OFFICIAL ABSTRACT and CERTIFICATION

Targeting Dihydroceramide Desaturase 1 (DES 1) as a Method to Overcome Anoikis Resistance in Basal Breast Cancer

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Despite advances in early stage breast cancer treatment, metastatic breast cancer still has low survival rates and limited therapies. Certain subtypes such as basal breast cancer (BLBC) are more aggressive and difficult to treat, often lacking any targeted therapies. Resistance to anoikis — a form of cell death — has emerged as an important biology allowing aggressive cancers like BLBC to metastasize. While sphingolipids (SLs) have been indicated as key mediators of cell death and are known to be altered in cancer, the relationship between SLs and anoikis resistance has not been definitively studied. Because of its broader role in anoikis resistance, the enzyme dihydroceramide desaturase (DES1) has been indicated as a potential target in metastatic disease.

The hypothesis considered whether targeting DES1 through both a genetic and pharmacological approach could overcome anoikis resistance in BLBC. By using CRISPR to knockout DES1 in 4T1 cancer cells and the inhibitors fenretinide and ABC294640 to inhibit DES1 function, it was shown that the loss of DES1 did overcome anoikis resistance by decreasing cell survival in anchorage independent conditions and reducing colony growth and tumorigenicity. These results indicate DES1 as a potential target for the future treatment of BLBC.

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