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Bone Marrow-Derived CXCR4$^+$ Cells Mobilized by M-CSF Participate in the Prevention of Cardiac Dysfunction after Myocardial Infarction in Mice

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Background: The monocyte (Mo)/macrophage (M ϕ) lineage might affect healing process after myocardial infarction (MI) through 2 possible mechanisms; cytokine secretion by activated Mo/M ϕ and neovascularization by this lineage-derived endothelial cell progenitor cells (EPCs). Since macrophage colony-stimulating factor (M-CSF) stimulates differentiation and proliferation of this lineage, we examined the effect of exogenous M-CSF administration on a murine MI model. **Methods and Results:** MI was produced by left coronary artery ligation in C57BL/6J mice. Recombinant human M-CSF (500 μ g/kg/day, n=25) or saline (control, n=24) was administered for 5 days after MI. M-CSF group showed significant reduction of infarct size and scar formation, and improvement of left ventricular function at 14 days after MI. Immunohistochemistry revealed M-CSF significantly increased macrophage infiltration (F4/80) and neovascularization (CD31), but not myofibroblast accumulation (α-SMA). Further, the CXCR4 ligand stromal cell-derived factor (SDF)-1 was upregulated in the infarcted area of both groups, whereas CXCR4$^+$ cells were increased only in M-CSF group. Real-time RT-PCR analysis showed downregulation of M-CSF receptor (c-fms) in the myocardium of M-CSF group. Furthermore, flow cytometry showed that M-CSF increased the number of monocytes (Mac-1$^+$/Gr-1$^-$) and CXCR4$^+$ cells, but not EPCs (CD34$^+$/Flk-1$^+$) in the peripheral circulation. **Conclusion:** These findings suggest that M-CSF prevents cardiac dysfunction and remodeling after MI through the recruitment of CXCR4$^+$ cells into the infarcted myocardium by the SDF-1/CXCR4 axis activation.

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Cationized Gelatin Delivery of a Plasmid Encoding Soluble Fas Mitigates Postinfarction Left Ventricular Remodeling

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We previously reported that postinfarction inhibition of Fas/Fas ligand interaction by an adenovirus-mediated soluble Fas (sFas) gene therapy blocked granulation tissue cell apoptosis, and thereby altered infarct tissue dynamics to significantly improve left ventricular remodeling and dysfunction at the chronic stage. However, the use of viral vectors for gene delivery is still limited in the clinical settings because the safety is not established yet. Recent development in nanotechnology has made it possible to control drug delivery as pleased (drug delivery systems, DDS), -e.g., the amount and speed of release of drugs immersed in cationized gelatin can be controlled by the nature of the particles. In the present study, we applied sFas gene delivery to the mice with large myocardial infarction (MI) using cationized gelatin-mediated DDS. In those mice, we confirmed a fewer granulation tissue cell apoptosis 7 days post-MI by TUNEL assay and electron microscopy and a significantly mitigated left ventricular dilatation and dysfunction 28 days post-MI based on echocardiographic and catheter-based hemodynamic examinations. The infarct scar of the sFas-treated mice was thick and contained abundant vessels and myofibroblasts that were likely preserved as the result of escaping from apoptotic death. In conclusion, the cationized gelatin-mediated DDS of sFas gene may become one of the therapeutic strategies against postinfarction heart failure, which is safer than the virus-mediated gene delivery.

Acute myocardial infarction, clinical (diagnosis / treatment)-7 (IHD)

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Pravastatin Therapy Before Percutaneous Coronary Intervention Decreases the Circulating Osteopontin Level in Patients with Acute Myocardial Infarction

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It is reported that pretreatment with statins causes myocardial protection during and after percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI). Osteopontin (OPN) is expressed in the myocardium in AMI. We examined the effect of pravastatin on the circulating OPN level. Thirty-three consecutive patients with AMI were randomized into control (Group C, n=14) and statin (Group S, n=19) groups and underwent PCI. Group S patients were administered 20 mg of pravastatin just after admission regardless of the serum cholesterol level and 10 mg of the drug everyday. Blood samples were obtained immediately after admission and on days 2, 3, 5, 7, and 14. Interval from AMI onset to PCI, infarct-related artery, PCI success, and medications except for statin were similar between 2 groups. The plasma OPN level reached the maximal value around day 3 after AMI and subsequently decreased in both groups. The maximal OPN level tended to be smaller in Group S than in Group C (708 ± 68 vs 929 ± 117 ng/ml, P=0.09). The area under the curve of OPN level for 14 days was significantly lower in Group S than in Group C (5170 ± 476 vs 7430 ± 871 ng/ml, P<0.05). Thus, pretreatment with pravastatin before PCI decreases the circulating osteopontin level in patients with AMI. This may be related to the myocardial protection effect of statin.

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Measurement of BNP and H-FABP in the Emergency Risk Stratification of Acute Myocardial Infarction

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Background BNP and H-FABP has been used to estimate the prognosis of AMI, few data are available in a combination of those cardiac markers. **Methods** We conducted a prospective study of 239 patients with AMI without renal failure whose BNP and H-FABP were measured on arrival at the emergency room. The primary end point was death from any causes in hospital.**Results** A total of 20 of the 239 patients died in hospital. The BNP levels ranged from 2.0 to 3,390 pg/ml. The H-FABP levels ranged from 1.3 to 3,300 pg/ml. The area under receiver-operating characteristics when each cardiac marker was used to differentiate death from survival was 0.67 in the BNP and 0.68 in the H-FABP. The prognostic accuracy of BNP at a cutoff of 61.8 pg/ml and H-FABP at a cutoff of 96.5 ng/ml were 75% and 60%, respectively. The patients were devived into 4 groups according to the BNP cutoff value and H-FABP cutoff value. The primary end point increased in a stepwise fashion among patients in increasing number of groups with group1 at 2.1% vs group2 at 3.7% vs group3 at 6.4% vs group 4at 30.4%.(p<0.0001)**Conclusion** The increased levels of both BNP and H-FABP appeared to be emergency predictor of risk in patients with AMI.