Mesenchymal Stem Cell Aging and Senescence Associated Extracellular Matrix Contributions to Breast Cancer Progression

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ABSTRACT

Age is a leading risk factor for developing breast cancer. This may be in part to the time required for acquiring sufficient cancer mutations; however, stromal cells that accumulate in tissues and undergo senescence eventually develop a senescence-associated secretory phenotype that alters the microenvironment to promote cancer. Our focus is on mesenchymal stem cells (MSCs) – stromal cells recruited to tumors due to their natural tropism for inflammatory tissues; MSCs have been shown to enhance the metastatic potential of tumor cells through direct interactions or paracrine signaling within the tumor. In the tumor, MSCs can differentiate into carcinoma-associated fibroblasts that play a central role in tumor growth and matrix remodeling. We recently investigated the molecular and mechanical differences in pre- and post- senescent MSCs and how their interactions with MDA-MB-231 breast cancer cells contribute to malignancy. Our data show post-senescent MSCs are larger and less motile, with more homogeneous mechanical properties than pre-senescent MSCs. In-depth omics analysis revealed differentially regulated genes and peptides including factors related to inflammatory cytokines, cell adhesion to the extracellular matrix, and cytoskeletal regulation. A 3D co-culture model was used to assess the effects of pre- and post- senescent MSCs on collagen matrix remodeling. Although post-senescent MSCs were far less motile than pre-senescent MSCs and less contractile with the matrix, they profoundly altered matrix protein deposition and crosslinking, which resulted in local matrix stiffening effects. Post-senescent MSCs also induced an invasive breast cancer cell phenotype, characterized by increased proliferation and invasion of breast cancer cells. This invasive breast cancer cell behavior was further amplified when MDA-MB-231 was co-cultured with a mixture of pre- and post- senescent MSCs; this result was attributed to matrix remodeling and soluble factor secretion effects of post-senescent MSCs, which enhanced the migration of pre-senescent MSCs allowing them to form tracks in the collagen network for cancer cells to follow. Finally, molecular inhibitors targeting actomyosin contractility and adhesion were used to alter MSC interactions with breast cancer cells. Actin depolymerizing agent and focal adhesion kinase inhibitor were most efficient and completely able to block the effects of post-senescent MSCs on MDA-MB-231 invasion in collagen gels. This comprehensive approach can be used to identify molecular pathways regulating heterotypic interactions of post-senescent MSCs with other cells in the tumor. Furthermore, the local matrix stiffening effect of post-senescent MSCs may play a critical role in breast cancer progression.