**The Tissue-specific Microenvironment in Primary Tumors and Metastases**

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Cancer cells within tumors exist in specialized niches in the microenvironment. The tumor cells are heterogeneous and can have properties as divergent as self-renewal, tumor initiation and repopulation potential, dormancy, evasion of cell death and metastasis. Metastasis is the major cause of poor outcome in breast cancer. The microenvironment is critical for regulating multiple aspects of tumor progression and metastasis. Understanding the processes involved in metastasis is critical for developing new preventative and therapeutic strategies We have analyzed the tumor microenvironment (TEM) and its function in tumor progression using in vivo imaging, genetic models of breast cancer, patient-derived xenografts, organotypic cultures and patient samples. We have found that the matrix environment and the innate immune cells responding to the primary tumor and infiltrating the metastatic sites are critical for regulating tumor invasion and metastasis. Indeed, the inflammatory microenvironment of metastatic sites was distinct from that of the parental tumor and the normal tissue, even before metastasis takes hold. Interplay between non-metastatic primary breast cancer and innate immune response, acting together to control metastatic progression. At the single-cell level that early stage metastatic cells possess a distinct stem-like gene expression signature. The metastatic cells and the microenvironment were distinct in different metastatic sites and from the primary tumor. Micrometastatic cells are distinct due to their increased expression of basal, stem cell, pro-survival, and dormancy-associated genes. In contrast, cells from macrometastases were similar to primary tumor cells, which were more differentiated and heterogeneous. We validated our findings with a large primary breast cancer tissue microarray, and pleural effusions from breast cancer patients. These results suggest that novel cancer immunotherapies that activate and augment the function of anti-tumoral myeloid subpopulations could have therapeutic potential and be clinically important for patients with advanced breast cancer.

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