Changes of soluble CD40 ligand in the progression of acute myocardial infarction associate to endothelial nitric oxide synthase polymorphisms and vascular endothelial growth factor but not to platelet CD62P expression

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Reported in vitro data implicated soluble CD40 ligand (sCD40L) in endothelial dysfunction and angiogenesis. However, whether sCD40L could exert that influence in endothelial dysfunction and angiogenesis after injury in acute myocardial infarction (AMI) patients remains unclear. In the present study, we evaluated the association of sCD40L with markers of platelet activation, endothelial, and vascular function during a recovery period early after AMI. To achieve this goal, the time changes of soluble, platelet-bound, and microparticle-bound CD40L levels over 1 month were assessed in AMI patients and correlated with endothelial nitric oxide synthase (eNOS) polymorphisms, vascular endothelial growth factor (VEGF) concentrations, and platelet expression of P-selectin (CD62P). The association of soluble form, platelet-bound, and microparticle-bound CD40L with CD62P expression on platelets, a marker of platelet activation, was also assessed to evaluate the role of CD40L in the thrombosis, whereas the association with eNOS and VEGF was to evaluate the role of CD40L in vascular dysfunction. This work shows for the first time that time changes of sCD40L over 1 month after myocardial infarct onset were associated with G894T eNOS polymorphism and with the VEGF concentrations, but not to the platelet CD62P expression. These results indicate that, in terms of AMI pathophysiology, the sCD40L cannot be consider just as being involved in thrombosis and inflammation but also as having a relevant role in vascular and endothelial dysfunction. (Translational Research 2015;166:650–659)

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Abbreviations: AMI = acute myocardial infarction; APC = allophycocyanin; Asp = aspartate; cTNT = cardiac troponin; CAD = coronary artery disease; CRP = C-reactive protein; CK = creatine kinase; eNOS = endothelial nitric oxide synthase; ELISA = enzyme-linked immunosorbent assay; FITC = fluorescein isothiocyanate; FAU = fluorescence arbitrary units; Glu = glutamic acid; LME = linear mixed effects model; MPs = microparticles; NO = nitric oxide; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCI = percutaneous coronary intervention; PBS = phosphate-buffered saline; PE = Phycoerythrin; CD62P = P-selectin; sCD40L = soluble CD40 ligand; SA = stable angina pectoris; VEGF = vascular endothelial growth factor

AT A GLANCE COMMENTARY

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Background

The influence of sCD40L in endothelial dysfunction and angiogenesis markers in AMI patients remains unclear. The influence of sCD40L in endothelial and vascular function in early stages after AMI was studied having platelet activation into account.

Translational Significance

It was found for the first time that time changes of sCD40L in AMI patients were associated with G894T eNOS polymorphism and VEGF concentrations, but not to the platelet P-selectin expression. In terms of AMI pathophysiology, sCD40L cannot be considered just as a marker of thrombosis and inflammation but has also a relevant role in vascular and endothelial dysfunction. A prognostic value for the sCD40L could be hypothesized along the progression of the disease in AMI patients. This may be of the utmost importance in clinical diagnostic of AMI.

INTRODUCTION

CD40L is a signaling molecule,[1-3] implicated in thrombosis and inflammatory response to vascular injury.[4-6] The relationship of CD40L with coronary artery disease (CAD) has been established,[2,7-9] as also its implication in endothelial dysfunction.[10-14] However, whether the soluble CD40 ligand (sCD40L) could also influence endothelial dysfunction after acute myocardial infarction (AMI) injury remains unclear.

In vitro studies have shown that sCD40L inhibits angiogenesis and also growth factor–induced human umbilical vein endothelial cell migration, which is achieved by generation of free radicals and inhibition of nitric oxide (NO) production.[10] The authors hypothesized that the sCD40L could inhibit reendothelialization of an injured vessel, thereby affecting the restenosis.[10]

Research efforts have been directed toward the finding of biomarkers to assess endothelial function and its correlation with AMI. Genetic indicators, such as the polymorphisms of endothelial NO synthase (eNOS) gene,[15,16] may provide insight into endothelial cells function.

Vascular endothelial growth factor (VEGF) is a well-known promoter of angiogenesis and an endogenous regulator of endothelial integrity.[17-19] The prognostic information provided by VEGF independently of other markers likely points toward an important role for angiogenesis in regulating myocardial repair and reperfusion after AMI.[17,20]

Current opinion suggests a differential role of CD40L (both soluble and membrane-bound forms, which includes microparticles in circulation)[21] at different stages of CAD, contrasting with the traditional view of an unvarying function of the CD40L-CD40-sCD40L system interactions in the disease.[6] In that perspective, no clear indication of the interplay of CD40L with endothelial and vascular function markers and their importance in the pathophysiology of the AMI has been obtained so far in human clinical studies. Therefore, the aim of this study was to evaluate the relationship of sCD40L with markers of platelet activation, endothelial and vascular function during an early recovery period after AMI. To achieve this goal, the time changes over 1 month of sCD40L levels were assessed in AMI patients and correlated with the CD40L expressed on platelets and microparticles, CD62P expression on platelets, and eNOS polymorphisms VEGF concentrations. The association of soluble form, platelet-bound, and microparticle-bound CD40L with CD62P expression on platelets was assessed to evaluate the role of CD40L in thrombosis, whereas the association with eNOS and VEGF was to evaluate the role of CD40L in vascular dysfunction. The sCD40L serum concentrations were measured and compared with the expression of CD40L on platelets and microparticles. Healthy volunteers (CTR) and longitudinally assessed stable angina (SA) patients were used as predictors of altered endothelial regulation in AMI.