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# Astrocytes Protect Brain Metastatic Breast Cancer Cells From Chemotherapy Through CX43 Dependent STAT1 Signaling in Co-Culture Spheroids

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## Abstract

Annually, over 200,000 cancer patients in the United States are diagnosed with brain metastases. Notably, brain metastatic breast cancer (BMBC) is the second most common, accounting for ~30% of all brain metastasis cases. BMBC typically has poor prognosis and is resistant to chemotherapy. In the brain tumor environment, metastatic cells interact with stromal cells, such as astrocytes, influencing tumor growth and protecting them from chemotherapy. Herein, we report a three-dimensional (3D) co-culture spheroid model to study astrocyte induced growth and chemoresistance in BMBC cells. We prepared co-culture spheroids of BMBC cells and human astrocytes (1:1 ratio) or only BMBC cell spheroids, cultured them in suspension for 7 days, and treated them with paclitaxel (PTX). Using proliferation and apoptosis assays our results demonstrate that tumor cells in co-culture spheroids were non-responsive to PTX, while the tumor cell spheroids were responsive. Moreover, the chemoprotection of tumor cells by astrocytes in co-culture spheroids was mediated by connexin 43 (CX43) dependent STAT1 signaling pathway. Accordingly, the inhibition of CX43 alleviated PTX resistance in co-culture spheroids. Our 3D co-culture spheroid platform could serve as a tool to study resistance to therapy in BMBC, and to identify combination treatments for therapy resistant BMBC.

**Keywords:** CX43 signaling; brain metastasis; breast cancer; chemoresistance; co-culture; spheroids.

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