A hybrid cell population generated through engulfment of mesenchymal stem cells by breast cancer cells enhances chemoresistance and metastasis

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The metastatic spread of breast cancer and the development of chemoresistance represent the leading causes of death in breast cancer patients. We have recently demonstrated that a subset of breast cancer cells (BCCs) engulfs mesenchymal stem/stromal cells (MSCs) with a resultant hybrid population that drives increased cancer cell dissemination. Herein, we identify and characterize a unique hybrid cancer cell population in clinical samples of primary invasive carcinoma and chemo-resistant breast cancer metastases. Using a co-culture model of patient-derived MSCs and BCCs, we demonstrate that MSC engulfment by BCCs gives rise to a hybrid cell population co-expressing both BCC and the MSC markers, which is enriched with multinucleated/polyploid and senescent cells. In a microfluidic cell pairing device, we obtained hybrid cells pairing a single DsRed-MSC with a single GFP-231 BCC, which showed higher cell viability compared to BCCs upon treatment with Paclitaxel (PTX). Interestingly, PTX treatment did not reduce distant metastasis in mice intracardially injected with hybrid cells compared to vehicle control group, whereas the senolytic drug Navitoclax induced a reduced metastatic spread compared to control. This study has unveiled the presence of a previously unrecognized hybrid cell population in metastatic breast cancer patients, characterized by senescent cells, which play a pivotal role in breast cancer chemoresistance and recurrence. Our data shed new light on the potential therapeutic strategies for combating these challenges in breast cancer management.