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Abstract Title:- Identification of hub genes involved in prolactin signaling and immuno-modulation in triple negative breast cancer- an in silico study

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Aims:-To identify differentially expressed genes (DEGs) in TNBC in the Asian population that are involved in prolactin signaling and to perform drug sensitivity and immunomodulatory studies using computational tools.

Methods:- About 251 DEGs from one TNBC GEO profile were extracted of which 161 were upregulated and 90 were downregulated. Only five genes were found to be involved in prolactin signaling pathway. Further functional and cellular attributions of these genes were studied through enrichment tools and the Kaplan-Meier plot was created. The overall survival data for each of these 5 genes was plotted. Drug sensitivity tools showed one gene to be most resistant. To understand this resistance the gene was further subjected to immuno-modulatory tools. Impact of these 5 DEGs was discussed in prolactin pathways.

Results:- Five genes, CCND1, SOCS2, ELF5, TNFRSF11A, and SHC4, were found to be actively involved in the prolactin signaling pathway. In TNBC, TNFRSF11A, CCND1 and SHC4 were overexpressed while ELF5 and SOCS2 were downregulated. Genes that were elevated had a negative link with overall survival correlation. There exists a strong correlation to tumor infiltration and gene expression which culminates to survival curve. CCND1, displayed positive correlation with macrophages and myeloid derived suppressor cells (MDSC) where overexpression combined with lower immune infiltration resulted in higher survival. Out of the 5 DEGs involved in prolactin pathway, CCND1 and SHC4 played a major role in TNBC pathway. SOCS2 had negative feedback in JAK-STAT pathway and TNFRSF11A was involved in cytokine-cytokine receptor interaction. CCND1 was found to be resistant to 23 out of the 30 drugs listed in the database while SHC4 showed positive correlation with 10 drugs but was weak.

Conclusions:- CCND1, TNFRSF11A and SHC4 are involved in cellular proliferation and SOCS2 inhibits the JAK-STAT pathway. The data was linked with survival plots, showing that overexpressed DEGs here impacted overall survival in TNBC patients. The immune infiltration in tumor microenvironments correlate with oncogenic upregulation of CCND1. Lower macrophage and MDSC infiltration with increased expression shows higher survival and thus is a potential candidate for targeted immunotherapy. All the genes here are involved in prolactin signaling while also converging with PI3K-AKT, JAK2/STAT and MAPK pathways commonly upregulated in cancers. CCND1 was also the most resistant to 23 of 30 chemotherapeutic drugs in the database currently in use. CCND1 in this study emerges to be a potential target for overall survival in TNBC.

Keywords:- TNBC, immune cell infiltrations ,Prolactin signaling, Drug resistance, CCND1