Role of Aging in Promoting the Pro-carcinogenic Cross-talks between Breast Luminal and Fibroblast Cells

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ABSTRACT

The strongest etiological factor for breast cancer is age. Stroma is composed of extracellular matrix and various cell types. It is maintained, repaired by fibroblasts, and is essential for epithelial function. During aging, these cells may undergo cellular senescence, which plays a role in suppressing carcinogenesis. On the other hand, senescent cells secrete factors that can stimulate nearby cells to proliferate and form tumors, suggesting that the senescence response is antagonistically pleiotropic. It is therefore plausible that the presence of senescent cells may create a pro-oncogenic tissue environment that could increase the development of cancer in an age-dependent manner.

I have shown that breast stromal fibroblasts changed the shape and inhibited the senescent state of luminal epithelial cells. The levels of the senescent proteins decreased in the proliferating epithelial cells. The loss of epithelial shape was confirmed by a decrease in the epithelial marker and an increase in the mesenchymal marker with time. This suggested the activation of the Epithelial-to-Mesenchymal Transition (EMT) process.

I have also shown that when primary stromal fibroblast cells were exposed to senescent luminal epithelial cells, led to an increase in the proliferation rate and activation of fibroblasts. The levels of the tumor suppressor proteins decreased, while the levels of α-SMA and SDF-1 were much higher. The migration/invasion abilities of these fibroblasts were strongly enhanced and secreted higher levels of MMP-9, MMP-13 and TGF-β-2. Furthermore, high levels of secreted SDF-1 and IL-6 were shown. Importantly, these fibroblasts triggered the EMT in breast cancer cells by enhancing their migratory/invasive abilities and increased level of various mesenchymal markers while decreased epithelial marker.

This shows that aging enhances the procarcinogenic abilities of breast luminal as well as stromal fibroblast cells. This provides a cellular and molecular explanation to the age-related increase in breast carcinogenesis, and the important role of stromal fibroblasts.