A novel cardioprotective mechanism mediated by bone marrow c-kit+mERα+ cell via paracrine IL-6

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Abstract

Cardioprotective actions of estrogen are well recognized for many years. Recent studies indicate a novel role of estrogen receptors (ER) in stem/precursor cell-involved cardiac repair. Taking into account that cardiac c-kit+ precursor cells are mainly recruited from bone marrow (BM) c-kit+ cell populations, we aimed here to elucidate the functional importance of ERα in BM c-kit+ precursor cells after ischemic heart injury. The c-kit+ cells were isolated from femurs and tibias of male wistar rats 7 days after myocardial infarction (MI) by magnetic activated cell sorting in combination with fluorescent activated cell sorting (FACS). After MI, the percentage of BM c-kit+ cells increased by 2.11 fold. BM c-kit+ cells, which expressed both intracellular and membrane (m)ERα, were shown to inhibit apoptosis of co-cultured cardiomyocytes in a paracrine manner. In addition, ERα stimulation could improve paracrine cardioprotection by BM c-kit+ cells. According to the expression of mERα, BM c-kit+ cells were further sorted using FACS into c-kit+mERα+ and c-kit+mERα- cell populations. Notably, BM c-kit+mERα+ cells were more potent in supporting paracrine cardioprotection than c-kit+mERα- cells both in vitro and in vivo. Further analysis revealed that BM c-kit+mERα+ cells were characterized by increased production of cardioprotection cytokines including IL-6 and IL-10. Importantly, blocking IL-6, but not IL-10, by neutralizing antibody abolished the protective effect of BM c-kit+mERα+ cell in supporting cardiomyocytes, indicating IL-6 was responsible for BM c-kit+mERα+ cell-mediated paracrine cardioprotection. Finally, the c-kit+mERα+ cell population was verified in peripheral blood of patients with heart failure. Thus, this work explains a novel cardioprotective mechanism mediated by BM c-kit+mERα+ cells via paracrine IL-6.