

Granulocyte-macrophage colony-stimulating factor promotes glucose transport and blastomere viability in murine preimplantation embryos.

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Abstract

Granulocyte-macrophage colony-stimulating factor (GM-CSF) secretion from epithelial cells lining the female reproductive tract is induced during early pregnancy by ovarian steroid hormones and constituents of seminal plasma. In this study we have investigated the influence of GM-CSF on development of preimplantation mouse embryos. Blastocyst-stage embryos were found to specifically bind (125)I-GM-CSF and analysis of GM-CSF mRNA receptor expression by reverse transcriptase-polymerase chain reaction indicated expression of the low-affinity alpha subunit of the GM-CSF receptor, but not the affinity-converting beta subunit (beta(c)), or GM-CSF ligand. GM-CSF receptor mRNA was present in the fertilized oocyte and all subsequent stages of development, and in blastocysts it was expressed in both inner cell mass and trophectoderm cells. In vitro culture of eight-cell embryos in recombinant GM-CSF accelerated development of blastocysts to hatching and implantation stages, with a maximum response at a concentration of 2 ng/ml (77 pM). Blastocysts recovered from GM-CSF-null mutant (GM^{-/-}) mice on Day 4 of natural pregnancy or after superovulation showed retarded development, with the total cell number reduced by 14% and 18%, respectively, compared with GM^{+/+} embryos. Blastocysts generated in vitro from two-cell GM^{-/-} and GM^{+/+} embryos were larger when recombinant GM-CSF was added to the culture medium (20% and 24% increases in total cell numbers in GM^{+/+} and GM^{-/-} blastocysts, respectively). Incubation of blastocysts with recombinant GM-CSF elicited a 50% increase in the uptake of the nonmetabolizable glucose analogue, 3-O-methyl glucose. In conclusion, these data indicate that GM-CSF signaling through the low-affinity GM-CSF receptor in blastocysts is associated with increased glucose uptake and enhanced proliferation and/or viability of blastomeres. Together, the findings implicate a physiological role for maternal tract-derived GM-CSF in targeting the preimplantation embryo, and suggest that defective blastocyst development contributes to compromised pregnancy outcome in GM-CSF-null mutant mice.