Cure of Breast Cancer-Year 6: Novel Approaches in the Therapy of Metastatic Breast Cancer Using Clinical Databases and 3D Organoid Model

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Among various subtypes of breast cancer, triple-negative breast cancer (TNBC) is well-known as aggressive cancer with frequent anticancer drug-resistance and easy metastasis. Nevertheless, the development of new drugs and functional studies for inhibiting the invasiveness of anticancer drug-resistant TNBC are still lacking. Here, we found that the metastatic ability of drug-resistant TNBCs was caused by an increase in inflammatory-mediated Programmed Death Ligand 1 (PD-L1/CD274). PD-L1/CD274 gene had a positive correlation with metastasis-mediated inflammation-related genes, Cell Division Cycle 20 (CDC20), Ubiquitin Specific Peptidase 1 (USP1), TNF Alpha Induced Protein 3 (TNFAIP3), and Caspase 1 (CASP1), which we previously identified, in only the TNBC subtype through the Breast Cancer Gene Expression Miner database containing 4,421 TNBC patient samples. PD-L1 resulted in high invasiveness of taxol- and cisplatin-resistant MDA-MB-231 and BT-549 TNBC cell lines. However, this cancer metastasis by PD-L1 was reduced by the inhibition of inflammation-related genes, CASP1 and CDC20. The exosome inhibitor, GW4869, also significantly reduced cancer cell invasion of chemotherapy-resistant TNBC, and interestingly, a decrease in PD-L1 expression was also observed in this result. Under the three-dimensional (3D) organoid model, we first found metastatic actin fibers on the cancer spheroid surface in the taxol- and cisplatin-resistant TNBC which were strongly prevented by the inflammation inhibitors (Necrostatin-1 and Necrosulfonamide) and exosome inhibitors (Manumycin A and GW4869). These results suggest that inflammation and exosome inhibitors might be novel strategies as anticancer drugs to treat chemoresistant TNBC patients by negatively regulating PD-L1 expression.

Awards Won: