Supplemental Figure legends

Supplemental Figure 1 Macrophage infiltration and myofibroblast accumulation. (**A**) Immunostaining for Mac3 in the infarct area of EPO- and saline (control)- treated hearts 14d after MI. Scale bars, 100μm. The number of Mac3-positive cells in the ischemic area was measured (n=4). $*P < 0.05$. (**B**) Immunostaining for αSMA (brown) of EPO- and saline (control)- treated hearts 14 d after MI. Scale bars, 100μm. The number of αSMA-positive cells in the ischemic area was measured (n=4). $*P < 0.05$.

Supplemental Figure 2 EPO activates the EPO-EPOR signaling pathways in cardiomyocytes. Western blotting of phospholylated Akt and ERK in the cardiomyocytes after EPO treatment. (**A**) Time dependency (EPO 100 U/ml). (**B**) Dose dependency (EPO 15 min stimulation). Insulin (1 mU/ml)-treated cardiomyocytes were used as a positive control. (**C**) Cardiomyocytes were infected with adenoviral vectors encoding dominant negative form of EPOR or LacZ at 10 MOI and treated with or without EPO (100 U/ml) for 15 min. (**D**) Detection of apoptotic cardiomyocytes using FITC-labeled TUNEL staining. PI3K inhibitor LY294002 (LY, 5 μM) and MEK inhibitor PD98059 (PD, 10μM) were added 15 min before EPO administration. The TUNEL-positive cardiomyocytes were counted (n = 6). $*P < 0.05$, $^{\#}P < 0.01$. (**E**) The expression of cleaved caspase-3 at 24 h after H_2O_2 treatment was analyzed by western blotting. Representative results from three experiments are shown.

Supplemental Figure 3 The size of cardiomyocytes after MI. The cross-sectional

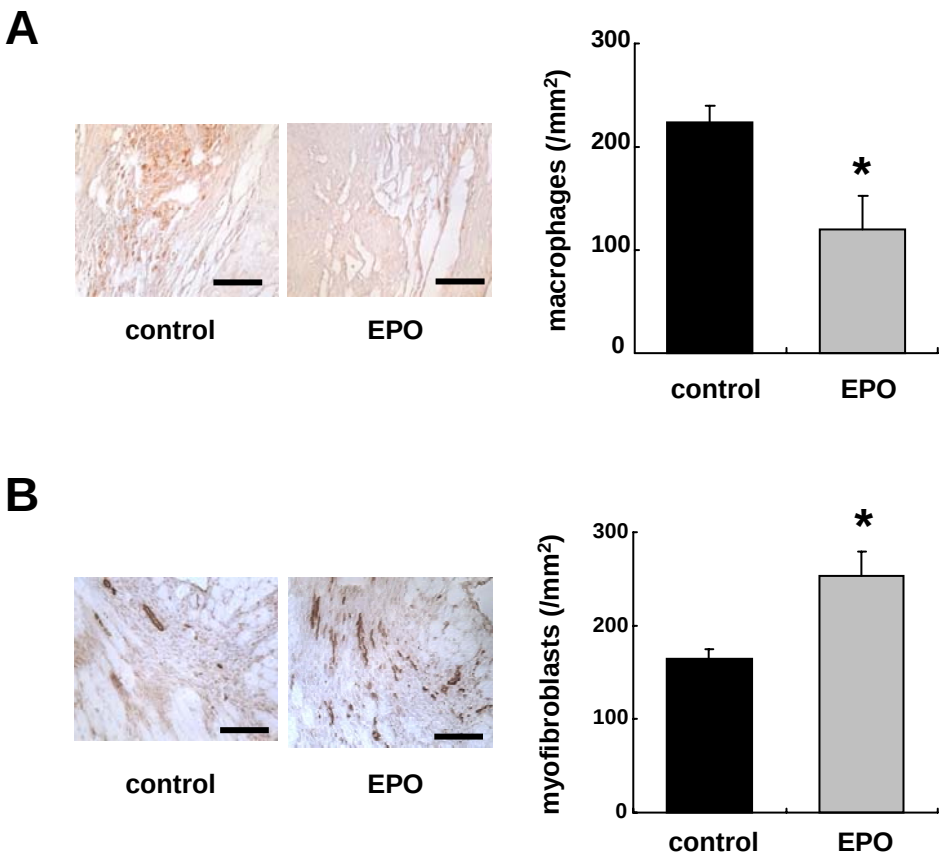
area of cardiomyocytes in the border area (MI group) or LV free wall (sham group) of EPO- and saline (control)-treated hearts was measured at 14 d after operation (n = 5).

Supplemental Figure 4 The VEGF and Shh knockdown in cardiomyocytes reduces the EPO-induced angiogenic effect. Endothelial cell proliferation assay was examined using BrdU incorporation (n = 5 per condition). HUVECs were treated with EPO-pretreated conditioned medium (pre-EPO) or saline-pretreated medium (control). siRNA targeting VEGF (**A**), Shh (**B**) or control RNA was introduced into cardiomyocytes followed by EPO-treatment for 48 h. Control is a commercially available negative control RNA. **P* < 0.05.

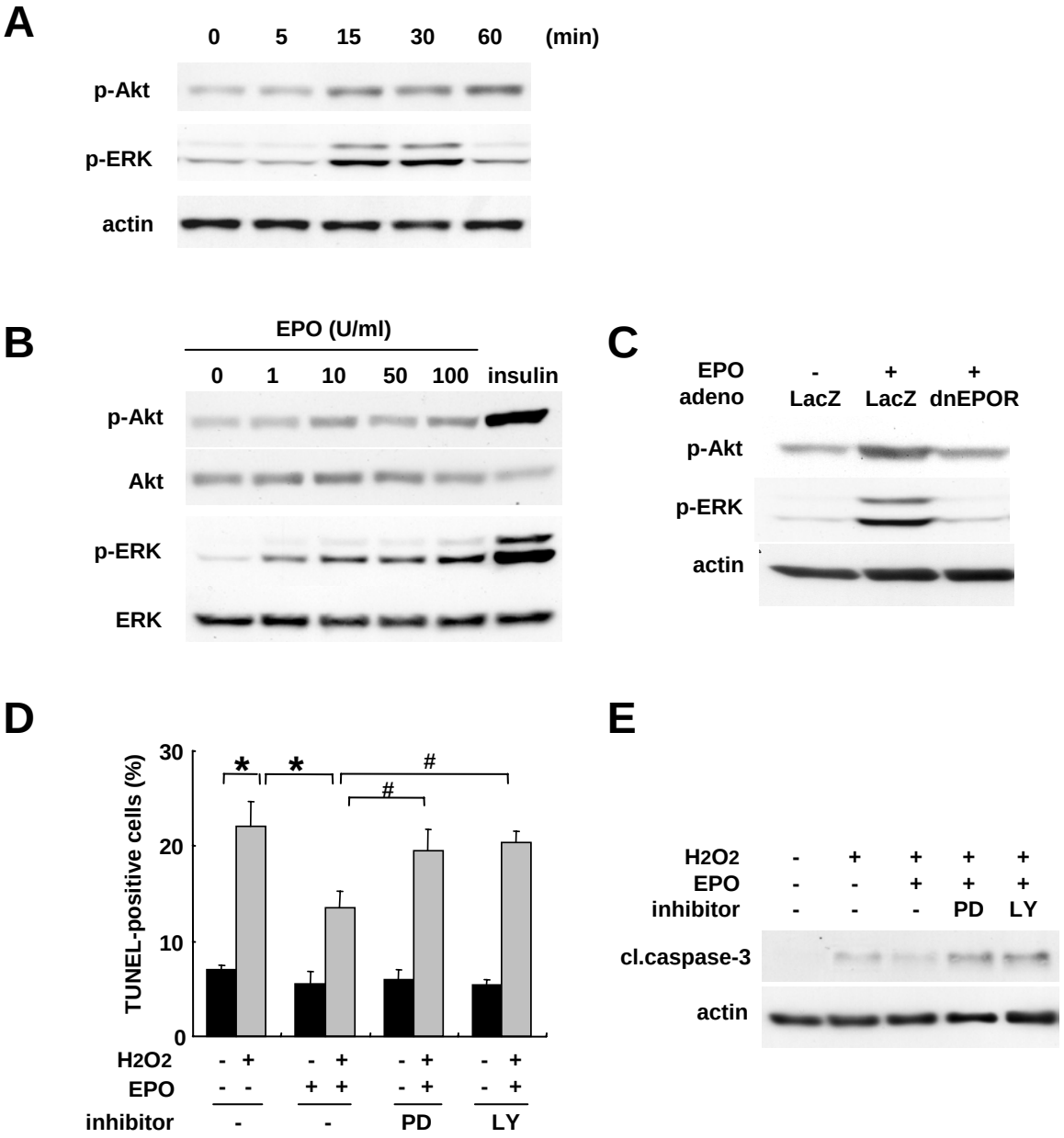
Supplemental Figure 5 The Shh expression in infarcted hearts. Representative western blots of Shh-N in the hearts from WT and RES mice at 4 d after MI are shown (n = 4).

Supplemental Figure 6 STAT3 is not involved in the protective effects of EPO. (**A**) Masson trichrome staining of WT and dnSTAT3-Tg hearts. **P* <0.05 (n=8-9) (**B**) TUNEL staining. EPO prevented H_2O_2-induced apoptotic death in dnSTAT3-infected cardiomyocytes as equally as LacZ-infected. Quantitative analysis of TUNEL-positive cells (%) was performed (n=5). **P* <0.05

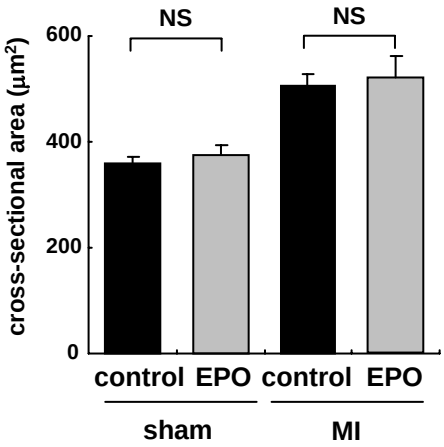
Supplemental Figure 1



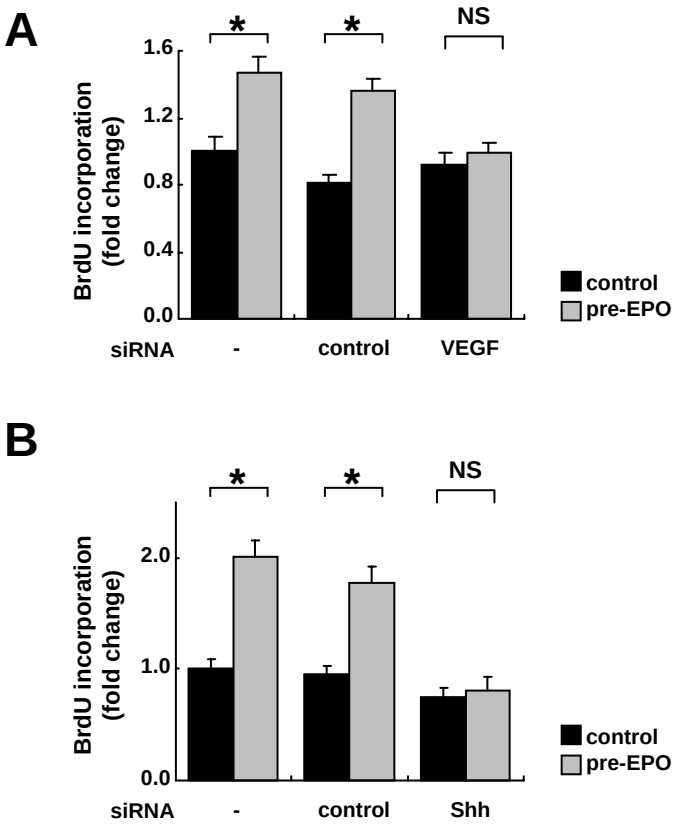
Supplemental Figure 2



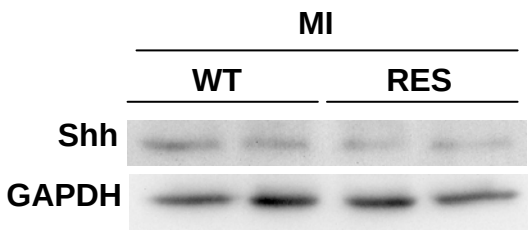
Supplemental Figure 3



Supplemental Figure 4



Supplemental Figure 5



Supplemental Figure 6