Abstract: **P5391**

**Systemic administration of high-mobility group box 1 can suppress adverse post-infarction ventricular remodeling in a rat infarction model by enhancing self-regeneration**

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**Background:** High-mobility group box 1 protein (HMGB1) reportedly enhances CXCR4-positive bone marrow-derived mesenchymal stem cell (BM-MSC) recruitment to damaged tissue to promote tissue regeneration.

**Purpose:** Our aim of this study is to evaluate whether systemic administration of HMGB1 might promote tissue repair in a rat myocardial infarction (MI) model.

**Methods:** We prepared 26 MI model rats with high ligation of the left coronary artery. Two weeks later, HMGB1 (3 mg/kg/day) or phosphate-buffered saline (control: 3 mL/kg/day) was administered for 4 days via femoral vein. Cardiac performance was evaluated by ultrasonography, left ventricular (LV) remodeling via immunostaining. We then used immunostaining to examine MSC recruitment to damaged tissue in green fluorescent protein bone marrow transplantation (GFP-BMT) model rats, and also performed intravital imaging using two-photon microscopy to visualize BM-cells recruitment in real time.

**Results:** Compared with control rats, there was a significant improvement in the left ventricular ejection fraction of the HMGB1 group (HMGB1 vs. control: 48.6% ± 5.5% vs. 33.6% ± 5.4%; p < 0.01) at 4 weeks after each administration. LV remodeling, characterized by interstitial fibrosis, cardiomyocyte hypertrophy, and a decrease of capillary density, was significantly attenuated in the HMGB1 group compared with control rats. On QT-PCR analysis, VEGF mRNA expression was significantly higher in the HMGB1 group than in the control (border zone: 1.6 ± 0.6 vs. 1.1 ± 0.2; p = 0.02, septal zone: 1.1 ± 0.1 vs. 0.9 ± 0.1; p < 0.01). In GFP-BMT rats, GFP+/PDGFR+ cells were significantly mobilized to the border zone in the HMGB1 group compared with control rats (1331 ± 197 vs. 615 ± 45/mm²; p < 0.01), leading to formation of newly developed vasculature (Figure 1). In intravital imaging, more GFP+ cells were mobilized to the infarction area in the HMGB1 group than in the control, which was further enhanced at 12h later. Additionally, SDF-1 expression in the peri-infarction area increased significantly in MI rats compared with normal rats (MI vs. normal; 2.1 ± 0.4 vs. 0.9 ± 0.1; p < 0.01), in where some cell-adhesions of vascular endothelial cells were destroyed.

**Conclusions:** Systemic administration of HMGB1 mobilized BM-MSCs to the damaged myocardium via the SDF-1/CXCR4 signaling complex. Those BM-MSCs might migrate to extracellular matrix in the border zone via the gap of each endothelial cell, leading to induction of angiogenesis and reduced fibrosis.
Figure 1: Systemic administration of HMGB1 recruits BM-MSCs to the damaged myocardium, leading to forming of newly developed vasculature (magnification as follows; A x100, B, C x600)