THE BEHAVIOR OF CELLS IN BREAST TUMORS DURING INVASION AND METASTASIS

Condeelis, J. S.

Albert Einstein College of Medicine Gruss Lipper Biophotonics Center, New York, United States

(john.condeelis@einstein.yu.edu)

Multi-photon microscopy (MPM) allows the direct observation of the behavior of individual cells in vivo. In mammary tumors MPM demonstrates that invasive/migratory carcinoma cells form migratory streams and intravasate when associated with macrophages. Taking advantage of this macrophage tropism allows collection of the migratory competent macrophages and tumor cells as live cells directly from the primary tumor. Expression profiling of these co-migratory tumor cells and macrophages has led to the surprising conclusion that both cell types exhibit embryonic expression patterns. Further analysis indicates that the tumor cells express genes associated with breast cancer stem cells, apoptosis and cell cycle arrest, and DNA repair. Consistent with this unusual expression pattern are the phenotypes of the isolated tumor cells: radiation and chemotherapy resistance, arrest in G0-1 and a greatly amplified ability of tumor cells to find and co-migrate with macrophages and intravasate. Consistent with the embryonic expression pattern is the observation that tumor cell migration with macrophages in vivo in mammary tumors is reminiscent of cell migration during morphogenesis in the embryonic breast.

The expression pattern unique to the migratory tumor cells is called the Invasion Signature. Invasion, adhesion and motility pathways identified in the Invasion Signature converge on the RhoC/Cofilin/Mena pathway identifying it as a master regulator of chemotaxis, invasion and dissemination of breast tumor cells in vivo. Using markers derived from the RhoC/Cofilin/Mena pathway, anatomical landmarks have been developed for use with breast cancer patients. One of these, composed of an intravasating carcinoma cell marked by Mena over-expression, and a peri-vascular macrophage, is called TMEM (Tumor Micro-Environment for Metastasis) in human breast tumors. Related markers of metastatic risk are MenaCalc (relative expression of Mena isoform 11a), Mena ratio (MenaINV/Mena 11a in fine needle aspirates of breast tumors), and cofilin x P-cofilin, a marker of activation of the Cofilin/Mena pathway in tumor cells. These related markers can be organized to represent progression from EMT to migration to intravasation. They predict metastatic risk in human invasive ductal carcinomas of the breast as shown in 4 retrospective clinical studies. The molecular mechanisms behind these markers are a major focus going forward.