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Insulin-like growth factor 1 opposes the effects of C-reactive protein on endothelial cell activation

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Abstract Emerging evidence demonstrates that high plasma C-reactive protein (CRP) levels or low plasma insulin-like growth factor 1 (IGF-1) concentrations may be separately associated with the increased risk of coronary artery disease or myocardial infarction. Interestingly, animal model studies and epidemiological investigations indicate that circulating IGF-1 and CRP levels have an inverse correlation. The present study aims to evaluate if IGF-1 can directly oppose the effects of CRP on endothelial cell (EC) activation. We found that IGF-1 rescues endothelial nitric oxide synthase activity and decreases the release of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 from ECs. We also showed that IGF-1 antagonizes the effects of CRP by activating the PI3K/Akt pathway and suppressing the JNK/c-Jun and MAPK p38/ATF2 signaling pathways, rather than inhibiting ERK1/2 activity. These findings provide evidence of the physiopathological mechanisms of endothelial activation and novel insights into the protective properties of IGF-1.

Keywords IGF-1 · CRP · Endothelial activation · PI3K/Akt · Atherosclerosis

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Introduction

Atherosclerosis was believed for decades to be a chronic inflammatory disease occurring in the arterial wall. As a well-known inflammatory biomarker, C-reactive protein (CRP) is released mainly by the liver into the vascular system in response to stress (e.g., inflammation). Accumulated data indicate that CRP is likely an important contributor to atherosclerosis and independent risk factor of future cardiovascular events [1–3]. Our previous study showed that CRP up-regulates receptors for advanced glycation end product expression in human endothelial cells (ECs) [4]. CRP directly stimulates the activation of ECs by inducing the secretion of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin as well as by antagonizing endothelial nitric oxide synthase (eNOS) activity, thereby resulting in the promotion of EC-monocyte adhesion, impaired vascular wound repair, and impaired vascular tone [1, 3].

The anti-inflammatory regulator insulin-like growth factor 1 (IGF-1) has been validated as a protective factor in cardiovascular diseases such as coronary heart disease [5–7]. IGF-1 is a 70-amino-acid single-chain polypeptide that mediates the processes of cellular growth, differentiation, proliferation, and survival against apoptosis. It is also a clinical drug approved by the Food and Drug Administration for the treatment of growth failure. Emerging evidence supports the hypothesis that reduced IGF-1 levels play a pivotal role in metabolic syndrome, dyslipidemia, atherothrombotic events, and other diseases [5–7]. To date, more than 15 epidemiological studies have documented that low-circulating IGF-1 levels among individuals are also an independent and powerful predictors of coronary artery disease or myocardial infarction. The relation between