Interleukin-33, matrix metalloproteinase-9, and tissue inhibitor of matrix metalloproteinase-1 in myocardial infarction

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Background/Aims: Acute coronary syndrome (ACS) is characterized by increased inflammatory processes and endothelial activation. We investigated the association between ACS and inflammatory mediators and matrix-degrading enzymes.

Methods: We prospectively enrolled 55 consecutive patients with ACS: 25 with unstable angina (UA) and 30 with non-ST elevated myocardial infarction (NSTEMI). For comparison, 25 age- and sex-matched subjects with no significant coronary artery stenosis were included as the control group. Peripheral serum levels of interleukin (IL)-33, matrix metalloproteinase (MMP)-9, tissue inhibitor of MMP-1, and C-reactive protein (CRP) were measured on admission, and at 12, 24, 48, and 72 hours after the initial evaluation.

Results: Compared to serum levels in the control group, serum levels of IL-33 decreased in the NSTEMI group (p < 0.05), and levels of MMP-9 and tissue inhibitor of matrix metalloproteinase (TIMP)-1 increased in the UA group (p < 0.01, p < 0.05, respectively) and NSTEMI group (p < 0.05, p < 0.05, respectively). IL-33 levels were significantly lower on admission than at 12 hours after the initial evaluation (p < 0.05). IL-33 levels were negatively correlated with MMP-9 levels (r = -0.461, p < 0.05) and CRP levels (r = -0.441, p < 0.05).

Conclusions: Elevated levels of MMP-9, TIMP-1, and decreased levels of IL-33 play a role in the development and progression of ACS.

Keywords: Inflammation; Interleukin-33; Matrix metalloproteinase 9; Myocardial infarction

INTRODUCTION

Coronary artery disease (CAD), a common manifestation of atherosclerosis, is responsible for a high percentage of morbidity and mortality in the Western world [1]. A large body of evidence supports the idea that inflammatory mechanisms play an important role throughout all phases of atherogenesis, from the formation of fatty streaks to the acute coronary event due to vulnerable plaque rupture [1-3]. Smooth muscle cells produce extracellular matrix (ECM), leading to the formation of the fibrous cap that covers the atheromatic plaque [4]. Conversely, proteases with collagenolytic properties counterbalance collagen synthesis. ECM degradation is mainly achieved through the action of matrix metalloproteinases (MMPs), a family of zinc- and calcium-dependent endopeptidases and macrophages proposed to be the main contributors of MMPs...
within the atherosclerotic plaque [5,6]. Interleukin (IL)-6, tumor necrosis factor-α, and IL-1β increase the expression of MMPs [7,8], whereas cytokines that exert atheroprotective actions reduce MMP production [9]. Among the MMPs, MMP-9 is highly expressed in the vulnerable regions of the atherosclerotic plaque and has been suggested to be causally involved in plaque rupture [10]. Plasma MMP-9 concentrations are elevated in patients with acute myocardial infarction (MI) [11-13]. Endogenous MMP activity is regulated by the tissue inhibitors of matrix metalloproteinase (TIMP), in particular TIMP-1, which binds to several MMPs with high affinity [14,15].

Several cytokines exert anti-inflammatory and atheroprotective actions. IL-33 is expressed in coronary artery smooth muscle cells [16], coronary artery endothelium [17], nonhigh endothelial venule endothelial cells [18], and cardiac fibroblasts, suggesting that IL-33 may play a role in various cardiovascular disorders [19]. In addition, IL-33 markedly increases levels of IL-4, -5, and -13, but decreases interferon (IFN)-γ levels in serum and lymph node cells. IL-33 may play a protective role in the development of atherosclerosis via the induction of IL-5 and oxidized low density lipoprotein (ox-LDL) antibodies [20]. The immunological response of Th1 type and its mediators (i.e., IFN-γ) is believed to accelerate atherosclerosis, whereas the response of Th2 type and its mediators (i.e., IL-4, IL-5, and IL-13) inhibit the development of atherosclerosis [20-23]. IL-33 reduces MMP release by intentionally decreasing IFN-γ levels having inflammatory effects and inhibits plaque rupture.

The correlation between the time course of serum concentration changes in IL-33, MMP-9, and TIMP-1 and the extent of acute coronary syndrome (ACS) during and after acute MI is unclear. Therefore, in the present study, we evaluated the serum concentrations of these markers at various time points in patients with ACS.

METHODS

Patients

The study population was composed of 55 patients with complaints of sudden chest pain who were admitted to the emergency department within the first 6 hours of pain onset. Exclusion criteria were as follows: a diagnosis of renal failure, collagen tissue disease, infection, vasculitis, depression, or somatization or having undergone angioplasty, bypass surgery, or open-heart surgery. The patient group was divided into two subgroups: patients with unstable angina (UA; n = 25) and those with non-ST elevated myocardial infarction (NSTEMI; n = 30). The leading symptom of ACS is typically chest pain. The working diagnosis of NSTEMI-ACS is a rule-out diagnosis based on the electrocardiogram showing a lack of persistent ST elevation. Biomarkers (troponins) further distinguish NSTEMI and UA [24]. The control group consisted of 25 patients who had no significant coronary artery stenosis (25% of luminal diameter) and were age- and sex-matched with the patient groups. The study was performed in compliance with the Declaration of Helsinki.

Venous blood samples were obtained when patients with NSTEMI were admitted to our hospital. Postadmission blood samples were obtained at 12, 24, and 48 hours after percutaneous coronary intervention. Blood samples were obtained from the control group in the morning. Triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), fibrinogen, troponin I, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and isoenzymes of phosphocreatine kinase (creatinine kinase-MB, CK-MB) were measured immediately. For other measurements, the blood samples were centrifuged at 1,500 ×g and 4°C for 10 minutes and stored at -86°C until analysis. Blood samples were drawn on admission and at 12, 24, and 48 hours after the onset of infarction for measuring MMP-9, TIMP-1, and IL-33 levels.

MMP-9 measurement

The concentrations of MMP-9 were determined in duplicate using the RayBio enzyme-linked immunosorbent assay (ELISA) kits (RayBiotech Inc., Norcross, GA, USA) designed to measure their pro and active forms. The detection limit of this assay was 10 pg/mL. Intra and interassay variations were less than 12%.

IL-33 measurement

IL-33 levels were determined using the ELISA Kit (USCN Life Science Inc., Houston, TX, USA). A mono-