Title: BRD8 is a therapeutic vulnerability for overcoming resistance to dual ER/HER2 blockade therapy in HR+/HER2+ breast cancer

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Scientific Abstract:

Hormone receptor (HR)-positive, HER2-positive breast cancers often develop resistance to endocrine and anti-HER2 therapies due to the heterogeneous expression of estrogen receptor (ER) and HER2 and the crosstalk of these growth-promoting pathways. However, how anti-HER2 agents activate ER and other growth-promoting pathways remains unknown. Single-cell RNA sequencing of BT474 breast cancer cells identified Bromodomain Containing Protein 8 (BRD8), an acetyl-lysine reader protein in the histone acetylase EP400 complex, as a pivotal mediator to activate ER in response to neratinib treatment. BRD8 expression was rapidly induced by various anti-HER2 agents (neratinib, lapatinib, and trastuzumab), and its depletion disrupted the crosstalk between ER and HER2 signaling pathways and rendered HR+/HER2+ cells and PDxOs more sensitive to anti-HER2 agents. BRD8, ER, and ER target genes are co-induced by neratinib in single-nucleus RNA and ATAC sequencing of a patient-derived xenograft (PDX). SnATAC-seq also reveals that the activated genes share open chromatin regions enriched in ER, forkhead box (FOX), and ETS family transcription factors (TF) binding motifs. FOX family TFs are well-known for regulating estrogen signaling, and ETS proteins have been shown to promote tumorigenesis. Since EP400 enhances H2AZ deposition and acetylation on chromatin, we performed H2AZ and H2AZac ChIP-sequencing in the presence or absence of BRD8 and neratinib treatment. We found that, in response to neratinib treatment, BRD8 activates ER, FOX, and ETS target genes through modulating H2AZac deposition and chromatin decompaction. This finding coincides with RNA-sequencing where BRD8 promotes cell growth in an ER-dependent and -independent manner. In line with these findings, patients who responded poorly to the anti-HER2 therapies exhibited higher levels of BRD8 target gene signature as compared to the responders. Furthermore, BRD8 knockout ablates the ER and HER2 signaling crosstalk and re-sensitizes neratinib-resistant HR+/HER2+ cells to neratinib. In summary, this work not only explains why ER signaling is activated upon anti-HER2 therapies but also identifies BRD8 as a druggable vulnerability for treating HR+/HER2+ breast cancer.

Written Lay Abstract:

New breast cancer treatments could target protein called BRD8

One type of breast cancer is called “hormone receptor-positive, HER2-positive” because it is made up of a mix of cells that express (have more of) the proteins estrogen receptor (ER) and HER2. This type of breast cancer often stops responding to cancer treatments that block ER or HER2.

Both ER and HER2 are proteins that increase growth of tumors by activating (starting) pathways in cells. ER and HER2 interact – they start pathways that overlap and interact with each other, which is why tumors can continue to grow even if a patient is given cancer treatment that blocks one of the proteins. Researchers want to understand how to stop this interaction and better treat this type of breast cancer.

For this study, researchers looked at breast cancer cells and found a protein called BRD8 that is part of the ER and HER2 pathways. BRD8 helps DNA fold, which affects what genes (sections of DNA) can be “on” and start pathways inside the cell. The researchers found that BRD8 opens DNA and allows ER and other cancer-related proteins (FOX and ETS proteins) to work and the cancer to grow and spread. They also found that BRD8 changes a histone (a type of protein that works with DNA) called HAZ, which also affects how DNA is folded and what pathways start.

Anti-HER2 cancer drugs called neratinib, lapatinib, and trastuzumab increase the amount of BRD8 in cancer cells. BRD8 worked inside the cells and allowed ER to start working, which led to the cancer growing and spreading. When the researchers blocked BRD8, the anti-HER2 cancer drugs worked better to stop the growth and spread of breast cancer.

This research tells us that patients with hormone receptor-positive, HER2-positive breast cancer could be better treated with both an anti-HER2 cancer drug and a drug that blocks BRD8.

Visual Lay Abstract:

New breast cancer treatments could block protein BRD8

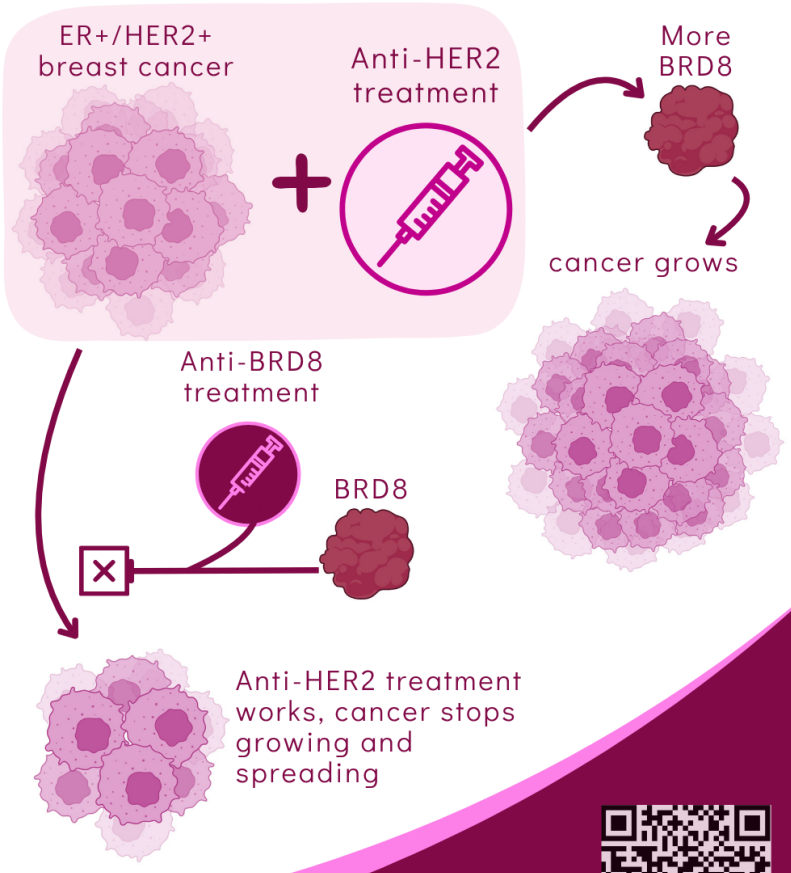
ER+/HER2+ breast cancer is very hard to treat

ER and HER2 are proteins that tell cancer cells to grow. They use connected paths inside cells to "talk" to each other. Even if a drug blocks one protein, the other protein keeps cancer growing.

Protein BRD8 makes cancer grow

Researchers found that protein BRD8 helps tell cancer cells to grow.

Anti-HER2 cancer treatments increase BRD8 in cancer cells, which tells cancer to grow again



Blocking BRD8 helps cancer treatments work better

In this study, researchers found that blocking BRD8 made cancer treatments work better.

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