

## Regenerative Therapeutic Effect of Statin Nanoparticle-Loaded Adipose-Derived Stem Cells on Myocardial Infarction

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**Abstract :** Background: Clinical trials of autologous adipose-derived stem cell (AdSC) therapy for ischemic heart diseases (IHD) are now on-going. We have investigated the hypothesis that combination of AdSCs and statin, an agent with pleiotropic effects, could augment the therapeutic effect on myocardial infarction (MI). Methods and Results: Human AdSC functions with different doses of simvastatin-conjugated nanoparticle (STNP) uptake were evaluated by in vitro assays. STNP promoted the migration activity without changing the proliferation activity, and also up-regulated growth factors. Next, MI was induced by LAD ligation in nude mice, and the mice were assigned in the following groups 3 days after MI: 1) PBS (control), 2) NP-AdSCs (50000 cells), 3) STNP, and 4) STNP-AdSCs (50000 cells). Cardiac functional recovery assessed by echocardiography was improved at 4 weeks after surgery in STNP-AdSC group. Masson's trichrome-stained sections revealed that LV fibrosis length was reduced, and the number of TUNEL-positive cardiomyocytes was less in STNP-AdSC group. Surprisingly, a number of de novo endogenous Nkx-2.5/GATA4 positive immature cardiomyocytes as well as massive vascular formation were observed in outer layer of infarcted myocardium despite of a few recruited/retained transfused STNP-AdSCs 4 weeks after MI in STNP-AdSC group. Finally, massive myocardial regeneration was observed 8 weeks after MI. Conclusions: Intravenously injected small number of statin nanoparticle-loaded hAdSCs exhibited a potent therapeutic effect inducing endogenous cardiac tissue regeneration.

**Keywords :** statin, drug delivery system, stem cells, cardiac regeneration

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