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TITLE: The Gender Divide: Does Donor Gender Matter for Mesenchymal Stem Cell Transplantation?

Acute myocardial infarction (MI) blocks major cardiac vessels, causing ischemic damage to cardiomyocytes. Mesenchymal stem cell (MSC)-based treatment strategies have been proposed to alleviate the consequences of MI either by offering structural support or by paracrine mechanisms. Here we investigate gender-specific MSC response to hypoxia *in vitro* and *in vivo*, both with and without the estrogen receptor agonist, 17β-Estradiol (EST), present. We hypothesized that female cells would show greater resistance to hypoxia and release greater pro-survival factors, and would therefore survive longer after transplantation.

MSCs expressing firefly luciferase were isolated from male and female L2G transgenic mice, allowing us to monitor cell survival using *in vivo* bioluminescent imaging. Cells were placed under hypoxic and normoxic conditions for 48h, with or without EST stimulation. Lactate Dehydrogenase (LDH) was measured to examine cell stress, and the MTT assay was used to analyze cell proliferation using an ELISA reader. No survival benefit was observed for female cells, and proliferation was reduced compared to male cells, independent of additional EST administration. A membrane array was used to measure the gender-specific cytokine release under hypoxia and normoxia. Of all twenty tested cytokines, only MCP-1, TIMP-1, and M-CSF were markedly produced by MSCs *in vitro*, and cytokine release was reduced in all groups under hypoxia. Interestingly, female MSCs produced a significantly higher amount of MCP-1 than male MSCs, independent of EST stimulation. No gender difference was observed for TIMP-1 or M-CSF.

In vivo, MIs were created in male FVB mice by ligation of the left anterior descending coronary artery. 250,000 cells were injected into the infarct border zone of each animal. The first group received untreated male cells; the second received female cells treated with EST for two days prior to surgery. MSC survival in vivo was limited, with signal depletion after 13-15 days. Male cells demonstrated greater proliferation during the first days, whereas the female + EST group showed accelerated cell death.

In conclusion, our hypothesis was not supported, and we are now investigating the potential relationship between the increased MCP-1 release by female MSCs and their accelerated cell death after transplantation.