BACKGROUND

Endogenous regenerative pathways may contribute to cardiovascular repair following ischaemic injury. Based on recent results in experimental studies, we investigated candidate endogenous chemical and cellular injury/repair responses in human myocardial infarction (MI).

METHODS

Circulating injury (eg, platelets) and repair (circulating CD34+ progenitor cells, serum vascular endothelial growth factor (VEGF) and thrombin b,4 and urokinase-Activated-Ser-Asp-Pro (AcSDKP)) responses were quantified 2 days and 3 months after acute MI. Progenitor cells in whole blood were quantified using flow cytometry, and cytokines were measured by immunoasssay. An automated analyser was used for haematological measurements. Invasive measures of coronary artery microvascular resistance and collateral supply were measured acutely using coronary thermodilution techniques. Cardiac function and remodelling were quantified by magnetic resonance imaging.

RESULTS

35 consecutive patients with MI (mean±SD age 58±10 years) were included. AcSDKP measured 2 days post-MI negatively predicted left ventricular ejection fraction (R²=0.43; p=0.024) and positively predicted left ventricular end-systolic volume index (R²=0.56; p=0.011) at 3 months. At follow-up, CD34+ count negatively predicted myocardial infarct mass (R²=0.29; p=0.015) and left ventricular end-systolic volume index (R²=0.20; p=0.02). In multivariable analyses, haemoglobin concentration measured 2 days post-MI negatively predicted coronary collateral supply (p=0.006), whereas red cell distribution width (p=0.004) and platelet count (p=0.0001) positively predicted coronary collateral supply. Serum VEGF at 3 months and change in VEGF were negative multivariable predictors of left ventricular end-diastolic volume index at 3 months (p=0.021 and p=0.006, respectively).

CONCLUSION

Circulating chemical and cellular responses participate in myocardial injury and repair and represent targets for therapeutic development.

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REFERENCES


CIRCULATING CHEMICAL AND CELLULAR INJURY/REPAIR RESPONSES ARE LINKED TO CARDIAC DYSFUNCTION AND REMODELLING IN HUMAN MYOCARDIAL INFARCTION

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MODULATION OF EXTRACELLULAR MATRIX PROTEIN EXPRESSION BY INTERLEUKIN 1 IN HUMAN CARDIAC MYOFIBROBLASTS: REGULATION BY P38 MAP KINASE

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The proinflammatory cytokine interleukin 1 (IL-1) elicits catabolic effects on the myocardial extracellular matrix (ECM) early after myocardial infarction but there is little understanding of its direct effects on cardiac myofibroblasts (CMF), a key cell type involved in the regulation of myocardial remodelling. We used a focused RT-PCR microarray to investigate the effects of IL-1 on expression of 41 ECM genes in CMF cultured from different patients, and explored the regulatory role of the p38 MAPK signalling pathway. IL-1 (10 ng/ml, 6 h) had only a minimal effect on mRNA expression of structural ECM proteins, including collagens, laminins, fibronecin and vitronectin. However, IL-1 induced marked increases in expression of several ECM proteases, including matrix metalloproteinases MMP-1 (collagenase-1), MMP-3 (stromelysin-1), MMP-9 (gelatinease-B) and MMP-10 (stromelysin-2). Conversely, IL-1 reduced mRNA expression of ADAMTS-1, a metalloproteinase that suppresses neovascularisation. IL-1 stimulated a small increase in expression of tissue inhibitor of metalloproteinases (TIMP)-1, but not TIMP-2. Data for MMPs 1, 2, 3, 9 and 10 and ADAMTS-1 were confirmed by quantitative real-time RT-PCR. IL-1 strongly activated the p38 MAPK pathway in human CMF, as determined by immunoblotting with phospho-specific antibodies. A p38 MAPK inhibitor SB203580 reduced IL-1-induced mRNA expression of MMP-3, but did not affect expression of any of the other MMPs studied. SB203580 also markedly reduced ADAMTS-1 mRNA expression.

In summary, IL-1 induces a distinct pattern of ECM protein expression in human CMF, in part regulated by p38 MAPK,