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Breast cancer cells and fibroblasts in co-culture: reciprocal influences on cell adhesion, membrane fluidity and migration

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The growing role of the reciprocal interaction between epithelial and stromal cells in the development and progression of breast cancer has been recognized. In particular, the migratory/invasive behaviour of tumor cells seems to be strongly influenced by their dialogue with neighbouring stromal cells. To verify if this cross-talk may affect some molecular and functional aspects of the cell biology correlated with the metastasizing vocation of the tumor cells (i.e. adhesion molecule expression, membrane fluidity, migration), we co-cultured estrogen receptor (ER)-positive, poorly invasive and low metastasizing (MCF-7) or ER-negative, highly invasive and metastatic (MDA-MB-231) breast cancer cells with fibroblasts isolated from breast healthy skin (normal fibroblasts, NFs) or from breast tumor stroma (cancer associated fibroblasts, CAFs) in monolayer or in a three-dimensional system (nodules). We previously reported the ability of NFs and CAFs to respectively induce or inhibit the epithelial adhesion molecule, E-cadherin, expression in MCF-7 cells. In the present study, the expression of the mesenchymal adhesion protein N-cadherin (N-cad) was investigated by confocal immunofluorescence microscopy on frozen nodule sections. An increase in N-cad levels was observed in CAFs, but not in NFs, as a result of the interaction with both kinds of epithelial cancer cells. CAFs, in turn, promoted an increase in N-cad level of MDA-MB-231 cells and induced its expression in MCF-7 cells, originally negative for N-cad.

Two-photon microscopy imaging of cells labeled with Laurdan, a membrane fluorescent probe, was used to investigate fluidity changes in plasma membranes of all the cell types in monolayer cultures. Tumor cell/fibroblast interaction enhanced fluidity of cancer cell membrane while tumor cells generally promoted an increase in fibroblast membrane packing density.

Cell tracking by confocal microscopy demonstrated that the interaction of mammary cancer cells with NFs or CAFs determined a definite increment in tumor cell migration velocity, even with a marked enhancement of the migration directionality induced by CAFs.

Our results demonstrate a reciprocal influence of mammary cancer and stromal cells on various adhesiveness/invasiveness features. In particular, an overall protumoral/-invasive effect of CAFs on both well- and poorly differentiated mammary cancer cells was exteriorized by reduction of cell adhesion, induction of membrane fluidity, and migration velocity and directionality, along with a promotion of epithelial-mesenchymal transition.