ABSTRACT

Breast cancer is the most common cancer globally and the primary cause of mortality and morbidity worldwide. Chemoresistance is a primary cause of breast cancer treatment failure, and protein-protein interactions are significant contributors to chemoresistance during different stages of breast cancer progression. In pursuit of novel biomarkers and relevant protein-protein interactions occurring during the evolution of breast cancer, we used a computational predictive biological (CPB) approach which identified an association of Integrin β1 (ITGB1) with chemoresistance and breast cancer stem cell (SCS) markers. ITGB1 activated the Focal Adhesion Kinase (FAK) pathway promoting invasion, migration, and chemoresistance in breast cancer by upregulating Erk phosphorylation. FAK also activated Wnt/Sox2 signaling, enhancing self-renewal in breast cancer.

Next, to understand the correlation between chemoresistance and self-renewal pathways, we explored how CSCs become resistant. Cells entering the quiescent state are often chemoresistant. We found that mammospheres, the subpopulation of breast cancer with self-renewal, enter the quiescent state after a particular time point. Further analysis suggested this quiescent state is maintained by the combined expression of Sox2 and Oct4 proteins that subsequently downregulates proteins associated with the G1-S transition of the cell cycle. A similar condition was observed during chemotherapeutic assault both *in vitro* and *in vivo*. Sox2 regulated the expression of all the proteins associated with dormancy in breast CSCs. Sox2 also regulated the expression of Oct4 that also regulated the expressions of quiescence-associated proteins. Thus, we concluded that Sox2 plays a central role in regulating chemoresistance in breast CSCs.

Then we explored the role of cancer stem cells in modulating the tumor microenvironment (TME). Conditioned medium from cancer stem cell enhanced cellular proliferation, epithelial to mesenchymal transition (EMT), and increased chemoresistance in breast cancer. MIF was the major component of the conditioned media that also induced similar effects both *in vitro* and *in vivo*. Further analysis revealed an increase in the Akt phosphorylation, which induced EMT and upregulated anti-apoptotic proteins. Hypoxic conditions enhanced MIF secretion from CSCs, and HIF-1α played a crucial role. So, in conclusion, this study revealed several novel mechanisms that were involved in breast cancer chemoresistance. Several critical molecules like ITGB1, Sox2, and MIF are identified, which can serve as biomarkers for combating chemoresistance in the future.

Keywords:

Breast cancer, Cancer stem cell, Self-renewal, Chemoresistance, Integrin signaling, FAK signaling, Sox2, Oct4, Tumor microenvironment, Quiescence, MIF, Akt pathway, Erk pathway.