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Bergfeld SA 2014



Abstract

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**See 1 citation in 2014 by Bergfeld SA:**

Mol Cancer Ther. 2014 Apr;13(4):962-75. doi: 10.1158/1535-7163.MCT-13-0400. Epub 2014 Feb 6.

Bone marrow-derived mesenchymal stromal cells promote survival and drug resistance in tumor cells.

Bergfeld SA¹, [Blavier L](#), [DeClerck YA](#).

Author information**Abstract**

Bone marrow mesenchymal stromal cells (BMMSC) have antitumorigenic activities. Here, we hypothesized that circulating BMMSC are incorporated into tumors and protect tumor cells from therapy-induced apoptosis. Adherent cells harvested from murine bone marrow and expressing phenotypic and functional characteristics of BMMSC were tested for their antitumor activity against murine 4T1 mammary adenocarcinoma and LL/2 Lewis lung carcinoma cells. BMMSC but not NIH3T3 or murine skin fibroblasts stimulated the expansion of 4T1 cells in three-dimensional (3D) cocultures, and conditioned medium (CM) from these cells increased the viability of 4T1 and LL/2 cells in two-dimensional (2D) cultures. 4T1 cells exposed to BMMSC CM exhibited a 2-fold reduction in apoptosis under low serum concentrations (0.5% to 1%). Furthermore, exposure of 4T1 and LL/2 cells to BMMSC CM increased their viability in the presence of paclitaxel or doxorubicin at therapeutic concentrations. This effect was accompanied by reductions in caspase-3 activity and Annexin V expression. When coinjected with 4T1 cells in the mammary fat pad of mice subsequently treated with doxorubicin, BMMSC (and not fibroblasts) also inhibited drug-induced apoptosis in tumor cells by 44%. We demonstrated that BMMSC were attracted by 4T1 and LL/2 cells but not by NIH3T3 cells in vitro and that when injected intravenously in 4T1 tumor-bearing mice, these cells (and not NIH3T3) were specifically detected in tumors within 12 to 18 days in which they preferentially localized at the invasive front. Overall, our data identify BMMSC as an important mediator of tumor cell survival and treatment resistance in primary tumors.

PMID: 24502925 [PubMed - indexed for MEDLINE] PMCID: PMC4000239 [Available on 2015-04-01]

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