.8 ± 0.5/HPF vs. torn section 2.8 ± 0.5/HPF, $p < 0.001$). Additionally, macrophage but not T lymphocyte infiltration was significantly increased in the torn section (Macrophage, non-torn section: 2.2 ± 0.6/HPF vs. torn section 5.7 ± 1.2/HPF, $p < 0.001$; T lymphocyte, non-torn section: 2.7 ± 0.9/HPF vs. torn section 2.4 ± 0.5/HPF, $p = 0.28$), as evidenced by increased positive staining for the macrophage marker CD68, as opposed to the T cell marker CD3.

Conclusion: IL-22 levels may correlate with the presence of acute TAD.

1. Introduction

Aortic dissection (AD) is a rare but lethal cardiovascular emergency. Due to its complex clinical evolution and rapid progression, AD has an extremely high mortality and can rapidly lead to the death of patients. The prevalence of AD in China was close related with uncontrolled hypertension, Marfan syndrome, use of cocaine and so on [1,2]. Recently, the widespread availability of surgery and intravascular stents has provided effective treatment for AD patients in China [3]. However, the overall mortality of acute AD remains high, especially in rural areas.

The exact molecular mechanisms underlying acute AD are still unclear. Data from clinical studies and experimental animal models indicate that increased infiltration by T helper 17 (Th17) cells and macrophages, as well as higher expression levels of inflammatory mediators, including IL-6 and IL-17, are observed in acute AD compared with normal aortic tissues. In addition, the signal transducer and activator of transcription-3 (STAT3) signaling pathway, which is considered to be an inflammatory pathway, is activated during AD

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progression [4–6]. This suggests that increased blood vessel inflammation may contribute to the progression of acute AD.

Interleukin-22 (IL-22) is an inflammatory cytokine and plays a role in many diseases by regulating inflammatory levels, both in vivo and in vitro [7–11]. It has been demonstrated that IL-22 participates in the development of arterial diseases by regulating the inflammatory response. In an induced atherosclerosis model involving high-fat-fed apolipoprotein E knockout mice, IL-22 deficiency led to a reduction in aortic plaque areas and decreased serum IL-6 levels [12]. Similarly, our previous study demonstrated that exogenous IL-22 aggravated the angiotensin II-induced inflammatory response in thoracic aorta and promoted the elevation of blood pressure [13]. However, whether IL-22 is involved in acute thoracic AD (TAD) is still unknown. The goals of the present study were to measure IL-22 levels in acute TAD patients and to investigate the underlying mechanisms.

2. Materials and methods

2.1. Collection and processing of human blood samples

This study protocol was approved by the Medical Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region. Patients (aged 25–80 years) who suffered from sudden chest pain and underwent computed tomography angiography (CTA) of the thoracic aorta at the People's Hospital of Guangxi Zhuang Autonomous Region from January 2016 to April 2017 were enrolled in this study. In the patients who were enrolled, parts of them combined with PAD, SLE, CAD or acute left heart failure, these complications may had an effect on the concentrations of IL-22, IL-6 and TNF-α. Therefore, these patients were excluded from the study. After the CTA of the aorta was performed and patients returned to the intensive care unit (ICU), patients or their families provided an informed consent and blood samples were collected in Vacutainer tubes containing sodium heparin. After centrifugation at 4000*g* for 20 min, the supernatants were collected and stored at − 80 °C until the beginning of the experiments. Patients were divided into two groups: non-AD (NAD, n = 24, including 8 cases of reflux esophagitis, 5 cases of gastric spasm, 4 cases of myocardial bridge, 3 cases of intercostal neuritis, 3 cases of anxiety disorder and 1 case with an unclear diagnosis but where TAD was excluded), and TAD (n = 56) (as shown in Fig. 1). The diagnosis of TAD was based on the computed tomography (CT) scan results.

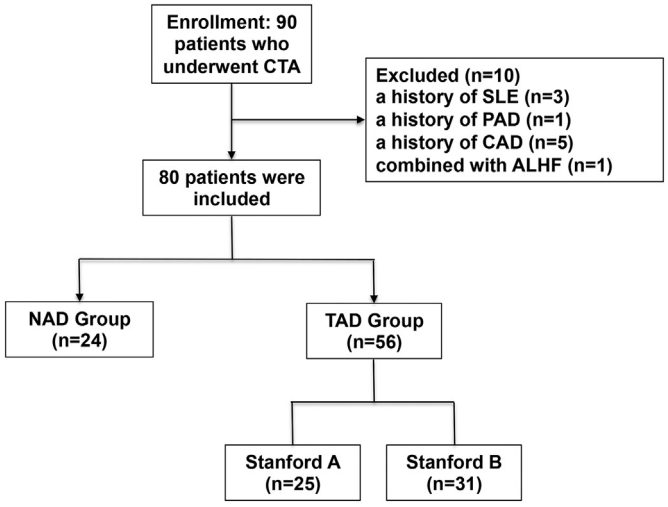

Fig. 1. The entry and exclusion criteria for all patients. CTA: computed tomography angiography; PAD: peripheral artery disease; SLE: systemic lupus erythematosus; CAD: coronary artery diseases; ALHF: acute left heart failure.

2.2. Measurement of IL-22, IL-6 and TNF-α

Samples were thawed at room temperature and plasma IL-22, IL-6 and TNF-α concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits following the manufacturer's instructions.

2.3. Collection of human aortic tissue samples

The thoracic aorta samples were obtained from the People's Hospital of Guangxi Zhuang Autonomous Region. Eight control samples were obtained from heart donors who had suffered traffic accidents and were declared brain-dead. The patients' families provided informed consent for donation, and aortic tissues were collected by a surgeon during the heart transplantation procedure. Donors had no history of cardiovascular disease, and aortic tissues showed no signs of pathology. Of the 56 acute TAD patients, 19 underwent emergency thoracic aorta replacement surgery and 12 of them or their families agreed to donate the aortic tissue, which was collected by the surgeon during the operation. This study protocol was approved by the Medical Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region.

2.4. Histological analysis

The aortic tissue was fixed with 4% neutral paraformaldehyde, embedded in paraffin, cut into 4–5-mm slices and mounted onto slides. To analyze the expression of IL-22 and IL-22R1, aortic tissue was stained with either anti-IL-22 or anti-IL-22 R1 antibodies (both from Abcam, England). In addition, anti-CD3 and anti-CD68 antibodies were used to stain T lymphocytes and macrophages, respectively, in order to determine the source of IL-22.

2.5. Western blot

The thoracic aorta tissue was lysed and the total protein extracted. After quantifying the protein concentration with a BCA Protein Assay Kit, 30 μg of total protein was loaded and run in 10% Laemmli sodium dodecyl sulfate (SDS) polyacrylamide gels. The samples were then transferred to Immobilon-FL PVDF membranes (Millipore, USA) and blocked with 5% nonfat milk. The membranes were incubated with anti-IL-22, anti-IL-22R1 and GAPDH (Cell Signaling Technology, USA) antibodies at 4 °C overnight. Incubation with the secondary antibodies was done at room temperature for 1 h. The blots were scanned using a two-color infrared imaging system.

2.6. Statistical analysis

The SPSS 19.0 software (SPSS Inc., Chicago, USA) was used to analyze all the data. IL-22, IL-6, and TNF-α levels, as well as information on the clinical characteristics were expressed as the median (minimum - maximum) and compared by means of the Mann - Whitney *U* test. Spearman's correlation analysis was used to calculate correlations between IL-22, IL-6, and TNF-α and clinical characteristics. To identify independent predictors of the presence of acute TAD, simple linear regression analyses and subsequent binary logistic regression analyses were performed. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Basic clinical characteristics of patients

Among the population who provided plasma for analysis, the incidence rate of smoking and uncontrolled blood pressure (HBP), as well as the levels of fasting glucose (Glu), white blood cells (WBC), creatinine (CREA), D-dimer and C-reactive protein (CRP), were significantly

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