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Tissue-specific MED1 LxxLL motifs play critical roles in HER2-driven breast cancers

Estrogen Receptor (ER) is a nuclear hormone receptor that plays important roles in normal mammary gland development as well as breast cancer growth and metastases. In a breast cancer setting, when ER is bound by estradiol, there is a recruitment of the multi-subunit transcriptional coactivator complex known as Mediator that acts as a bridge between ligand-bound ER and RNA polymerase II. This recruitment results in ER-responsive gene expression that promotes growth and metastasis of breast cancer cells.

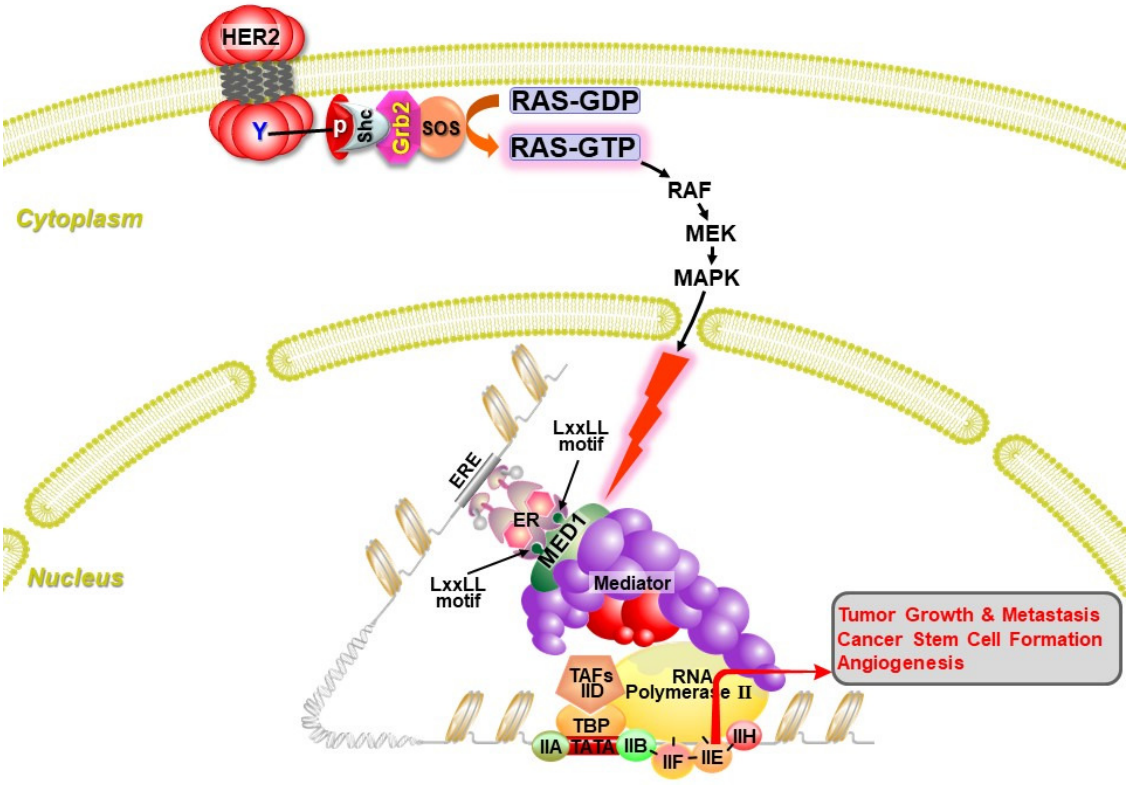

Fig. 1. Tissue-Specific MED1 LxxLL Motifs Play Critical Roles in HER2-driven Breast Tumorigenesis and Metastasis. MED1 (shown in green) interacts directly with ER through its two LxxLL motifs (indicated by arrows) to mediate its functions. Our data indicates critical roles for these motifs in HER2+ breast cancer tumor growth and metastasis, cancer stem cell formation, and new blood vessel formation or "angiogenesis.".

A subunit of the Mediator complex known as Mediator subunit 1, or MED1, is responsible for the direct interaction between ER and the rest of Mediator, through its two LxxLL motifs (shown in green Fig. 1). Our lab has previously generated a MED1 mutant mouse model where both of its LxxLL motifs were mutated to LxxAA that has previously been characterized to disrupt the interaction between ER and Mediator. Surprisingly, while this MED1 mutant mouse did show developmental delays in the pubertal mammary gland,

the mice were viable and fertile and there were no defects in other ER-responsive tissues like the uterus or bone, indicating a tissue-, gene-, and cell-specific role for MED1s interaction with ER.

The MED1 gene is located within the HER2 amplicon in the chromosome 17q12 region and in almost all cases, MED1 coamplifies with the HER2 oncogene in breast cancer. The HER2 receptor tyrosine kinase is a transmembrane protein that is overexpressed in approximately 20-30% of breast cancers. Previous research and our lab have pinpointed MED1 as a point of crosstalk between the ER and HER2 signaling pathways that confers resistance of HER2+/ER+ breast cancer cells to anti-estrogen therapies. Although we have shown MED1 having a functional role in ER/HER2-mediated therapeutic resistance, little is known whether the MED1 LxxLL motifs play a part in HER2-mediated breast tumorigenesis.

To investigate this question further, we have crossed the above mentioned MED1 LxxLL-motif mutant mouse with a transgenic mammary tumor prone mouse whose tumorigenesis is under the control of the HER2 oncogene. The resultant progenies, labeled "HER2/MED1$^{KI/KI}$," mice, exhibited significantly delayed tumor onset and growth, in addition to a decrease in the number of metastatic lung tumor nodules. Furthermore, we saw a dramatic loss in cancer stem cell (CSC) formation, decreased cell growth and inhibited formation of new blood vessels, or "angiogenesis." In addition, we investigated the underlying mechanisms by which MED1 and its LxxLL motifs function to elicit these effects and determined a role for Insulin-like growth factor 1 (IGF-1) hormone signaling, which we confirmed in both breast cancer cell lines and human patient samples. Together, our findings suggest an important function for MED1's LxxLL motifs in HER2-controlled breast cancer tumorigenesis. Moreover, our study demonstrates the potential for a MED1 LxxLL-motif targeted treatment strategy that could potentially mitigate unwanted side effects on other tissues that are commonly seen with current anti-estrogen therapies for HER2+/ER+ breast cancer patients.

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Publication

HER2-Driven Breast Tumorigenesis Relies upon Interactions of the Estrogen Receptor with Coactivator MED1.
Yang Y, Leonard M, Zhang Y, Zhao D, Mahmoud C, Khan S, Wang J, Lower EE, Zhang X
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