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THE ROLE OF GENE IN CARDIOVASCULAR DISEASES

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Abstract:

Interleukin (IL)-18 plays a key role in atherosclerosis and its complications. Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels. Cardiovascular disease includes coronary artery diseases (CAD) such as angina and myocardial infarction (commonly known as a heart attack). Other CVDs include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis. The present study investigated the genetic variability of 4 genes of the IL-18 system—IL18, IL18R1, IL18RAP, and IL18BP—in relation to circulating IL-18 levels and cardiovascular mortality.

Key Words: *coronary disease, genetics, interleukins, inflammation, prognosis.*

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INTRODUCTION [1-3]:

In recent years, increasing evidence has emerged from experimental and epidemiological data that interleukin-18(IL-18), a proinflammatory cytokine involved in both innate and acquired immune responses,1–3 plays a key role in the inflammatory response that contributes to atherosclerosis. Increased IL-18 expression has been localized in human atherosclerotic plaque and associated with plaque instability [4,5]. Animal models support the role of IL-18 in atherosclerotic lesion development and plaque vulnerability as well as the beneficial effect of inhibiting IL-18 on plaque progression and composition. Circulating IL-18 levels were strongly predictive of future cardiovascular mortality in the AtheroGene prospective cohort of patients with coronary artery disease (CAD).This predictive role of IL-18 levels was further confirmed in the large population-based cohort of initially healthy men of the Prospective Epidemiological Study of Myocardial Infarction (PRIME). However, it remains unclear whether elevation of IL-18 has a causative role or is simply the consequence of an ongoing inflammatory process that is associated with the development of atherosclerotic lesions. Several genes are involved in the IL-18 pathway and might contribute, alone or in combination, to IL-18 variability and in turn affect disease risk.

In this study we examined serum concentrations of IL-18 in patients with CHF to examine whether the cytokine was involved in the pathophysiology of this syndrome.

METHOD:

Subjects included 34 consecutively recruited patients (20 men and 14 women aged 42–83 years, mean 64 years) who had chronic, stable symptomatic heart failure representing New York Heart Association (NYHA) functional class II–IV for more than two months. The cause of heart failure was dilated cardiomyopathy (DCM) in 20 patients, and old myocardial infarction (OMI; more than three months previously) in 14 patients. Seventeen patients were classified according to the standards of the NYHA as functional class II, 14 patients as class III, and three patients as class IV. No significant differences were evident between patients in different functional classes with respect to age, sex, or left ventricular ejection fraction (data not shown). Patients with significant concomitant diseases such as infections, renal failure, cancer, or autoimmune diseases were excluded. In 14 consecutively recruited patients with stable angina pectoris without CHF (SAP) who also were studied, the diagnosis of angina was based on: a history of chest pain on exercise; documented ST depression with chest pain in a treadmill exercise test; angiographically proven stenosis causing narrowing of diameter exceeding 50% in at least one major epicardial coronary artery; and absence of segmental asynergy in biplanar left ventriculography. As controls, we included 10 healthy subjects who had no evidence of ischemic heart disease and normal physical examinations, resting ECG, and echocardiograms. All patients gave informed consent in advance for their participation, and the ethics committee at our institution approved the protocol. [4-5]

Fasting blood samples were collected in the morning after rest in the supine position for 20 minutes. Blood was withdrawn from an antecubital vein into non-heparinised tubes and kept on ice, and then centrifuged at 1710 g for 15 minutes at 4°C. Immediately after centrifugation, serum samples were stored at −80°C until they were assayed. Concentrations of TNFα (lower limit of detectability, 0.5 pg/ml) and IL-6 (lower limit of detectability, 0.2 pg/ml) were determined by enzyme linked immunosorbent assays (QuantiGlo, R&D Systems, Minneapolis, Minnesota, USA), as were concentrations of IL-18 (lower limit of detectability, 25.6 pg/ml) (MBL, Nagoya, Japan). Left ventricular measurements were obtained from standard two dimensional and M mode echocardiography.

Data are expressed as mean (SEM). Analysis of variance (Kruskal-Wallis test, followed by the Mann-Whitney U test) was used for statistical comparisons. Spearman's rank correlation test was used for correlations. A value of $p < 0.05$ was considered to indicate significance [6,7].

RESULTS:

No significant difference in age, heart rate, or systolic blood pressure was present between patient groups. However, the mean ejection fraction was significantly lower in CHF patients (DCM or OMI) than in SAP or control subjects). Serum IL-18 concentrations did not differ significantly between SAP and controls (81 (9.1) v 86 (18) pg/ml)). Serum IL-18 concentrations in CHF patients were significantly higher than in non-CHF subjects (CHF v non-CHF, 255 (30) v 83 (9.0) pg/ml, $p < 0.001$). Serum IL-18 concentrations in the DCM group and the OMI group did not differ significantly (284 (49) v 212 (20) pg/ml). Serum TNFα concentrations also were higher in patients with CHF than in non-CHF subjects (1.9 (0.3) v 1.1 (0.1) pg/ml, $p < 0.05$).However, a significant correlation was seen between serum IL-18 and TNFα concentrations in patients with CHF.

DISCUSSIONS:

Because serum IL-18 concentration was significantly related to serum TNFα concentration and NYHA class, increased IL-18 release may trigger the elevation in TNFα and modulate the symptoms of CHF. However, the mechanisms of IL-18 elevation and pathophysiologic roles of increased serum IL-18 concentration remain to be

elucidated. Discrepancies concerning IL-18 concentrations and cardiac function or cachexia might indicate that IL-18 does not play an important role in CHF. However, varying concentrations of circulating IL-18 binding proteins might mask the correlation between serum IL-18 and other parameters.

CONCLUSION:

We have shown for the first time that serum IL-18 was raised in CHF patients, in whom elevations correlated with poorer cardiac functional class and higher TNFα concentrations. IL-18 appears likely to participate in the pathophysiology of CHF, but its specific functional action and possible clinical implications remain to be clarified.

ABBREVIATIONS:

CHF, congestive heart failure
DCM, dilated cardiomyopathy
IGIF, interferon γ inducing factor
IL, interleukin
OMI, old myocardial infarction
SAP, stable angina pectoris without CHF
TNF, tumor necrosis factor.

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