Role of High-Mobility Group Box 1 (HMGB1) redox state on cardiac fibroblasts activities and heart function after myocardial infarction

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Background: HMGB1 is a nuclear factor that when secreted, is able to signal tissue damage. HMGB1 is also implicated in cardiac regeneration and remodeling after myocardial infarction (MI). The extracellular HMGB1 activity depends on its redox state: the fully-reduced-HMGB1 has chemotactic effect while the disulfide-HMGB1 induces cytokines expression.

Purpose: To examine the role of HMGB1 redox isoforms and the non-oxidizable mutant 3S-HMGB1 on human cardiac fibroblasts (hcFbs) functions in vitro and evaluate their effects on cardiac remodeling in vivo.

Methods: The responses to fully-reduced-HMGB1 or 3S-HMGB1 in different conditions were evaluated through Boyden chamber migration. The expression of HMGB1 receptors was evaluated by FACS. Pro-inflammatory cytokines expression was assessed by qRT-PCR. C57BL/6 mice were infarcted using left antherior descending artery ligation and 4 hours after infarction were injected in the peri-infarcted area with vehicle, fully-reduced-HMGB1 or 3S-HMGB1 and euthanized after 4 weeks.

Results: Fully-reduced-HMGB1 and 3S-HMGB1, but not disulfide-HMGB1, were able to induce hcFbs migration and both proteins inhibited hcFbs cell adhesion. Only the 3S-HMGB1 was resistant to oxidation and, indeed, its chemotactic effect was maintained in presence of H2O2. HcFbs express CXCR4 but not TLR4 and RAGE. Treatment of cells with AMD3100 abolished migration induced by fully-reduced-HMGB1 but not in response to 3S-HMGB1 suggesting an higher affinity of the 3S mutant for CXCR4. In addition, CXCR4/- mouse embryonic fibroblasts did not migrate in response to fully-reduced-HMGB1 or 3S-HMGB1. Furthermore, disulfide-HMGB1 or 3S-HMGB1 did not modulate pro-inflammatory cytokines levels. In vivo experiments showed that infarcted mice receiving fully-reduced-HMGB1 exhibited a significant recovery of cardiac function while treatment with 3S-HMGB1 determined an increase in LV dilation and infarct size and a worsening in LV function, compared to the vehicle. Finally, only fully-reduced-HMGB1-treated mice presented a thicker wall of the infarcted area and no sign of cardiomyocytes hypertrophy.

Conclusions:HMGB1-induced migration of hcFbs is CXCR4 dependent, and both fully-reduced- and 3S-HMGB1 influence hcFbs activities in vitro. However, the 3S-HMGB1 is also active in oxidizing conditions that may occur soon after MI. Whether this is the reason for the 3S-HMGB1-dependent worsening of the infarcted heart function and adverse remodeling observed in vivo has to be determined.