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, which includes a scaffold of extracellular matrix proteins and a network of supporting cells and growth factors [1]. 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 differentiation into carcinoma associated fibroblasts that promote tumor growth, invasion, and angiogenesis [2].

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 [3]. 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 colocalized 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 [4].

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 [5]. We showed that coculture 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-β [6]. 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.

Figure 1: (A-C) Adhesion of fluorescently labeled stromal cells to MCF7 and MDA-MB-231 breast cancer cell monolayers. (D-E) Directional velocity (16-hour period) of breast cancer cells cultured alone or with MSCs in collagen.