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"Mapping the Genomic Landscape of Triple-Negative Breast Cancer and COVID-19"

Background: Triple-negative breast cancer (TNBC) is the most aggressive and lethal form of breast cancer. Clinically TNBC is defined as cancers lacking the expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2). Currently, there are no effective targeted therapies, and cytotoxic chemotherapy remains the most effective therapeutic modality. Clinical management of TNBC has further been complicated by the outbreak of the ongoing COVID-19 pandemic. TNBC patients have comprised immune systems, which makes them susceptible to SARs-CoV-2 infection and poorer clinical outcomes. There is an urgent need to understand the association between TNBC and COVID-19. The objective of this investigation was to identify a signature of genes, network states and signaling pathways associating TNBC with COVID-19. We hypothesized that genomic alterations in women diagnosed with TNBC and COVID-19 could lead to measurable changes associating the two diseases and that these alterations affect gene regulatory networks and signaling pathways driving the two diseases.

Methods: We addressed the hypothesis using publicly available RNA-Seq data from women diagnosed with TNBC, comprising of 115 tumors and 113 control samples from The Cancer Genome Atlas (TCGA) and women diagnosed with COVID-19, comprising of 38 COVID-19 and 13 control samples from the Gene Expression Omnibus (GEO). We compared gene expression levels between cases and controls within each disease. Genes associated with each disease were then evaluated for association with both diseases to identify a signature of genes associated with both diseases. The signature was validated using genes experimentally confirmed and known to be involved in the immune system. Validated genes associated with both diseases were subjected to network and pathway analysis to discover network states and signaling pathways driving the two diseases.

Results: Comparing gene expression levels between tumors and controls revealed a signature of 16,495 significantly differentially ($P<0.05$) expressed genes associated with TNBC. Comparing gene expression levels between COVID-19 and controls revealed a signature of 5,298 significantly differentially ($P<0.05$) expressed genes associated with COVID-19. Evaluation of the two sets of genes revealed a signature of 1,754 associated with both TNBC and COVID-19, including the 152 genes known to be involved in the immune system. Additionally, the investigation revealed signaling pathways driving the association between the two diseases including the following: Kinase, cytokine, DNA repair, and cell cycle signaling pathways.

Conclusion: The investigation revealed a signature of genes, molecular networks and signaling pathways associating TNBC and COVID-19. Further research is recommended to define the molecular mechanisms underpinning the association between the two lethal diseases.