

Tumor associated mesenchymal stem cells protect ovarian cancer cells from hyperthermia through CXCL12

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Hyperthermic intraperitoneal chemotherapy (HIPEC) has shown promise in the treatment of ovarian carcinosis. Despite its efficiency for the treatment of peritoneal carcinosis from digestive tract neoplasia, it has failed to demonstrate significant benefit in ovarian cancers. It is therefore essential to understand the mechanism underlying the resistance to HIPEC in ovarian cancers. Mesenchymal Stem Cells (MSC) play an important role in the development of ovarian cancer metastasis and resistance to treatments. A recent study suggests that MSCs may be cytotoxic for cancer cells upon heat shock. In contrast, we describe the protective role of MSC against hyperthermia. Using cytokine arrays we determined that tumor associated MSC (TAMC) secrete pro-tumoral cytokines. We studied the effect of hyperthermia in co-culture setting of TAMC or bone marrow derived-MSC (BM-MSC) associated with ovarian cancer cell lines (SKOV3 and CaOV3) with polyvariate flow cytometry. We demonstrate that hyperthermia does not challenge survival of TAMC or BM-MSC. Both TAMC and BM-MSC displayed strong protective effect inducing thermotolerance in ovarian cancer cells (OCC). Transwell experiments demonstrated the role of secreted factors. We showed that CXCL12 was inducing thermotolerance and that inhibition of CXCL12/CXCR4 interaction restored cytotoxicity of hyperthermia in co-culture experiments. Targeting the interaction between stromal and cancer cells through CXCL12 inhibition might restore hyperthermia sensitivity in ovarian cancers, and thus improve HIPEC efficiency.