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[Gastric Cancer](#)

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Stem Cell Therapy With Mesenchymal Stem Cells Induces Apoptosis in Advanced Gastric Adenocarcinoma, and Docetaxel Inhibits Epithelial Mesenchymal Transition

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Background: Advanced gastric adenocarcinoma is an aggressive disease with few available effective therapies.

Methods: We obtained advanced gastric adenocarcinoma cells from the antrum, proximal duodenum, and omentum of patients via endoscopic biopsy, and from the 25 lymph nodes within the connective tissue around the stomach and metastatic lesions via laparotomy. Using these cells, we developed animal models with metastatic advanced gastric adenocarcinoma. Mesenchymal stem cells (MSCs) were isolated from bone marrow aspirates of healthy donors and were injected in-situ in the advanced gastric adenocarcinoma and metastatic sites on the animal models.

Results: The MSCs engrafted with the microenvironment of advanced gastric adenocarcinomas. After 1 month, bioluminescence imaging exhibited inhibition of tumor growth by induction of apoptosis with enhancement of PARP cleavage and activation of caspase 8. Upregulation of CHK-2 indicated DNA damage and cell cycle arrest. However, interaction of MSCs and advanced gastric adenocarcinoma cells at the tumor stromal interface facilitated systemic dissemination of metastasizing tumor cells with mesenchymal qualities in a process known as epithelial to mesenchymal transition (EMT), after upregulation of antiapoptotic dominant oncogene bcl-2, which acts as a tumorigenic stimulus due to inhibition of type I programmed cell death, or apoptosis. Treatment with docetaxel downregulated bcl-2 due to phosphorylation, inhibiting EMT. Subsequently, expression of EMT markers, such as N-cadherin,

International Society of Gastrointestinal Oncology
2009 Gastrointestinal Oncology Conference
October 1–3, 2009

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E-cadherin, Sk-Br-3, Snail, Twist, and vimentin was inhibited. The inhibition of the oncogene dominant effect of bcl-2 led to downregulation of FOS, NCOA4, FYN, IGF-IR, SDF-1a, VEGF, MCP-1, and MMP11. Flow cytometry exhibited cell cycle arrest at the G2/M phase after microtubule polymerization. Besides type I programmed cell death, we observed upregulation of beclin-1 tumor suppressor gene after bcl-2 phosphorylation, which caused autophagy. Finally, a bystander killing effect of advanced gastric adenocarcinoma cells was demonstrated on transmission electron microscopy.

Conclusions: Stem cell therapy with MSCs eradicates advanced gastric adenocarcinoma cells, while docetaxel treatment inhibits EMT and subsequent metastatic spread.