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Spontaneous fusion of breast cancer cells with mesenchymal stem cells: Support for a long-standing hypothesis on cancer metastasis

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Ninety percent of cancer-related deaths are due to secondary tumors, or metastases, that form at sites far removed from the primary tumor. To successfully relocate in the body, a tumor cell must acquire transient properties that enable dissemination, followed by the reestablishment of the original primary phenotype at a distant site. Exactly how this is accomplished is yet unclear and therefore reliable treatments are lacking. Here we test a long-standing, but technically challenging, hypothesis that spontaneous fusion of tumor cells with cells of stromal lineage give rise to hybrid cells capable of dissemination and new tumor growth. Here we analyzed the ability of breast cancer cells to spontaneously fuse with mesenchymal stem cells. We used breast cancer cells with different degrees of aggressiveness (T47D which is non metastatic, and MDA-MB-231 which is metastatic) and normal breast epithelial cells MCF10a. To enable these studies, we have developed a powerful tool for the detection of fusion products *in vitro* that utilizes bimolecular fluorescence complementation. Using this tool, we found that MSCs fuse spontaneously with all breast epithelial cell types. Interestingly, this fusion occurs to a greater extent between MSCs and the breast cancer cells T47D and MDA-MB-231 ($P < 0.05$) compared to normal breast epithelium suggesting that cancer cells more readily fuse with MSCs. In addition, we found that hypoxia stimulates a significant increase in fusion between MSCs and non-metastatic breast cancer cells T47D ($P<0.05$) which is intriguing given the hypoxic nature of the tumor microenvironment relative to healthy tissue. And finally, hybrids are more migratory than breast cancer cells both in terms of accumulated distance and velocity. These results suggest that cell fusion might contribute to the ability of cancer cells to disseminate from the primary tumor site and perhaps metastasize. Future follow-on studies may uncover new strategies for cancer treatment and/or preventing metastatic spread.

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