

Epithelial-stromal dialogue in breast cancer: implications for cell adhesion

Cristiana Angelucci¹, Gina Lama¹, Gabriella Proietti¹, Cristina Fabbri², Giuseppe Maulucci³, Riccardo Masetti² and Gigliola Sica¹

¹ Institute of Histology and Embryology, Faculty of Medicine "A. Gemelli", Catholic University of the Sacred Heart, Rome, Italy

² Department of Surgery, Breast Unit, Faculty of Medicine "A. Gemelli", Catholic University of the Sacred Heart, Rome, Italy

³ Institute of Physics, Faculty of Medicine "A. Gemelli", Catholic University of the Sacred Heart, Rome, Italy

Stromal fibroblasts have been reported to interfere with proliferation and invasion of cancer cells. Our objective was to elucidate, using a three-dimensional coculture system (nodules), the interaction between a human, estrogen receptor-positive, well differentiated breast cancer cell line (MCF-7) and fibroblasts isolated from breast healthy skin (normal fibroblasts, NFs) or from breast tumor stroma (cancer associated fibroblasts, CAFs) in terms of cell growth and adhesion. The cell proliferating fraction of each cell type was evaluated by immunohistochemical detection of two cell cycle-associated nuclear proteins: Ki67 and proliferating cell nuclear antigen (PCNA). The expression of epithelial adhesion molecule E-cadherin was investigated in MCF-7 cells by confocal immunofluorescence microscopy. The MCF-7 cells/CAF mixed nodules showed a significantly larger proportion (50%, $p < 0.001$, Tukey's multiple comparison test) of Ki67-positive tumor cells with respect to that observed in MCF-7 cells/NFs (30.6%, $p < 0.001$) or MCF-7 (34.8%, $p < 0.001$) nodules. MCF-7 cells seemed to have no influence on the growth of both kinds of fibroblasts. Similar results were obtained with PCNA, even though a more heterogeneous and less intense nuclear staining was observed. Immunofluorescence analysis showed that in MCF-7 cells/NFs nodules E-cadherin expression level in tumor cells was about 2.5 fold higher than that observed in MCF-7 cultured alone and about 16 fold higher than that showed by MCF-7 cells cocultured with CAFs. These data support the hypothesis that the activated fibroblasts residing in the breast tumor stroma are able to transmit mitogenic signals to the epithelial cancer cells. Concerning cell adhesion, our results clearly demonstrate the ability of CAFs to negatively affect cell-cell contacts of epithelial cells by strongly reducing E-cadherin expression. The crosstalk of tumor cells with NFs seems to play a crucial role in preventing disruption of cell junctions, cell shape changes and migration.

Key words

Epithelium, stroma, breast cancer, cell growth, adhesion, E-cadherin