Macrophase migration inhibitory factor is a novel biomarker and promotes cardiac inflammation following acute myocardial infarction


Introduction

Myocardial ischemia or infarction (MI) is a severe clinical situation. Inflammation occurs soon after MI exacerbating myocardial injury, dysfunction and ventricular remodeling. Early quantification of myocardial damage and control of the extent of post-MI inflammation are crucial for optimal patient management.

As a key pro-inflammatory cytokine, Macrophase migration Inhibitory Factor (MIF) induces leukocyte infiltration and other pro-inflammatory actions. Released rapidly from vesicles upon ischemia, MIF has been shown to regulate inflammation in both mouse and rat models. It remains unclear whether MIF promotes inflammatory responses in patients with acute MI.

Therefore we examined 1) circulating MIF as a biomarker for myocardial damage post-MI, and 2) MIF expression by peripheral blood mononuclear cells (PBMCs) and its influence on the expression of other inflammatory factors following acute MI.

Methods

Forty-two AMI patients, 10 stable angina (SA) patients and 10 healthy volunteers (age/gender matched) were recruited while cardiac magnetic resonance imaging (CMR) was performed at day-3 and 3-month post MI.

Blood samples were collected upon admission (n=42) and day 3 (n=32) post-MI.

PBMCs were separated and cultured for 24 hrs. Effects of a MIF inhibitor (COR100140, 50 µM), neutralising anti-MIF monoclonal antibody (mAb, 5 ng/ml), IL-1β (10 ng/ml) and rhMIF (5 ng/ml) were tested.

Levels of MIF, matrix metalloproteinase-9 (MMP-9), interleukin-1β (IL-1β) in the plasma or PBMC supernatant were examined by ELISA or by RT-PCR (for mRNA).

Results

Plasma MIF levels at day 1 post MI are correlated with the extent of ischemic Injury. Plasma MIF levels correlated with known biomarkers of infarct size such as peak levels of Troponin I (TnI) or Creatine kinase-MB (CK) and CMR derived infarct size and left ventricular ejection fraction (LVEF).

Inhibition of MIF attenuated MI induced production of MIF, MMP-9 and IL-6 in PBMCs isolated from control subjects or patients at day 1 and 3 after MI. Increased mRNA (upper panel) and protein level (lower panel) of MIF (A), MMP-9 (B) and IL-6 (C) were observed in PBMCs at day-3 post MI while anti-MIF interventions either by COR100140 (COR) or anti-MIF mAb abolished the up-regulation. n=10-15, *P<0.05 vs. CTL or MI at day 1 (MI d1), †P<0.05 vs. MI at day 3 (MI d3) without intervention.

Conclusion

Following acute MI, MIF levels serve as a novel biomarker for the degree of cardiac injury and also bear predictive value for acute and chronic cardiac remodelling.

PBMCs are important cellular sources of MIF post-MI, and inhibition of MIF attenuates PBMC activation induced by either acute MI or IL-1β, suggesting that MIF is a potential therapeutic target for post-MI inflammation.