Cellular Senescence Alters Tumor Microenvironment Interactions Forcing Cancer Progression

Michelle Dawson, Deepraj Ghosh

Gordon Research Conference: Signal Transduction by Engineered Extracellular Matrices

July 22-27, 2018, Andover, NH (MD, GRC Poster Presentation)

ABSTRACT

Mesenchymal stem cells (MSCs) that accumulate in the primary tumor due to their natural tropism for inflammatory tissues enhance the metastatic potential of tumor cells through direct interactions with tumor cells or paracrine signaling within the tumor microenvironment. MSCs also undergo senescence, which leads to increased production of pro-inflammatory cytokines and matrix-degrading enzymes. Senescence is a critical mechanism of limiting abnormal growth and cancer development through tumor suppression; however, senescent cells that accumulate in tissues eventually develop a senescence-associated secretory phenotype that alters the microenvironment to promote cancer. Increased understanding of the biophysical properties of senescent MSCs and how they mediate cell-cell interactions in the tumor may be useful in identifying novel biomarkers for senescent stromal cells in tissues or aggressive cancer cells that form in an aging stroma. A high-content single cell biophysical approach was used to define the mechanical properties of pre- and post- senescent MSCs. Our data shows post-senescent MSCs are larger and less motile, with more homogeneous mechanical properties than their pre-senescent counterparts. A robust molecular screening approach combining genome-wide microarray analysis with mass spec-based proteomics was used to establish the molecular differences in pre- and post- senescent MSCs. Our data show a consistent correlation of up and down regulated gene and peptide expression. A 3D co-culture model was used to assess the effects of pre- and post- senescent MSCs on breast cancer cell motility and invasion in 3D collagen gels. Post-senescent MSCs induced an invasive breast cancer cell phenotype, characterized by increased spreading of breast cancer cells in collagen**,** increased numbers of invading cells, and morphological elongation of breast cancer cells. Surprisingly, this invasive breast cancer cell behavior was further amplified when breast cancer cells were co-cultured with both pre- and post-senescent cells.