Expression Level and Significance of e HSP90 in Peripheral Blood of Patients with Coronary Heart Disease in Guangdong Region: Postprint

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Abstract

Objective To investigate the role and significance of e HSP90 in the pathogenesis and progression of coronary heart disease. Methods A total of 101 patients with coronary heart disease of Guangdong origin and 31 control subjects, hospitalized in our hospital from June 2013 to June 2016, were enrolled. Clinical data were collected, and peripheral blood e HSP90 levels were measured. The relationship between peripheral blood e HSP90 levels and disease status in coronary heart disease patients was analyzed. Results Peripheral blood e HSP90 levels were significantly elevated in coronary heart disease patients compared with the control group ($P<0.01$). Peripheral blood e HSP90 levels were higher in patients with unstable coronary heart disease than in those with stable coronary heart disease (92.17 ± 23.63 ng/L vs 15.84 ± 15.83 ng/L,$P<0.01$). Peripheral blood e HSP90 levels were higher in coronary heart disease patients with heart failure than in those without heart failure (93.04 ± 22.94 ng/L vs 81.49 ± 20.44 ng/L,$P<0.05$). There was no statistically significant difference in peripheral blood e HSP90 levels between coronary heart disease patients with class IV and class III heart failure ($P=0.158$). Conclusion Blood e HSP90 levels are associated with disease status in Guangdong coronary heart disease patients and may serve as a potential serological marker for disease severity upon further in-depth investigation.

Full Text

Preamble

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Expression and Significance of eHSP90 in Peripheral Blood of Patients with Coronary Heart Disease in Guangdong

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Abstract

Objective: To investigate the role and significance of extracellular heat shock protein 90 (eHSP90) in the development and progression of coronary heart disease (CHD).

Methods: A total of 101 Guangdong-native CHD patients and 31 healthy controls hospitalized between June 2013 and June 2016 were enrolled. Clinical data were collected and peripheral blood eHSP90 levels were measured. The relationship between peripheral blood eHSP90 concentration and disease status in CHD patients was analyzed.

Results: Peripheral blood eHSP90 levels were significantly elevated in CHD patients compared to the control group ($P<0.01$). Unstable CHD patients exhibited higher eHSP90 levels than stable CHD patients (92.17 ± 23.63 ng/L vs. 15.84 ± 15.83 ng/L, $P<0.01$). CHD patients with heart failure showed higher eHSP90 levels than those without heart failure (93.04 ± 22.94 ng/L vs. 81.49 ± 20.44 ng/L, $P<0.05$). No significant difference was observed in peripheral blood eHSP90 between CHD patients with NYHA Class IV and Class III heart failure ($P=0.158$).

Conclusion: Blood eHSP90 levels correlate with disease severity in Guangdong CHD patients and warrant further investigation as a potential serological marker for CHD progression.

Keywords: coronary heart disease; eHSP90 ; heart failure

Introduction

Coronary heart disease is a pathophysiological process initiated by atherosclerotic plaque rupture and thrombosis under various risk factors, leading to luminal stenosis or occlusion, myocardial ischemia, and potentially myocardial infarction [1-2]. During this process, myocardial cell injury triggers massive secretion of intracellular substances such as creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI), which have become established serum markers for CHD diagnosis [3-4]. Heat shock protein 90 (HSP90) is a highly conserved protein comprising 1-2% of cytosolic proteins and exists in two isoforms, and [5]. In recent years, secreted Hsp90 (eHSP90) in peripheral blood has attracted increasing attention due to its demonstrated associations with tumorigenesis, inflammation, and

cellular injury [6-7]. However, the relationship between eHSP90 and CHD onset or severity remains poorly characterized.

This study investigates peripheral blood eHSP90 expression levels in Guangdong CHD patients to preliminarily explore its clinical significance and potential role in CHD pathogenesis.

Methods

1.1 General Data

We enrolled 101 Guangdong-native CHD patients diagnosed at our hospital between June 2013 and June 2016, including 64 males and 37 females. Among them, 51 had stable angina pectoris (SAP) and 50 had unstable angina pectoris (ACS) . According to coronary lesion morphology, 35 patients had Type A lesions, 30 had Type B1, 21 had Type B2, and 15 had Type C. Based on the number of affected vessels, 43 had single-vessel disease, 36 had double-vessel disease, and 22 had triple-vessel disease. Thirty-one healthy individuals from our medical examination center served as controls, with no major organ disease or malignancy.

Exclusion criteria: Severe hypertension; trauma or surgery within 4 weeks; any malignancy; non-atherosclerotic cardiomyopathy; severe valvular disease; myocardial hypertrophy; autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis; pulmonary fibrosis; and acute or chronic infectious diseases.

1.2.1 Detection of Peripheral Blood eHSP90

Upon admission, 5 mL of venous blood was collected from each patient. Samples were centrifuged within 2 hours (3000 r/min, 4°C) for 15 minutes. Approximately 1.5 mL of serum was aliquoted and stored at -80°C until batch analysis. eHSP90 levels were measured by ELISA (Cloud Clone, USA) using an automated microplate reader (BIO-RAD, USA).

1.2.2 Statistical Analysis

All data were analyzed using SPSS 19.0 software. Continuous variables were expressed as mean ± standard deviation. Multiple independent samples were compared using non-parametric tests, while one-way ANOVA was used for intergroup comparisons. Two-group comparisons of continuous variables were performed using t-tests, and pairwise comparisons within groups used the SNK method. $P<0.05$ was considered statistically significant.

Results

2.1 Differences in Clinical Characteristics and Blood eHSP90 Between Stable and Unstable CHD Patients

No significant differences in gender or age distribution were observed among the healthy control, stable CHD, and unstable CHD groups. Both stable and unstable CHD patients showed significantly higher eHSP90 levels compared to healthy controls. Moreover, eHSP90 levels were significantly elevated in the unstable CHD group compared to the stable CHD group (P<0.01,).

2.2 Differences in Clinical Characteristics and Blood eHSP90 Across Coronary Lesion Types

No significant differences in gender or age distribution were found among the healthy control, Type A, Type B1, Type B2, and Type C groups. All CHD subgroups (A, B1, B2, and C) exhibited significantly higher eHSP90 levels than healthy controls. While no significant differences were observed between Type B1 and Type A or between Type B2 and Type C, eHSP90 levels in Type B2 were significantly higher than in Type A, and Type C showed significantly higher levels than both Type B1 and Type A (P<0.01,).

2.3 Differences in Clinical Characteristics and Blood eHSP90 by Number of Affected Coronary Vessels

No significant differences in gender or age distribution were noted among groups. Patients with double-vessel and triple-vessel disease showed significantly higher eHSP90 levels compared to healthy controls. eHSP90 levels were significantly elevated in double-vessel disease compared to single-vessel disease, and further increased in triple-vessel disease, though the difference between double- and triple-vessel disease was not statistically significant ().

2.4 Differences in Blood eHSP90 Between CHD Patients With and Without Heart Failure

Heart failure represents a severe complication of CHD. Comparison of CHD patients with and without heart failure revealed significantly higher eHSP90 levels in those with heart failure (93.04±22.94 ng/L) compared to those without (81.49±20.44 ng/L, P=0.041,).

2.5 Differences in Blood eHSP90 Across Cardiac Function Classes in CHD Patients With Heart Failure

We further compared eHSP90 levels among CHD patients with different NYHA functional classes. While eHSP90 levels were lower in Class III (87.33±23.36 ng/L) than in Class IV heart failure (101.29±20.81 ng/L), this difference did not reach statistical significance (P=0.158,).

Discussion

Hsp90 is a major stress protein that is rapidly synthesized and activated during stress responses. Its primary functions include regulating protein aggregation, folding, transmembrane transport, and translocation, thereby stabilizing the cytoskeleton and acting as a molecular chaperone. This represents one of the key mechanisms by which cells resist early stress-induced injury [8-9].

Previous studies have demonstrated that intracellular HSP90 can reduce CHD development by regulating eNOS-mediated NO synthesis [10] and modulate the PI3K-AKT signaling pathway to decrease apoptosis [11]. Research on CHD patients has shown elevated total serum HSP90 levels compared to controls, which is considered a cardiovascular self-protective mechanism [12-13]. Additionally, HSP90 can be actively secreted extracellularly under stress or released from necrotic cells, where it binds to TGF- 1 receptors to promote myocardial fibrosis [14].

What then is the role of eHSP90 in CHD? Recent findings indicate that among the two HSP90 isoforms, the secreted eHSP90 is the primary functional form [6]. Our results demonstrate that eHSP90 expression is significantly elevated in CHD patients compared to healthy controls. Unstable CHD patients show markedly higher eHSP90 levels than stable patients, and levels increase with the number of affected coronary vessels. Further analysis revealed that CHD patients with heart failure exhibit higher eHSP90 levels than those without, and levels tend to increase with higher heart failure class, though the difference was not statistically significant, likely due to insufficient sample size. These findings indicate that eHSP90 expression closely correlates with CHD severity.

But does elevated eHSP90 actively participate in CHD pathogenesis? Studies in other contexts have shown that eHSP90 promotes tumor cell proliferation and metastasis [15-17], enhances extracellular matrix synthesis by fibroblasts to facilitate tissue remodeling [14,18], and induces inflammatory cytokine production [19-20]. We therefore hypothesize that while intracellular Hsp90 in cardiovascular cells (endothelial cells, cardiomyocytes) participates in early cytoprotection during stress, secreted eHSP90 may trigger inflammatory responses and myocardial remodeling that promote CHD progression. Future studies will investigate the direct effects of eHSP90 on coronary vessels and elucidate the underlying mechanisms.

In summary, Hsp90, as an important stress protein, plays a significant role in the ischemic and hypoxic environment of CHD. eHSP90 levels correlate closely with disease severity and may serve as a serological marker for CHD progression and prognosis.

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Note: Figure translations are in progress. See original paper for figures.