Critical role of defensins in respiratory viral infection induced breast cancer progression

Respiratory viral infections (RVI) such as influenza and COVID19 impact the host systemic immune system along with causing deleterious chronic inflammatory responses and respiratory distress. While the role of chronic inflammation in cancer is well-established, the role of RVI on tumorigenesis is poorly defined. To study the role of RVI on breast cancer, we first infected murine respiratory epithelial cells (mRES) with murine sendai virus (mSV), an analog for human parainfluenza virus. These infected mRES were co-cultured with 4T1 murine breast cancer cells in 1:1 dilution on a single 2D plate and also in trans-well format. Both in co-culture and transwell culture we saw a 40-80% ($p<0.05$) increased proliferation of breast cancer cells. Similarly, when 4T1 cells were treated with the supernatant collected from infected mRES cells in 1:5 dilution, also demonstrated a 2.3 fold increased breast cancer cell proliferation. The cytokine analysis from the supernatant collected from infected mRES cells demonstrated a 17-23 fold enhanced secretion of α/β-defensins. Direct treatment of α-defensin (cyptidin-4, 10 pg/mL) and β-defensin-3 (mBD3, 20 pg/mL) on 4T1 cells demonstrated enhanced expression of chemokine metastatic receptor, CXCR4 (4.3 fold), angiogenic factor, VEGF (12.8 fold) and cell division favoring factor, CDK2 (8.1 fold). Further, analysis of infected mRES cells demonstrated upregulation of toll-like receptor 2 (TLR2) and NOD-like receptor protein 3 (NLRP3) expression. Interesting, co-cultured of infected mRES with syngeneic murine CD4+T cells induced exhaustion phenotype ($PD1^+$ and $CTLA4^+$) differentiation of CD4+T cells. Taken together, these data suggest that respiratory viral infections through induction of cancer cell proliferation and inhibiting anti-tumor adaptive immune responses promote breast cancer proliferation.