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RESEARCH HIGHLIGHT

# Tamoxifen and ERα36: Fertilizing the seeds of breast cancer metastasis

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**Hormonal therapies including tamoxifen have been a mainstay for the treatment of breast tumors that express the classical estrogen receptor ERα66. Wang et al. now report that tamoxifen may paradoxically stimulate ALDH-expressing breast cancer stem cells via activation of the ERα66 variant ERα36.**

One of the greatest advances in breast cancer therapy has been the stratification of tumors into subtypes based on expression of estrogen receptor (ER), progesterone receptor (PR), and HER2. Tumors that express ER, known as ER-positive breast cancers, are the most common subtype of breast cancer, accounting for ~ 70% of early-stage breast cancer diagnoses. They are highly curable, with 20-year disease-free survival rates approaching 80% for earliest stage tumors.

Estrogen signaling is mediated by binding of 17β-estradiol (E2) to ER, which initiates a signaling cascade resulting in downstream activation of numerous transcription factors. Two estrogen receptors, ERα and ERβ, have been described to signal via genomic and non-genomic pathways. These two receptors regulate unique genes, and in fact can serve opposing functions. Current clinically-utilized ER assays test for the primary alpha receptor, ERα66. Several other ERs and related proteins have been described. For example, estrogen related receptor beta (ERRβ) is found in embryonic stem cells, and is involved in cellular self-renewal. ERα36, a truncated variant of ERα66 without transcriptional activity, has been described and is thought to function via a non-genomic signaling pathway.[1] Interestingly, the expression of ERα36 is independent of ERα66, and thus it is expressed in a subset of cells in both ER-positive and ER-negative breast cancers.

The mainstay of therapy for ER-positive tumors is endocrine therapy, consisting of tamoxifen or aromatase inhibitors. Endocrine therapies work via preventing estrogen stimulation of the estrogen receptor and downstream signaling, although by different mechanisms. Aromatase inhibitors inhibit peripheral conversion of androgens into estrogen via the aromatase enzyme, thereby decreasing circulating levels of estradiol. Tamoxifen, a selective estrogen receptor modulator (SERM), acts as an estrogen antagonist in certain tissues, including breast tissue.

While endocrine therapy is highly effective, some tumors recur in spite of endocrine therapy. Cancer stem cells (CSCs) are postulated as a mechanism of tumor recurrence. These cells, which comprise a small portion of most ER-positive tumors, are thought to mediate tumor initiation, metastasis, and treatment resistance. Furthermore, the important clinical issue of dormancy in $ER^+$ breast cancer has been attributed to this cell population. In ER-positive tumors, CSCs identified by the expression of aldehyde dehydrogenase (ALDH1) are often found to be negative for ERα66, and the mitogenic effects of estrogen on this cell population have been thought to be indirect involving paracrine effects.[2]

In a recent paper in *Cell Research*, Wang et al. add to the evolving story the importance of ERα36 in breast cancer with a report that stimulation of ERα36 promotes metastasis via promotion of ALDH1A1-positive CSCs.[3, 4] This group has previously reported that expression of ERα36 is related to resistance to tamoxifen, and that estrogen signaling via ERα36 regulates the maintenance of breast CSCs.[5] In the current study, they analyzed ERα36 expression in 1677 breast cancer samples, and convincingly showed that ERα36 expression was correlated with tumor size, grade, and lymph node involvement. They further found that ERα36-positive tumors were more likely to recur as metastatic disease, regardless of ERα66 status. In patients who received tamoxifen, those with ERα36-positive tumors showed shorter metastasis-free survival than those with ERα36-negative tumors, although this may in fact be due to ERα36 itself, not a negative effect of tamoxifen therapy. In contrast to the effects of tamoxifen, they show that the clinical benefit of aromatase inhibitors is independent of ERα36 expression. They conclude that these differential clinical outcomes are due to the stimulatory effect of tamoxifen on ERα36-expressing cells, a finding consistent with but not proven by the clinical data.

They present compelling pre-clinical data linking ERα36 and CSCs and demonstrate that tamoxifen stimulates ERα36-expressing CSCs, increasing their capacity for migration, invasion, and tumor initiation. Furthermore, they show that this occurs via the regulation of ALDH expression. It has previously been demonstrated that ALDH is a marker of breast CSC and a predictor of poor clinical outcome.[6] The current work adds increasing evidence for an important functional role of ALDH. It also suggests that estrogen may have a direct mitogenic effect on breast CSC which is mediated by ERα36. In addition, this study suggests that tamoxifen resistance may in part be mediated by ERα36, and that CSCs are responsible for the effect.

The authors propose that tumors could be screened for ERα36 expression, and that tamoxifen should not be used for tumors that express ERα36. However, this suggestion is counter to numerous clinical studies demonstrating the effectiveness of tamoxifen in both therapeutic and preventative settings. A meta-analysis published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in ER-positive breast cancer demonstrated ~ 30% reduction in breast cancer mortality with 5 years of tamoxifen therapy.[7]

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Interestingly, however, there are some clinical data suggesting a paradoxical effect of tamoxifen consistent with the Wang et al. data. A meta-analysis of studies utilizing SERMs in prevention of breast cancer demonstrated a 38% reduction in breast cancer incidence.[8] However, long-term results of one of the largest chemoprevention trials demonstrated a trend toward increased breast cancer deaths in the group treated with tamoxifen as compared to placebo.[9] Furthermore, results of numerous studies reveal superior efficacy of aromatase inhibitors compared to tamoxifen.[10] This may be in part due to mechanisms related to ERα36 signaling as described.

A growing body of literature on ERα36 suggests that expression of this ER variant may be of important clinical significance. In the absence of clinical trial data, it is premature to recommend a change in clinical practice based on ERα36 expression. However, the data presented in this paper as well as previous studies provide a strong rationale for designing clinical trials to further elucidate the role of ERα36 across the spectrum of breast cancer.

## ADDITIONAL INFORMATION

**Competing interests:** MSW has financial holdings and is a scientific advisor for OncoMed Pharmaceuticals, Verastem, and MedImmune and receives research support from MedImmune.

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