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Biophysical interactions of stromal cells with invasive breast cancer cells

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The progression of cancer from a benign mass of abnormal cells to a malignant tumor requires the development of a tumor-promoting microenvironment. MSCs are recruited to the tumor microenvironment from nearby tissue and bone marrow in response to tumor-secreted soluble factors. Within the tumor, MSCs can differentiate into carcinoma associated fibroblasts that promote tumor growth, invasion, and angiogenesis. Though stromal cell recruitment in response to soluble factors has been well-documented, the involvement of cell adhesion is not fully understood. Cell adhesion molecules, including cadherins and integrins, play a critical role in cancer progression. Alterations in cell adhesion molecules are associated with the epithelial-mesenchymal transition, a mechanism by which cancer cells become more invasive. We sought to understand if changes in cell adhesion molecules during cancer progression affected the engraftment of stromal cells such as fibroblasts and MSCs. We show that stromal cells are less likely to spread and adhere to non-invasive MCF7 breast cancer cells (Fig. 1A-B) than to more invasive MDA-MB-231 breast cancer cells (Fig 1A, C). Cadherin 11 and 2 were co-localized at sites of adhesion and blockade of cadherin 11 on stromal cells reversed this adhesive response, providing insight into stromal cell engraftment in invasive tumors. Within the tumor cells encounter 3D heterogeneous networks of collagen-rich extracellular matrix (ECM). To model the 3D tumor microenvironment, MSCs and breast cancer cells were embedded in 3D collagen matrices, and time-lapsed cell and particle tracking were used to analyze cell migration and matrix remodeling. We showed that co-culture with MSCs does not alter the migration of less invasive MCF7 (Fig. 1D) but causes MDA-MB-231 invasive breast cancer cells to elongate and directionally migrate (Fig. 1E). Small molecule inhibitor studies revealed MSC-induced directional migration is mediated by TGF-b1. This work provides insight into MSC interactions with invasive breast cancer cells within the tumor microenvironment and potential therapeutic targets to halt invasion and metastasis

Biography

Michelle R Dawson is an Assistant Professor of Molecular Pharmacology, Physiology, and Biotechnology and Biomedical Engineering at Brown University. She has served as ad-hoc reviewer for 20+ journals along editorial board member for 2 journals. She's an active member in the Biomedical Engineering Society and American Institute of Chemical Engineers. Her lab is actively investigating the complex and dynamic intracellular signaling cascades that control cytoskeletal stiffening, force transmission, and directed motility in normal tissues and tumors. Cells undergo rapid changes in shape and organization during migration, which is dynamically controlled by cytoplasmic polymers that mechanically support the cell structure and spatially organize the contents of the cell. These studies will increase our understanding of (i) stem cell homing, (ii) tumor cell metastasis, and (iii) chemotaxis

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