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Targeting STAT3 in Triple Negative Breast Cancer Using GSK3β and Integrin Inhibitors

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Table of Contents

Abstract

Triple negative breast cancer (TNBC) is the most aggressive subtype of breast cancer and is known for its chemoresistance and high rate of recurrence. TNBC lacks the hormone receptors that are found in other types of breast cancer, and therefore cannot be treated with hormonal therapies. Although the initial response to chemotherapy is favorable, many TNBC patients experience a recurrence of this cancer at a secondary location and this recurrence is often more lethal than the original tumor. The Signal Transducer and Activator of Transcription (STAT) pathway is a major contributor to cancer growth and metastasis, and STAT3 is constitutively active in TNBC. STAT3 activation is associated with promotion of proliferation, metastasis, and chemoresistance, and is therefore a potential therapeutic target. A STAT3 gene signature generated from TNBC cells treated with a STAT3 siRNA was analyzed using the publicly available online tool called CLUE from the Broad Institute. Through CLUE, potential STAT3 inhibitors were identified from drugs that had a similar gene signature. Two of these drugs, an integrin inhibitor and a GSK3β inhibitor, have shown the ability to synergistically decrease cell viability and reduce the expression of STAT3 target genes in 2D cultured TNBC cells. Individually, each drug reduces the migratory ability of TNBC cells. These data provide evidence that targeting STAT3 is a viable option in the development of TNBC therapeutics, and that the combination should be further investigated to determine the synergistic mechanism.