Joined forces of cancer cells and fibroblasts in invasion

A. Glentis, Y. Attie, V. Gurchenkov, DM. Vignjevic*
UMR144/CNRS, Institut Curie, 12 rue Lhomond, 75005 Paris, danijela.vignjevic@curie.fr
* Corresponding Author

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Abstract

In carcinoma *in situ*, the basement membrane represents a physical barrier that prevents spreading of primary tumor to adjacent tissues. Thus, the basement membrane must be breached to allow cancer cells to escape the primary tumor and invade the adjacent stroma. It is believed that cancer cells perforate basement membrane. However, stromal cells such as carcinoma-associated fibroblasts also secrete matrix proteinases. Therefore, the question is who is invading whom – do cancer cells invade stroma or possibly stroma is invading tumor cells? Using human colon cancer cells and primary human fibroblasts isolated from tumors and adjacent normal tissues, we address if cancer cells and fibroblasts are invading the basement membrane simultaneously or they work together but have distinct functions.

Once the BM becomes compromised, cancer cells migrate through the stroma towards the blood vessels, allowing dissemination of the tumor and formation of metastasis. At this invasive stage, cancer cells migrate either collectively, as multicellular sheets or chains, or as individual cells. Both isolated single cells and the leader cells of multicellular clusters develop cellular protrusions called lamellipodia and filopodia. In cells migrating in planar substratum, lamellipodia represent the main cellular engine for locomotion, whilst filopodia are believed to be used as guidance organelles to interpret signals from the microenvironment. However, this has never been experimentally documented in other than neuronal and endothelial cells. The question remains, do cancer cells use filopodia as guiding organelles? We address if filopodia are guiding organelles for cell migration on 2D and in 3D matrices using a spheroid chemoattraction assay. Finally, we are testing if fibroblasts are helping cancer cell invasion in 3D collagen gels.