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ERBB2–Estrogen Receptor Interplay in Breast Cancer: Molecular Complexity, Tumor Heterogeneity, and Therapeutic Opportunities

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ABSTRACT

Human epidermal growth factor receptor 2 (HER2/ERBB2) is one of the most intensively investigated oncogenes in breast cancer research. Its amplification or over-expression defines a biologically aggressive subtype of breast cancer, historically associated with poor prognosis. Estrogen receptor (ER) signaling represents another dominant axis of breast carcinogenesis, governing tumor growth, differentiation, and response to endocrine therapy. Accumulating evidence demonstrates that ER and HER2 pathways are deeply interconnected through bidirectional molecular crosstalk, influencing tumor heterogeneity, therapeutic sensitivity, and resistance mechanisms. This review comprehensively synthesizes current knowledge on ERBB2 structure and signaling, ER biology, ER–HER2 crosstalk, receptor heterogeneity and discordance, clinical subtypes, and resistance to targeted therapies. In addition, emerging biomarkers and novel therapeutic vulnerabilities are discussed. A detailed understanding of ERBB2–ER interactions provides a rational framework for personalized and combinatorial treatment strategies in breast cancer.

Keywords: *ERBB2 and HER2; Estrogen receptor; Breast cancer heterogeneity; Targeted therapy; Endocrine resistance*

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1. INTRODUCTION

Breast cancer is a heterogeneous malignancy characterized by substantial variability in molecular drivers, clinical behavior, and therapeutic response. The routine classification of breast cancer based on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/ERBB2) expression has transformed patient management by enabling biomarker-guided therapy [1, 2,3]. Among these markers, ERBB2 has emerged as a critical oncogenic driver, with amplification or protein overexpression observed in approximately 20–30% of invasive breast cancers [1,4,5]. HER2-positive tumors are typically associated with high proliferative capacity, early metastasis, and poor clinical outcome in the absence of targeted therapy [4,6].

The introduction of HER2-targeted agents, particularly trastuzumab, has dramatically improved survival outcomes and redefined HER2 positivity from a uniformly adverse prognostic factor to a predictive biomarker of therapeutic benefit [4,7]. Parallel to HER2 biology, ER signaling plays a central role in breast carcinogenesis, with ER-positive tumors accounting for the majority of cases and demonstrating substantial responsiveness to endocrine therapies [8,9]. Importantly, ER and HER2 pathways do not function in isolation. Instead, extensive bidirectional crosstalk exists between these signaling networks, shaping tumor evolution, therapeutic resistance, and disease relapse [10,11].

This review provides an integrated overview of ERBB2 and ER signaling in breast cancer, emphasizing molecular mechanisms of interaction, tumor heterogeneity, receptor discordance, and evolving therapeutic strategies.

2. MOLECULAR BIOLOGY OF ERBB2 (HER2)

The ERBB2 gene encodes a 185-kDa transmembrane receptor tyrosine kinase that belongs to the epidermal growth factor receptor (EGFR/ERBB) family [1,10]. Unlike other ERBB family members, HER2 lacks a known soluble ligand and is constitutively maintained in an active conformation, rendering it a preferred heterodimerization partner for other ERBB receptors [10,12]. HER2-containing dimers exhibit potent signaling activity, leading to sustained activation of downstream oncogenic pathways.

Upon dimerization, HER2 triggers phosphorylation cascades involving the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway and the RAS/RAF/MEK/ERK pathway, both of which promote cell proliferation, survival, metabolic reprogramming, angiogenesis, and extracellular matrix remodeling [12,13,14]. Aberrant activation of these pathways is strongly associated with aggressive tumor behavior and metastatic potential (figure 1).

HER2 overexpression most commonly arises from gene amplification; however, several studies demonstrate that HER2 protein overexpression may also occur in the absence of amplification, particularly in estrogen receptor–positive tumors and ductal carcinoma in situ (DCIS) [15]. This observation highlights the complexity of HER2 regulation and suggests that transcriptional and post-transcriptional mechanisms contribute to HER2-driven oncogenesis.

3. ESTROGEN RECEPTOR SIGNALING IN BREAST CANCER

The estrogen receptor is a nuclear hormone receptor that functions as a ligand-activated transcription factor regulating genes involved in cell cycle progression, differentiation, and survival [8,9]. Upon estrogen binding, ER undergoes conformational changes that facilitate dimerization, DNA binding at estrogen response elements, and recruitment of co-regulatory proteins [16].

ER-positive breast cancers are typically dependent on estrogen signaling for growth, making endocrine therapies such as tamoxifen, aromatase inhibitors, and fulvestrant highly effective treatment options [8,17]. Nevertheless, resistance to endocrine therapy remains a major clinical challenge. One key mechanism underlying endocrine resistance involves growth factor receptor signaling, particularly through HER2-mediated kinase activation [14,18].

HER2-driven phosphorylation of ER enables ligand-independent activation of ER transcriptional programs, thereby bypassing estrogen deprivation and diminishing the efficacy of endocrine agents [14,18]. This molecular interaction underscores the importance of ER–HER2 crosstalk in breast cancer progression.

4. ER–HER2 CROSSTALK AND SIGNAL INTEGRATION

ER and HER2 signaling pathways engage in extensive bidirectional crosstalk that profoundly influences breast cancer biology [10,11]. HER2 activation can suppress ER expression while simultaneously activating ER through post-translational phosphorylation, creating a dynamic feedback loop that enhances tumor adaptability [18]. Conversely, ER signaling can regulate the expression of growth factor receptors and their ligands, further reinforcing pathway integration (figure 1).

Molecular studies have demonstrated increased cross-phosphorylation and co-activation of ER and HER2 in ER-positive/HER2-positive tumors, particularly in the context of tamoxifen resistance [18]. In such tumors, tamoxifen may paradoxically exhibit agonistic activity due to altered co-regulator recruitment and HER2-driven signaling, resulting in de novo or acquired resistance [18].

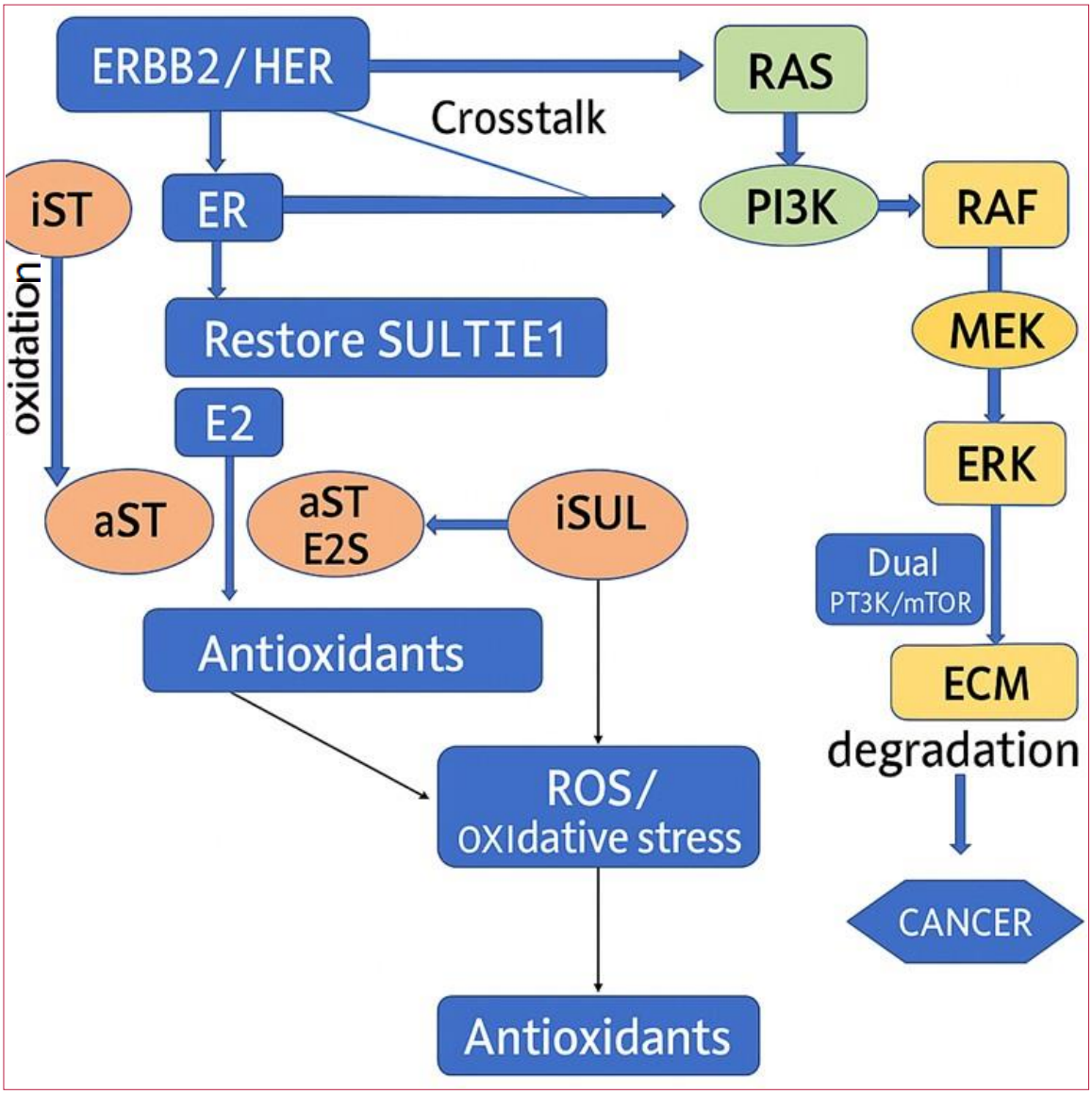

Figure 1. Schematic illustration of estrogen receptor and HER2 signaling pathways, highlighting key nodes of molecular crosstalk and downstream effector pathways.

5. TUMOR HETEROGENEITY AND RECEPTOR DISCORDANCE

Intra-tumoral heterogeneity is a defining feature of breast cancer and represents a major obstacle to effective treatment [12]. Tumors often consist of multiple subclones with distinct molecular profiles, enabling adaptive responses to therapeutic pressure. Receptor discordance between primary tumors and metastatic lesions is well documented, particularly for ER and PR status [19,20]. In contrast, HER2 status demonstrates relatively high concordance, although clinically relevant discordance still occurs [8,9]. Such changes may result from clonal selection, genetic evolution, or technical variability in receptor assessment.

Importantly, receptor conversion has direct therapeutic implications, as treatment decisions in metastatic disease are frequently based on receptor status. These findings support re-biopsy and reassessment of biomarkers whenever feasible [19].

6. CLINICAL SUBTYPES AND PROGNOSTIC IMPLICATIONS

Breast cancer subtypes defined by ER, PR, and HER2 expression exhibit distinct biological and clinical characteristics [5,6,21]. ER-positive/HER2-positive tumors represent a biologically unique subgroup with intermediate behavior between luminal and HER2-enriched cancers (figure 2). In the pre-trastuzumab era, HER2 positivity conferred poor prognosis even in ER-positive disease; however, the advent of HER2-targeted therapy has substantially improved outcomes [4,11].

Triple-negative breast cancer (TNBC), characterized by the absence of ER, PR, and HER2 expression, remains associated with aggressive behavior, high metastatic potential, and limited targeted treatment options [21]. Comparative analyses emphasize the critical prognostic and predictive value of receptor-based classification.

7. THERAPEUTIC STRATEGIES TARGETING HER2 AND ER

7.1 HER2-Targeted Therapies

Trastuzumab, a monoclonal antibody against HER2, revolutionized the treatment of HER2-positive breast cancer by significantly reducing recurrence and mortality [4]. Subsequent agents, including pertuzumab, lapatinib, neratinib, and tucatinib, have expanded the therapeutic landscape [7,22,23]. Antibody–drug conjugates such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) further enhance efficacy by delivering cytotoxic payloads directly to HER2-expressing cells [22,5].

7.2 Dual ER–HER2 Targeting

Given the extensive ER–HER2 crosstalk, combined targeting strategies have gained increasing attention. Clinical and preclinical studies demonstrate that dual inhibition of ER and HER2 pathways improves antitumor efficacy and delays resistance, particularly in ER-positive/HER2-positive disease [22,24,25].

7.3 Mechanisms of Resistance

Resistance to HER2-targeted therapy may arise through multiple mechanisms, including PI3K/AKT/mTOR pathway hyperactivation, ER reactivation, redox imbalance, and adaptive signaling rewiring [13,14,26]. Understanding these mechanisms has prompted investigation of rational combination therapies incorporating kinase inhibitors, endocrine agents, and redox modulators.

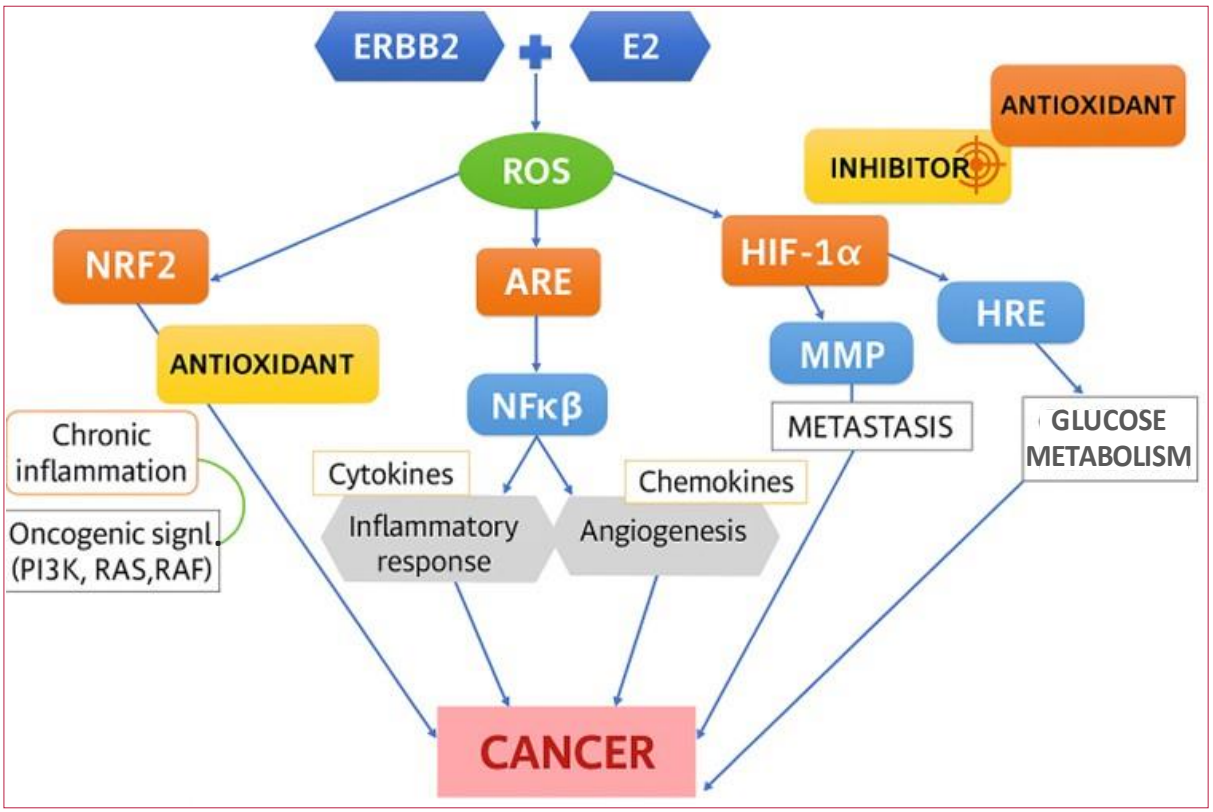

Figure 2. Major mechanisms of resistance to HER2-targeted therapies and potential combinatorial treatment approaches.

8. EMERGING BIOMARKERS AND THERAPEUTIC VULNERABILITIES

Recent research has identified novel molecular regulators associated with aggressive HER2-positive breast cancer (table 1). Nuclear respiratory factor 1 (NRF1) is overexpressed in ER/PR-negative, HER2-positive tumors and may serve as a prognostic biomarker and therapeutic target [10]. Similarly, CXCR4 expression correlates with metastatic potential and is regulated by estrogen through PI3K/AKT and MAPK pathways [26].

Table 1. Summary of therapeutic vulnerabilities associated with ER–HER2 signaling networks.

Summary Table of Therapeutic Vulnerabilities

Pathway Node	Functional Role	Therapeutic Target(s)
SULT1E1	Estrogen detoxification, redox balance	Nrf2 activators, SULT1E1 expression enhancers
ERBB2 / ER	Hormone-receptor crosstalk	HER2 mAbs/TKIs + ER antagonists
PI3K–AKT–mTOR	Growth, ECM degradation, survival	Dual PI3K/mTOR inhibitors, Akt inhibitors
RAS–ERK	Cell proliferation & survival	MEK inhibitors, combination therapy
ROS	DNA damage, signaling amplification	Antioxidants, ROS-scavengers
CSNK1G2	Modulates tamoxifen sensitivity	CK1γ2 modulators + endocrine agents

9. FUTURE PERSPECTIVES

Advances in molecular profiling continue to refine our understanding of ERBB2-driven breast cancer. Integration of genomic, transcriptomic, and metabolomic data is expected to enable more precise patient stratification and personalized therapy. Future clinical trials focusing on adaptive and combination strategies will be critical to overcoming therapeutic resistance.

10. CONCLUSION

ERBB2 and estrogen receptor signaling represent interdependent drivers of breast cancer biology. Their complex crosstalk underlies tumor heterogeneity, therapeutic response, and resistance. Continued exploration of ER–HER2 interactions will be essential for optimizing treatment strategies and improving outcomes for patients with breast cancer.

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