

AMD3100, a CXCR4 Antagonist, Augments Mobilization and Incorporation of Bone Marrow-Derived Endothelial Progenitor Cells into Sites of Myocardial Neovascularization

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Background: SDF-1/CXCR4 axis is recognized to play key regulatory roles in the trafficking and homing of human CD34+ cells to bone marrow (BM). We hypothesized that AMD3100, a CXCR4 antagonist, augmented mobilization and incorporation of BM-derived endothelial progenitor cells (EPCs) into sites of myocardial neovascularization. Methods and Results: Wild-type mice after an induction of myocardial infarction (MI) received either AMD3100 (125µg, single s.c.) or saline (control). LV systolic and diastolic dimensions, and fractional shortening in the AMD group 2 and 4 weeks after MI were preserved ($P<0.01$), and LV systolic and end-diastolic pressures in the AMD group 4 weeks after MI were improved ($P<0.05$), resulting in the improved survival in the AMD group after MI ($P<0.05$). Histological assessments indicated an increased capillary density and a decreased % fibrosis to LV area in the AMD group 4 weeks after MI ($P<0.05$). Significant increases in circulating EPCs, assessed by EPC culture assay, 1 and 2 weeks after MI were observed in the AMD group ($P<0.05$). These data were further supported by FACS, which disclosed a significant increase in Sca-1/Flk-1 positive cells in AMD vs. control mice, whereas progenitor cell pool in BM was prevented to be exhausted after the mobilization into circulation. This was supported by evidence that MMP-9 expression in BM was enhanced in the AMD group and no differences were observed in the progenitor pool between MMP-9^{-/-} mice with and without AMD3100. To evaluate effects of AMD3100 on BM-derived EPCs at the sites of myocardial neovascularization, we established MI models using mice transplanted with BM from transgenic donors expressing β -galactosidase transcriptionally regulated by endothelial cell-specific Tie-2 promoter. More X-gal positive cells were observed at ischemic sites in the AMD group 1 and 2 weeks after MI ($P<0.05$). Fluorescent immunohistochemistry 1 week after MI documented a marked increase in cells that were double positive for β -gal and isolectin B4 in the AMD group. Conclusions: CXCR4 antagonist preserves chronic LV function after MI in part by augmenting mobilization and incorporation of BM-derived EPCs into sites of myocardial neovascularization.