

Antibody to Granulocyte-Macrophage Colony-Stimulating Factor Reduces the Number of Activated Tissue Macrophages and Improves Left Ventricular Function Following Myocardial Infarction in a Rat Coronary-Artery Ligation Model.

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Introduction

Recent studies have shown granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes infarct expansion and inappropriate collagen synthesis in the infarcted ventricle. Thus suggesting, enhanced proliferation of monocytes and macrophages at the time of acute myocardial infarction (MI) may have deleterious effects on left ventricular (LV) remodeling. This study was designed to determine if blocking the effects of GM-CSF alters LV remodeling and hemodynamics in rats with acute MI.

Hypothesis: Pretreatment of rats with GM-CSF antibody prior to MI will inhibit monocyte and macrophage migration limiting LV remodeling and preserving LV function.

Materials & Methods

Acute MI was created by ligating the left coronary artery of rats; treatment with the GM-CSF antibody (5mg/kg) was initiated 24 h prior to coronary ligation. Closed chest echocardiography and solid-state micromanometers were used to measure outcome variables 3 weeks after ligation. N=6-10 in each group. Samples were then processed for standard histology and immunohistochemistry using anti-CD68 antibody.

Results

The GM-CSF antibody increased ($P<0.05$) LV ejection fraction (37 ± 3 vs $47\pm 5\%$) and decreased ($P<0.05$) LV end-systolic diameter (0.75 ± 0.12 vs 0.59 ± 0.05 cm) with no changes in LV systolic pressure (109 ± 4 vs 104 ± 5 mmHg), LV-end diastolic pressure (22 ± 4 vs 21 ± 2 mmHg), LV-end diastolic diameter (0.96 ± 0.04 vs 0.92 ± 0.05 cm), or Tau (25.4 ± 2.4 vs 22.7 ± 1.4 msec).

Results (continued)

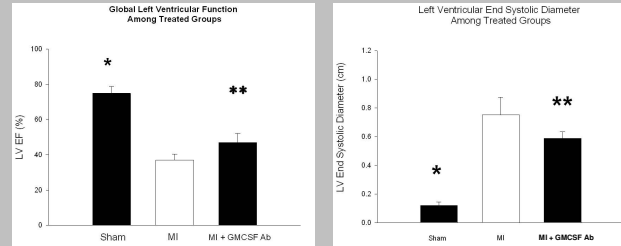


Figure 1. LVEF (%) among treated groups. Sham (N=5), MI (N=10), MI + GMCSF Ab (N=12). Data are mean \pm SE. * $p<0.05$ vs. all groups ** $p<0.05$ vs. MI and Sham

Figure 2. LVESD (cm) for Sham, MI and MI + GMCSF Ab. Data are mean \pm SE. N=4 in Sham, N=5 in MI and N=9 for MI + GMCSF Ab. * $p<0.05$ vs. MI+ GMCSF Ab. ** $p<0.05$ vs. MI.

Results (continued)

Additionally, immunohistochemistry analysis using anti-CD68 antibody demonstrated significantly lower numbers of activated tissue macrophages in infarcted myocardium of antibody-treated animals compared to saline controls (81 ± 21.24 CD68 vs. 195 ± 31.7 positive cells per 0.105 mm², respectively). No difference in neovascularization was seen between the two groups.

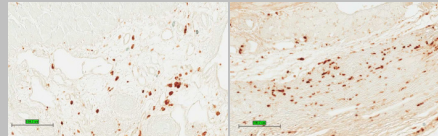


Figure 3. Representative immunohistochemistry results from CD-68 antibody (activated macrophages) for GMCSF-Ab treated hearts (left) and NaCl-treated hearts (right). Scale bars = 100 μ m.

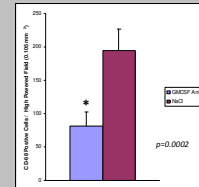


Figure 4. CD-68 positive cells per high powered field

Results (continued)

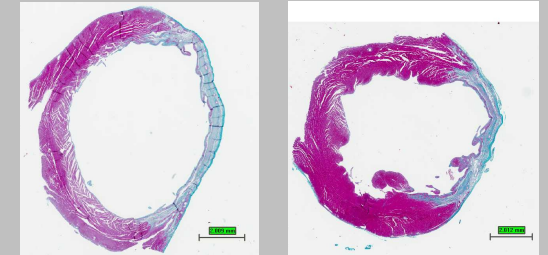


Figure 5. Representative trichrome staining of left ventricle cross-sections from NaCl control (left) and GMCSF-Ab treated (right) hearts. Scale bars = 2.0 mm. Image Analysis courtesy Flagship Biosciences LLC. (www.flagshipbio.com)

	Infarct Area (mm ²)	Total Area (mm ²)	% Infarct
NaCl -Treated	10.48	30.9	34.76%
GMCSF-Ab Treated	6.01*	34.28	16.39%**

Table 1. Morphometry analysis of NaCl-treated hearts (N=5) and GMCSF-Ab treated hearts (N=5) using Aperio whole slide scanned images and the ImageScope Software v10.0.36.1808. * $p<0.02$; ** $p<0.01$

Morphometry analysis revealed significantly larger infarct areas in NaCl-treated animals compared to GMCSF-Ab treated hearts. Additionally, the percent infarct area was significantly lower in GMCSF-Ab treated hearts.

Conclusions

We report improvements in LV ejection fraction and partial reversal of LV remodeling using an antibody against GM-CSF initiated one hour prior to MI. These findings suggest that inhibition of monocyte and macrophage migration may be beneficial in the treatment of heart failure after MI.