Understanding the Competition Between STAT3 and STAT5 in Breast Cancer

Alexandra Temple

Introduction

Around 13% of women will develop invasive breast cancer during their lifetime [1]. In 2020, 2.3 million women were diagnosed with breast cancer globally [2]. The most aggressive form, Triple Negative Breast Cancer (TNBC), has the highest recurrence and metastasis rates with the fewest treatment options available, and accounts for 10 to 15% of all invasive breast cancers [3]. Due to its aggressive nature, TNBC usually results in a worse prognosis than other invasive breast cancers (4,5). TNBC lacks estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2), limiting the treatment options available (4,5), which provides an opportunity to develop novel therapeutics targeting TNBC and other invasive breast cancers.

The Signal Transducer and Activator of Transcription (STAT) family consists of seven members, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 where STAT5a and STAT5b are often grouped together as STAT5. Previous research has found STAT3 to play an important role in breast cancer. It is involved in cancer initiation, progression, metastasis, chemotherapy resistance, and immune invasion (5). STAT3 is inappropriately active in 70% of all breast cancers but is most associated with TNBC [4]. STAT3 functions primarily through the JAK/STAT signaling pathway. Upon stimulation by a hormone or growth factor, tyrosine kinase receptors will come together to phosphorylate Janus Kinase (JAK). JAK then phosphorylates STAT3 which dimerizes with another phosphorylated STAT3 (pSTAT3) and can translocate into the nucleus to regulate transcription of certain target genes. Inappropriately active STAT3 is an indicator of a poorer prognosis, making it a desirable target for novel treatments.

(INSERT JAK/STAT PATHWAY PIC)

STAT5 has also been found to be inappropriately active in some breast cancers [5]. Previous studies have shown that STAT3 and STAT5 share a subset of overlapping binding sites and thus can regulate expression of the same gene [4]. Interestingly, when both STAT3 and STAT5 are concurrently active, STAT5 can outcompete STAT3 for binding to certain genes and STAT3 can outcompete STAT5 for binding to other genes [5]. Additionally, STAT3 and STAT5 can have reciprocal effects on certain overlapping target genes. For example, STAT3 enhances BCL6 expression, whereas STAT5 represses it. Concurrent activation of both STAT3 and STAT5 is often associated with a more favorable prognosis compared to activation of STAT3 alone, thus promoting the question of whether the overlapping target genes play a significant role in breast cancer progression and metastasis.

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There are currently 110 known overlapping binding sites for STAT3 and STAT5 in two-dimensional cell culture. However, breast cancer cells do not just grow in a singlular monolayer within the body. Thus, the 3D model allows cells to grow in spheres rather than adhere to the culture dish, providing a better model that more closely mimics the interactions of cells within the body.

(INSERT 2D VS 3D PIC)

Therefore, we can study the overlapping binding sites with a more comprehensive model to better understand the competition in binding between STAT3 and STAT5.

Results

References

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