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"A Novel NSC Small Molecule Inhibitor, Inhibits Proliferation of Triple-Negative Breast Cancer Cells Through Upregulation of NR4A Family Genes."

Background: Triple-negative breast cancer (TNBC) is known to be the most aggressive form of breast cancer. Challenges in treatment have occurred due to the absence of well-defined molecular targets and high invasive, proliferative capacities of these cells. Common treatments for TNBC include combinations of surgery, radiation, and chemotherapy; however, there is usually minimal success. This can be attributed to the high recurrence rate. Therefore, with the lack of success in treating patients with TNBC, novel and efficacious therapies are needed. We have found a small molecule inhibitor with potent anti-tumor activity against TNBC cells.

Methods: By using next-generation sequencing (NGS), we observed that the NR4A family genes had the largest fold change in treatment vs. control with a significant p-value, which led to us primarily focusing on these genes. A series of experiments were repeated to ensure the results remained consistent. Different dosages of the NSC small molecule inhibitor were used to treat the MDA-MB-231 cell line. Results showed that the higher dosages lead to higher expression of NR4A. Results were confirmed with the q-RT-PCR technique, done in triplicate. To further investigate, the basal expression of the NR4A family genes was measured in different cancer cell lines as well as the normal cell line. While all NR4A family genes had significant fold change, the largest fold change between the cancer cell lines and the normal cell lines was in gene NR4A2, narrowing the focus to one gene in particular. Next, we focused on comparing our results to clinical data that was available through METABRIC (Molecular Taxonomy of Breast Cancer International Consortium), using a dataset of 2,000 clinically annotated breast cancer patients. With the raw data provided, we analyzed the gene expression of NR4A2. Different subtypes of breast cancer, grade, and tumor stage were used as differentiating factors. Finally, we examined overall survival for NR4A2.

Results: Our data shows that the novel NSC small molecule inhibitor reduced the proliferation of MDA-MB-231 TNBC cells through upregulation of NR4A family genes. Analyzing the results from METABRIC, it was evident that the lowest expression of NR4A2 was shown in TNBC and grade 3, which is consistent with the hypothesis that NR4A2 is a tumor suppressor. Through the analysis of the overall survival data, it can be determined that higher expression of NR4A2 has a longer survival rate than that of lower expressing cancers.

Conclusion: In summary, our data indicated that NSC small molecule inhibitors exhibit anti-tumor activity in TNBC cells, through upregulation of the NR4A2 gene. Further investigation of the potential of NSC small molecule inhibitors as an attractive therapeutic drug for TNBC would be needed.