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TNF-alpha mediated modulation of cell biophysical properties enhances cell adhesion and transendothelial migration

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Tumor necrosis factor alpha (TNF-alpha) is a widely studied inflammatory cytokine involved in apoptosis, cell survival, inflammation and tumor angiogenesis. It has also been shown to promote cell migration and cytoskeletal rearrangement. We hypothesized that TNF-alpha promotes prometastatic changes in normal mammary epithelial cells by altering their biophysical properties. These changes likely facilitate adhesive interactions with the extracellular matrix (ECM) and promote cell migration and metastasis. We carried out atomic force microscope cell stiffness measurements of the mammary epithelial cell lines. The obtained force-indentation curves were fitted to the Young's modulus. In addition, AFM single cell force spectroscopy (SCFS) was used to measure cell adhesion to collagen type I. Further, adhesion receptor distribution and cell to cell adhesion measurements were conducted to reveal if inflammatory conditions promoted cell transendothelial migration. We found that TNF-alpha treatment decreased the measured cell stiffness of mammary epithelial cells. These changes facilitated enhanced mammary epithelial cell adhesion to collagen following TNF-alpha stimulation, which was largely mediated by increased tether formation. Further, we determined that combined treatment with TNF-alpha and INF-gamma enhanced cell transendothelial migration. AFM adhesion mapping revealed greater adhesion receptor clustering near HUVEC junctions. This facilitated enhanced cell adhesion as measured by SCFS. Taken together, our results implicate that pro-inflammatory mediators, such as TNF-alpha, play an important role in modulating epithelial cell biophysical properties toward a more metastatic cell phenotype.