Taking the 'low' into consideration: Discussions on redefining HER2 status in breast cancer (Review)

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Abstract. Breast cancer is classified, based on human epidermal growth factor receptor 2 (HER2) status, as HER2-positive or HER2-negative, guiding eligibility for HER2-targeted therapies. A HER2-low tumor is a type of breast cancer, which is defined by immunohistochemistry scores of 1+ or 2+ with negative *in situ* hybridization. Technological advances in HER2 testing, along with improved diagnostic precision, have increased the recognition of the HER2-low subgroup. HER2-low tumors may represent a distinct biological and clinical entity. Molecular profiling further demonstrates the unique transcriptomic and mutational signatures of HER2-low tumors, particularly within hormone receptor-positive contexts. In addition, clinical trials such as DESTINY-Breast04, demonstrate notable efficacies for novel antibody-drug conjugates, such as trastuzumab-deruxtecan, in patients with HER2-low tumors. This challenges the conventional HER2 stratification and suggests guideline revisions in order to acknowledge the HER2-low status. The present review synthesized knowledge regarding HER2 biology, pathology and molecular features, and highlighted the clinical relevance and therapeutic implications of redefining HER2 status to include the HER2-low subgroup. Recognizing HER2-low as a discrete classification may refine patient stratification, optimize therapeutic selection and improve clinical outcomes in breast cancer management.

Contents

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1. Introduction

Breast cancer is a notable global health issue, with 2.3 million new cases and 670,000 mortalities worldwide in 2022 and by 2050, new cases are expected to rise by 38%, with mortalities increasing by 68% (1). Human epidermal growth factor receptor (HER)2-low breast cancer refers to tumors that have HER2 expression levels with an immunohistochemistry (IHC) score of 1+ or 2+ without HER2 gene amplification, which is determined using single or dual probe *in situ* hybridization (ISH) tests. Clinically, these tumors are categorized as HER2-negative and are further classified as Luminal A/B or triple-negative breast cancer (TNBC) subtypes based on the expression of hormone receptor (HR) (2,3). IHC and ISH are the main biological techniques used to assess HER2 status in patients with breast cancer. Therefore, these techniques guide therapeutic decision-making. However, different preanalytical and analytical variables, such as the use of fixative agents or the antigen retrieval methodology, can compromise the accuracy of the tests, leading to discrepancies between laboratories (4). To enhance the sensitivity and precision during the detection of HER2 expression levels, adherence to standardized testing guidelines along with the development of novel quantitative assays, such as automated fluorescence-based technologies and reverse transcription-quantitative PCR, are necessary (5-7).

Patients with HER2-positive breast cancer were treated with a combination of chemotherapy and monoclonal antibodies. However, advances in HER2-targeted therapies, particularly antibody-drug conjugates (ADCs) such as trastuzumab emtansine and trastuzumab deruxtecan (T-DXd), has enhanced the precision of targeting cancer cells. Patients with HER2-low breast cancer may benefit from these novel therapeutics, as the cytotoxic agents are delivered directly to the cancer cells while the toxicity to the healthy tissues

is minimized (8,9). Clinical studies demonstrate positive responses and clinical benefits in patients with HER2-low breast cancer receiving ADCs based treatments (10,11). This highlights the need to update current guidelines to recognize HER2-low as a distinct pathological entity. Such a shift may improve treatment selection, clinical outcomes and the integration of innovative therapies.

The present study investigated the current pathology and molecular biology guidelines and techniques used to determine HER2 status in breast cancer. Additionally, the present study reviewed the molecular biology of the HER2 receptor including its role in breast cancer pathogenesis and progression, and highlighted its involvement in tumor growth, survival and metastasis. Additionally, the concept of HER2-low breast cancer was discussed.

2. Molecular classification of breast cancer

Breast cancer molecular subtyping was first introduced in 2000, in a study highlighting the differences between gene expression profiles in tumors (12). Initially, breast cancer was classified into three groups according to the differences in gene expression profiles, namely, Luminal, HER2-positive and basal. This work was fundamental for identifying subgroups of patients with breast cancer and different prognostic outcomes, which influenced individualized clinical management (12,13).

The current guidelines divide breast cancer into five distinct categories depending on the immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 (14). Additionally, the Ki-67 antigen, a marker of cellular proliferation, serves a crucial role in classification, as it notably impacts disease prognosis and survival rates (15,16). The recognized subtypes include Luminal A and B, HER2-enriched (HER2-positive), and basal and normal-like (16).

Luminal A. As per the 2013 St. Gallen consensus, the Luminal A subtype of breast cancer is characterized as ER and/or PR-positive (levels of ≥20%) and HER2-negative with low levels (<14%) of the Ki-67 antigen, which indicates a slow tumor growth (15). Luminal A is the most common subtype and represents 50-60% of all types of breast cancer (17). This subtype is associated with a favorable prognosis, low risk of recurrence and high overall survival rates (13,15). A study by Prat *et al* (13) demonstrates that patients with IHC-defined luminal A breast tumors have an increased disease-free survival (DFS) when PR levels exceed 20% (13). Patients with Luminal A tumors benefit from endocrine therapy but have a poor response to chemotherapy (18).

Luminal B. Luminal B breast cancer is characterized as ER and/or PR-positive with high levels (≥14%) of the Ki-67 antigen, which explains the fast growth and worse prognosis compared with Luminal A (15). Expression of HER2 is observed in Luminal B tumors, with ~30% of cases with HER2-positive breast cancer, as determined using IHC, being the Luminal B subtype. Overall, Luminal B constitutes 10-20% of Luminal breast cancer. Compared with the Luminal A subtype, Luminal B shows increased expression of proliferation-related genes including *avian myeloblastosis viral oncogene homolog*, *γ-glutamyl hydrolase, lysosomal-associated protein transmembrane-4β, nuclease sensitive element binding protein 1* and *cyclin (CCN)E1*, as well as increased expression of growth receptor signaling genes such as the insulin-like growth factor 1 receptor and the fibroblast growth factor receptors (17,19,20). Compared with Luminal A tumors, Luminal B tumors have an improved response to chemotherapy but demonstrate a higher rate of visceral recurrence as well as lower survival rate between diagnosis and relapse (12,15-18,21).

HER2-positive. HER2-positive tumors account for 10-15% of all types of breast cancer and are defined by high expression levels of the *HER2* gene, as well as other genes associated with the HER2 pathway and/or *HER2* amplicon located in the 17q12 chromosome [such as erythroblastic oncogene B (*ERBB)*2 and growth factor receptor-bound protein 7] (15,22). The HER2-positive group is subcategorized according to the HR expression levels, namely luminal HER2 (ER, PR and HER2-positive with Ki-67 levels of 15-30%) and HER2-enriched (HER2-positive, ER and PR-negative with Ki-67 levels >30%) (16). HER2-positive tumors are sensitive to chemotherapy; however, they are associated with a worse prognosis compared with Luminal tumors (17,23). The poor outcome is mainly due to the higher risk of early relapse, and thus requires the use of targeted agents such as the anti-HER2 monoclonal antibody (15,17,23). Among the HER2-positive group, the HER2-enriched subtype is the most common (accounting for 31-76%) and has higher levels of ERBB2 mRNA and protein as well as a higher activation of the EGFR-HER2 signaling pathway. The HER2-enriched tumors have an improved response to anti-HER2 treatments in both early (adjuvant) and pre-surgical (neoadjuvant) settings, regardless of whether HER2 is clinically positive. Only approximately half of clinically HER2-positive tumors (based on IHC 3+ scores) are HER2-enriched (16). This HER2-enriched subtype can also occur in tumors that are clinically HER2-negative, which currently are not treated with HER2-targeted therapies (16).

Basal-type. Basal-type breast cancer represents 15-25% of all types of breast cancer and are the most homogeneous of all subtypes. The current and commonly accepted IHC definition includes tumors that are negative for ER, PR and HER2, but positive for CK5/6 and/or EGFR (24). Due to being negative for ER, PR and HER2 RNA, the term triple-negative is widely used instead of basal, although there is only partial overlap between the two subtypes (24). The precise classification of basal-type breast cancer remains a notable challenge. A previous study reveals up to a 30% mismatch between transcriptomic-based and IHC-based identification methods (25).

Triple-negative tumors are a heterogenous group, including both basal and non-basal subtypes, which differ in clinical features and molecular profiles, especially in terms of therapeutic targets. The low expression of genes that regulate tight junctions and cell-cell adhesion, such as claudins 3, 4 and 7, occludin and E-cadherin, is a feature of one of the numerous triple negative subtypes (26,27). The term 'basal' refers to tumors defined by specific gene expression profiles, which are identified using microarrays. Microarray analysis

distinguishes basal-type from non-basal-type breast cancer by its unique gene expression profile, which is characterized by the high expression of basal cytokeratin genes (such as CK5, 14 and 17) and the notable lack of expression of genes for the hormone receptors [such as estrogen receptor 1 (*ESR1*) and PR gene] and HER2. The term 'triple-negative' indicates the absence of ER, PR and HER2, and the term 'basal-like' describes tumors that are identified using IHC based on four or five protein markers (such as high molecular weight keratins and EGFR) (25,28). A study by Burstein *et al* (29) further investigates the different TNBC subtypes using RNA and DNA profiling. It distinguishes four clinically relevant subtypes of TNBC, namely Luminal-AR (LAR), mesenchymal (MES), basal-like immune-suppressed (BLIS) and basal-like immune-activated (BLIA), which are characterized by distinct molecular signatures (29). Epidemiologically, TNBC most commonly occurs in premenopausal women and is strongly associated with the presence of BRCA1 mutations. Basal types of breast cancer are characterized by the notable poor prognosis and reduced metastasis-free survival, despite being chemo-sensitive (15,25).

Normal-like type. Although originally described as part of the classification, normal-like breast cancer is not included in the prediction analysis of microarray 50 (PAM50) molecular classification at present. Due to its low invasive tumor cell content, it is hypothesized that this group often results from a high proportion of normal (non-tumor) breast tissue in the sample, which leads to a misleading expression profile (17,28). There is evidence supporting little to no notable survival rate differences between normal-like and Luminal A subtypes, thus excluding the need to recognize the normal-like subtype as a distinct subtype of breast cancer (23).

3. Molecular biology and molecular pathology of HER2-positive breast cancer

Among the aforementioned molecular subtypes of breast cancer, HER2-positive tumors represent a biologically distinct group that are characterized by amplification or overexpression of the *ERBB2* gene, which encodes HER2. This group not only has notable implications for prognosis but also guides targeted therapeutic strategies, such as the use of monoclonal antibodies (such as trastuzumab) and small molecule tyrosine kinase inhibitors (such as Lapatinib) (30). Therefore, understanding the molecular classification framework is essential for contextualizing the role of HER2 in breast cancer pathogenesis. The following section investigated the molecular pathology of HER2 and highlighted its biological functions and mechanisms of dysregulation, as well as its relevance to its clinical characteristics.

HER2 is a member of the ERBB-EGFR family of surface tyrosine kinase receptors. As a transmembrane receptor, it consists of an extracellular ligand-binding domain, a single-pass transmembrane helix and an intracellular domain with intrinsic tyrosine kinase activity. Unlike other ERBB family members, HER2 lacks a known ligand and is primarily activated through homo- or heterodimerization with other ERBB receptors, such as EGFR (ERBB1), HER3 (ERBB3) and HER4 (ERBB4) (31,32). While dimerization in the ERBB family is typically ligand-dependent, the overexpression or high local concentration of HER2 can promote spontaneous homo- or heterodimerization, particularly with HER3. Upon activation, HER2 undergoes autophosphorylation at key tyrosine residues within its intracellular domain, initiating downstream signaling cascades, including the PI3K/AKT and RAS/MAPK pathways, which regulate pivotal cellular functions including proliferation, survival and differentiation. The persistent signaling that occurs due to *HER2* gene amplification and overexpression enhances cellular proliferation, survival and metastatic potential while inhibiting apoptosis, which contributes to tumor aggressiveness (33). In addition, HER2 overexpression alters the tumor microenvironment by modulating angiogenesis, immune evasion and the epithelial-mesenchymal transition, further facilitating disease progression (32,34,35). HER2-positive breast cancers have been reported to occur in up to 15-30% of all cases of breast cancer (36) and is associated with an aggressive clinical phenotype, which is characterized by increased disease aggressiveness, higher recurrence rates and a poorer prognosis (37).

4. HER2-low breast cancer

Previously, HER2-low types of breast cancer were classified and treated as HER2-negative tumors and therapeutic interventions were determined by the presence or absence of specific biomarkers (for example HRs), expression of genetic mutational signatures, as well as other factors such as the stage of the disease and the overall condition of the patient (10). However, following the results of the DESTINY-Breast04 clinical trial (10), the therapeutic management of HER2-low breast cancer underwent a notable change. In this phase 3 trial, the efficacy of T-DXd is assessed in patients with HER2-low metastatic breast cancer and previous chemotherapy treatment. Compared with the control group of patients that are treated with chemotherapy as chosen by the physician, the T-DXd-treated group have markedly longer progression-free and overall survival. These findings highlight the clinical relevance of the HER2-low patient population and highlights the need to redefine the classification of HER2 status (10).

After the aforementioned trial, the American Society of Clinical Oncology (ASCO)-College of American Pathologists (CAP) reevaluated and updated the guidelines regarding testing, evaluation and interpretation of HER2 status in breast cancer specimens (3). The updated HER2 testing guidelines from ASCO-CAP are a nuanced approach to the classification of breast cancer and aim to improve the diagnostic accuracy and optimize the selection of treatments. The key changes suggest the mandatory HER2 testing for all newly diagnosed patients with invasive breast cancer and the retesting of metastatic cases when clinically required. While the largest invasive tumor component remains the primary target for testing, smaller lesions should also be assessed and documented if they exhibit a difference in HER2 expression levels.

IHC scoring follows a 3-tier system as follows: A score of 0 for no or faint staining in ≤10% of cells; a score of 1+ for faint and incomplete staining in >10% of the cells; a score of 2+ for weak to moderate complete staining in >10%; and a score of 3+ for intense complete staining in >10% of the

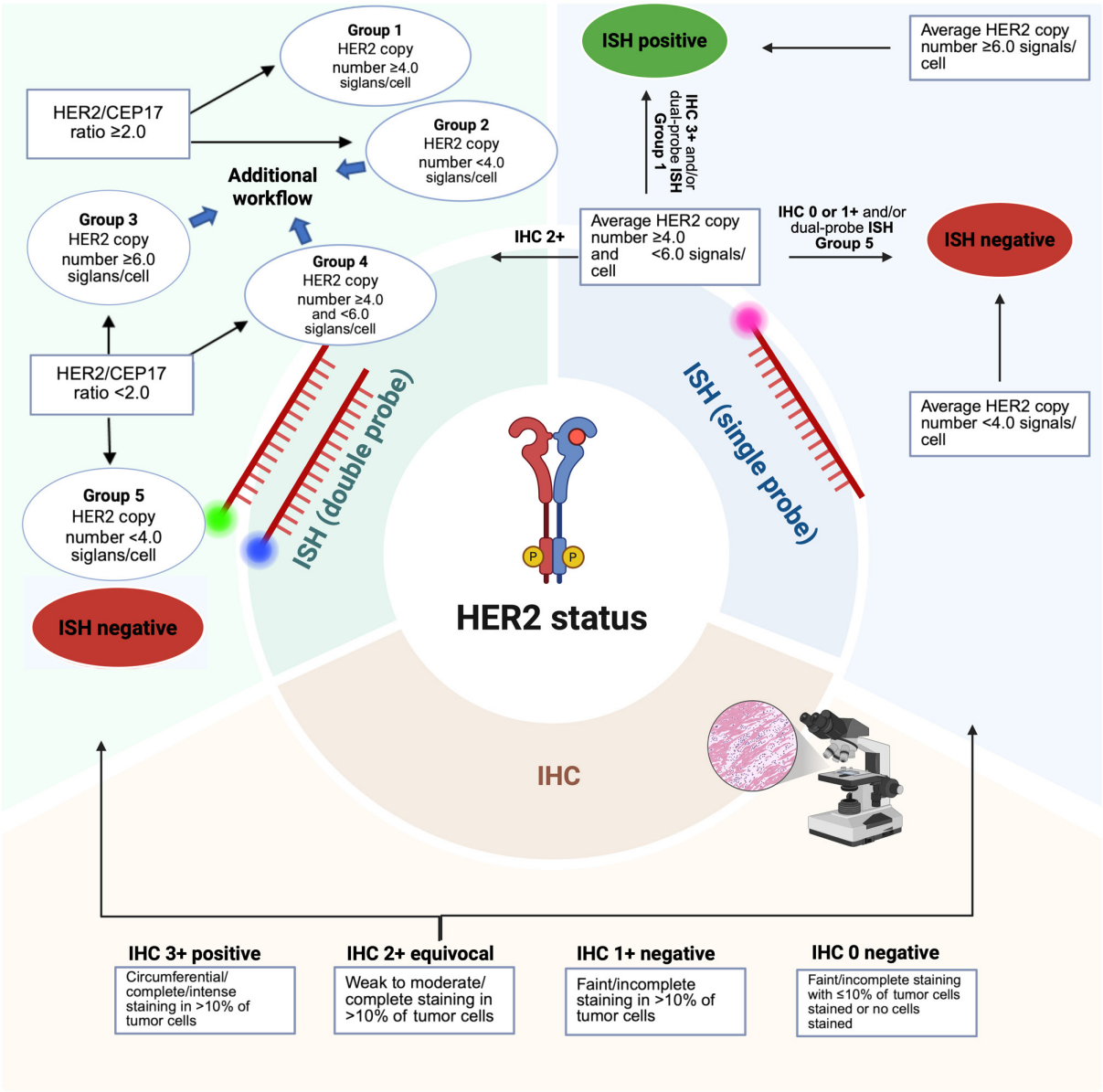

Figure 1. Laboratory workflow for HER2 assessment in tissue samples of breast cancer, based on guidelines from the College of American Pathologists (https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/recommendations-for-human-epidermal-growth-factor-2-testing-in-breast-cancer). HER2 assessment usually begins with IHC (scores of 0-1+ are negative, 2+ are equivocal and 3+ are positive). Molecular investigation is required for equivocal cases. Single-probe FISH assesses *ERBB2* copy number, while dual-probe FISH compares *ERBB2* to CEP17, which improves the accuracy. IHC, immunohistochemistry; ISH, *in situ* hybridization; FISH, fluorescence ISH; *ERBB*, *erythroblastic oncogene B*; CEP17, chromosome enumeration probe 17. Created in BioRender (publication license, Georgiou, A. (2025); https://BioRender.com/3140k7k).

cells. This system classifies HER2 status as negative (a score of 0), equivocal (a score of 2+; requiring ISH confirmation) or positive (a score of 3+), reducing ambiguity. According to the current guidelines, HER2-low (an IHC score of 1+ or 2+ with negative ISH testing) is a distinct subgroup that has notable therapeutic implications. The CAP guidelines highlight the importance of standardized pre-analytical variables (such as optimal initial test validation and optimal internal quality assurance), accurate documentation of tissue handling, assay validation and the use of quality controls in order to enhance laboratory proficiency and ensure precise HER2 classification for optimal patient treatment (3). Fig. 1 presents the CAP guidelines for the laboratory workflow of HER2 assessment in breast cancer tissue, as aforementioned.

5. Molecular and clinicopathological features of HER2-low breast cancer

Due to advancements in diagnostic technologies and targeted therapies, interest in elucidating the molecular and distinct clinicopathological characteristics of HER2-low tumors has increased. Understanding these features may refine the classification, prediction of therapeutic responses and optimization of the treatment strategies for patients with HER2-low breast cancer.

A study by Schettini *et al* (38) investigates the molecular pathology of HER2-low breast cancer by analyzing clinicopathological and PAM50 gene expression level data. The findings reveal that HER2-low tumors are notably more

prevalent in patients with HR-positive breast cancer (65.4%) compared with patients with TNBC (36.5%). Furthermore, compared with patients with HER2 negative tumors, HER2-low tumors are associated with more advanced clinicopathological stages of the disease, including larger primary tumor sizes and increased nodal involvement, as well as an older median age at diagnosis (59 vs. 55 years). The distribution of PAM50 intrinsic subtypes also varies between HER2-low tumors. Tumors were predominantly classified as Luminal A (50.8%) and Luminal B (28.8%), with smaller fractions of basal-like (13.3%), HER2-enriched (3.5%) and Normal-like (3.5%) subtypes. In addition, subtype distribution varies at the transcriptional level, with Luminal A and B showing a higher ERBB2 mRNA expression level compared with basal-like tumors that demonstrate lower levels. Furthermore, the aforementioned study reveals distinct gene expression profiles between HER2-low and HER2 negative tumors. Compared with HER2 negative tumors, proliferation-associated genes (such as *CCNB1* and *E1*), basal-like-associated genes (such as *Keratin 14* and *5*) and tyrosine-kinase receptors (such as EGFR and fibroblast growth factor receptor 4) are downregulated in HER2-low tumors, while Luminal-associated genes (such as *BCL-2, BCL-2-associated athanogene-1, forkhead box α 1, ESR1, PR, G protein-coupled receptor 160* and *androgen receptor*) are overexpressed. Taken together, these findings highlight the potential implications of HR status in HER2-low breast cancer and indicates that HR-positive/HER2-low tumors probably constitute a distinct biological entity compared with TNBC/HER2-low tumors (38).

In another study by Agostinetto *et al* (39), a retrospective analysis of patients with primary breast cancer from The Cancer Genome Atlas (n=804) further elucidates the molecular characteristics of HER2-low tumors. The aforementioned study reveals HER2-low breast cancer accounts for 51% of the cohort, with the majority being HR-positive (82%). Additionally, analysis of PAM50 intrinsic subtypes reveals that HER2-low/HR-positive tumors are predominantly classified as Luminal A (54.4%) and B (54.5%). This suggests that in this molecular subgroup, HR signaling and expression of Luminal genes are the primary oncogenic promoters, instead of HER2 itself. Furthermore, HER2-low tumors demonstrate notably higher ERBB2 mRNA levels compared with HER2-negative tumors (39).

Additionally, a study by Zhang *et al* (40) investigates the molecular profile of HER2-low breast cancer using a cohort of 523 female patients stratified into three groups based on HER2 status. The findings confirm that the HR-positive status is predominant in HER2-low tumors (87.4%) and reveals that HER2-low tumors have notably lower Ki-67 expression levels compared with both HER2-negative and HER2-positive tumors. Furthermore, the IHC-based molecular subtype distribution demonstrates that the majority of patients with HER2-low breast cancer are classified as Luminal B (58.9%) or A (28.6%) tumors, with only a small proportion classified as TNBC (12.5%). In addition, targeted sequencing identifies distinct mutational patterns among the three HER2 subgroups. HER2-low tumors demonstrate notably higher mutation frequencies in *PTEN*, *GATA binding protein 3*, *core-binding factor subunit β* (*CBFB*) and *AKT1* genes compared with HER2-positive tumors, as well as increased mutation rates in *CBFB*, *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α* (*PIK3CA*), *mitogen-activated protein kinase kinase kinase 1* and *AT-rich interaction domain 1A* compared with HER2-negative tumors (40).

Another similar study supports the aforementioned findings, highlighting the predominance of Luminal B transcriptomic features in HER2-low tumors (41). Moreover, HER2-low tumors exhibit mutation rates for *TP53* and *PIK3CA* that are closer to those in HER2-positive types of cancer compared with HER2-negative types of cancer (41).

6. HR-HER2 crosstalk

The findings from the aforementioned studies highlight the interplay between HER2 and HR and their influence on the molecular pathobiology of HER2-low breast cancer. HR and HER2 status are critical biomarkers in the diagnosis, prognosis and therapeutic management of breast cancer, with ~10% of patients with breast cancer exhibiting concurrent expression of both (42). A deeper understanding of how HR signaling influences the molecular landscape of HER2-low tumors is essential, as it may provide insights into the mechanisms underlying tumorigenesis and holds important implications for optimizing therapeutic strategies for this specific subtype.

At the molecular level, an ER binding site is present within an intronic region of the *HER2* gene, where it serves a regulatory role in modulating the expression of HER2. Dysregulation of this pathway is particularly relevant in the context of endocrine resistance in breast cancer (43). A study by Hurtado *et al* (44) demonstrates that the paired box 2 (PAX2) transcription factor functions as a cis-regulatory repressor of HER2 transcription in the presence of tamoxifen. Their findings reveal that PAX2 binding suppresses the expression of HER2, which contributes to the therapeutic efficacy of tamoxifen (44). Conversely, overexpression of HER2 is a well-established feature of tamoxifen-resistance in breast cancer, highlighting its role in mediating endocrine therapy resistance (44). Amplified in breast cancer-1 (AIB1), is a transcriptional co-activator of ER that is frequently overexpressed in tamoxifen-resistant tumors. AIB1 promotes both ER signaling and HER2-induced oncogenic pathways, facilitating tumor progression and therapeutic resistance in experimental models (45-47). Additionally, the study by Hurtado *et al* (44) identifies a competitive interaction between PAX2 and AIB1 at the HER2 cis-regulatory site. This competition determines the transcriptional output of ERBB2 in response to tamoxifen. Silencing of PAX2 using siRNA restores AIB1 occupancy at the regulatory element, which increases HER2 transcription and sustains tumor cell proliferation despite tamoxifen treatment. These findings suggest that the balance between PAX2 and AIB1 at ER-bound enhancer elements is a critical determinant of tamoxifen response and resistance in ER-positive breast cancer (44).

Emerging evidence indicates that the interplay between HR and HER2 serves a role in shaping the molecular biology and clinical behavior of HER2-low breast cancer. In a pooled analysis of individual patient data from four prospective neoadjuvant clinical trials, 2,310 patients with HER2-non-amplified primary breast cancer treated with a neoadjuvant combination of chemotherapy are evaluated. Among these, 1,098 tumors (47.5%) identify as HER2-low, with the majority (64.0%) being

HR-positive. Patients with HER2-low tumors exhibit a notably lower pathological complete response (pCR) rate compared with those with HER2-negative tumors (29.2 vs. 39.0%). This difference is particularly evident in the HR-positive subgroup. Patients with HR-positive and HER2-low breast cancer demonstrate lower pCR (17.5%) compared with those with HR-positive and HER2-negative breast cancer (23.6%), while no notable difference in the pCR is observed in the HR-negative subgroup (48).

7. Conclusions

Breast cancer, one of the most prevalent types of cancer worldwide with 2.3 million new cases in 2022 (1), has been a focal point of scientific research for decades. Breakthroughs in molecular biology revolutionize the current understanding of this disease and redefine the therapeutic management of patients, leading to improvements in patient survival and quality of life.

HER2-low breast cancer represents a distinct and emerging subclass, with growing evidence suggesting its unique molecular, pathological and clinical features. This highlights the need to refine diagnostic criteria, incorporate advanced molecular assays and update pathology guidelines to ensure accurate identification and stratification of patients with HER2-low breast cancer. The integration of the HER2-low classification into routine clinical practice presents several challenges, including standardized and reproductible methodologies, clear cut-off points and updated evidence-based guidelines. Future research should focus on refining diagnostic thresholds, validating predictive biomarkers and developing quantitative assays in order to improve the diagnostic accuracy. As precision oncology continues to advance, recognizing the distinct biology of HER2-low breast cancer will not only improve patient diagnosis, but will also enhance treatment outcomes through the integration of novel, targeted therapeutic strategies, under the scope of precision medicine.

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Authors' contributions

AG and ES equally contributed to the preparation of the manuscript, including the conceptualization, review of the literature, writing of the manuscript and preparation of the image. VZ supervised the project, provided scientific insight and assisted during the writing and correct use of the scientific language in the manuscript. DS, SA and VZ revised and edited the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

AG, ES, SA and VZ declare that they have no competing interests. DS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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