Cancer cells exploit key signaling pathways in order to survive, proliferate, and metastasize. Understanding the intricacies of the aberrant signaling in cancer may provide new insight into how to therapeutically target tumor cells. The goal of my research was to explore the role of two modulators of transmembrane signaling, the secretory pathway and cell surface proteolysis, in the aggressiveness of breast cancer cells. To study the role of the secretory pathway, I focused on the family of endoplasmic reticulum (ER) chaperones. I found that several ER chaperones were upregulated in breast cancer cells grown under anchorage-independent conditions as mammospheres versus those grown under adherent conditions. Furthermore, certain members of the protein disulfide isomerase (PDI) family were consistently upregulated in two different cell lines at both the mRNA and protein levels. Knocking down these PDIs decreased the ability of the cells to form mammospheres. I demonstrated that the requirement for PDI chaperones in mammosphere growth is likely due to an increased flux of extracellular matrix (ECM) components through the ER. Next, I examined the role of cell surface proteolysis in modulating the aggressiveness of breast cancer cells. Cell-surface metalloproteases release soluble growth factors from cells and activate the corresponding growth factor receptors. I determined that specific metalloproteases (ADAM9 or ADAM12), modulate the activation of Epidermal Growth Factor Receptor (EGFR). I demonstrated that EGFR activation enhances the CD44+/CD24- cell surface marker profile, which is a measure of cancer cell aggressiveness. I found that the MEK/ERK pathway, which is a downstream effector of EGFR activation, modulates the CD44+/CD24- phenotype. When DUSP4, a negative regulator of the MEK/ERK pathway, is lost, activation of EGFR by metalloproteases no longer plays a significant role in cancer cell aggressiveness. Finally, I examined the importance of metalloproteases in the regulation of Programmed-death ligand 1 (PD-L1), a transmembrane protein expressed by some cancer cells that plays a major role in suppressing the immune system. I demonstrated that cell-surface metalloproteases have the ability to cleave PD-L1 and release its receptor-binding domain to the extracellular environment. Collectively, these data indicate that (a) ER chaperones support anchorage-independent cell growth, (b) metalloproteases are important in regulation of an aggressive phenotype through the EGFR/MEK/ERK pathway, and (c) metalloproteases cleave PD-L1, a key component of immunosuppression in cancer.

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