Review

Cancer Research

HER2 and Breast Cancer Stem Cells: More than Meets the Eye

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Abstract

The development of HER2 targeting agents has dramatically altered the natural history of HER2-positive breast cancer and is often cited as a prime example of the effectiveness of molecularly targeted therapy. Emerging data suggest that the remarkable clinical efficacy of these agents may be related to their ability to target the breast cancer stem cell (CSC) population. A new study suggests that the regulation of BCSCs by HER2 may extend to breast cancers that do not display *HER2* gene amplification. In these tumors, HER2 is selectively expressed in the CSC population, and this expression is regulated by the tumor microenvironment. In mouse models, trastuzumab blocked growth of these HER2-negative tumors when administered in the adjuvant setting but had no effect on established tumors. These studies provide a potential biologic explanation for retrospective analysis of clinical trials, which surprisingly suggest that the clinical benefits of adjuvant trastuzumab may extend to women currently classified as HER2-negative. In addition to having significant implications for breast cancer therapy, these studies suggest the need to reevaluate the role of HER2 in regulating CSCs in other tumor types. Furthermore, these studies suggest that effective adjuvant therapies may need to target the CSC population. *Cancer Res; 73(12); 3489–93. ©2013 AACR.*

Breast Cancer: A Poster Child for Molecularly Targeted Therapeutics

The therapy of breast cancer provides one of the best examples of the clinical benefits of molecularly targeted therapeutics. Development of these therapies has resulted from realization that the spectrum of breast cancer encompasses distinct molecular subtypes, which have characteristic gene expression profiles, natural histories, and which respond to different therapies. These molecular classifications also reflect major drivers of these cancer subtypes including the steroid hormone receptors, estrogen receptor (ER), and progesterone receptor (PR), and the growth factor receptor HER2. The development of reliable hormone receptor and HER2 assays has led to the classification of breast cancers as ER-positive (ER^+), PR-positive (PR^+), $HER2^+$, or triple-negative. The use of hormonal therapy for ER^+ disease and HER2-targeted agents for $HER2^+$ disease represents one of the greatest advances in clinical oncology and illustrates the tremendous potential of molecularly targeted therapeutics. In fact, the use of hormonal agents and HER2 targeting agents in the adjuvant setting accounts for a major portion of the significant decrease in breast cancer mortality over the past 20 years (1, 2).

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The Plot Thickens

Despite the success of hormonal and HER2 targeting agents, many women with breast cancer, who receive these agents in the adjuvant setting, still relapse. Furthermore, almost all women with advanced breast cancer develop resistance to these targeted therapies, as well as to chemotherapy, and as a result, metastatic breast cancer remains incurable. The selection of therapy based on molecular subtype of breast cancer assumes that cell populations within an individual tumor are homogeneous and, thus, will uniformly respond to these treatments. This assumption has been challenged by the cancer stem cell (CSC) hypothesis, which posits that many cancers, including breast cancer, are hierarchically organized and driven by a population of cells that displays stem cell properties. Furthermore, accumulating evidence suggests that these CSCs mediate tumor metastasis and by virtue of their relative resistance to chemotherapy and radiotherapy contribute to treatment relapse (3, 4). Breast CSCs can be identified by virtue of their expression of marker proteins such as $CD44^+/CD24^-$ or aldehyde dehydrogenase (5, 6). CSCs, which constitute a small subset of cells in human breast cancers, give rise to other CSCs through the process of self-renewal, as well as generate the non–stem cell populations forming the tumor bulk. Although CSCs and bulk tumor cells may share genetic signatures, they display distinct gene expression patterns by virtue of epigenetic regulation. As a result, CSCs and bulk cell populations within an individual tumor may be driven by distinct pathways. This suggests that effective therapy may require selective targeting of these distinct cell populations. This level of molecular heterogeneity is superimposed upon genetic clonal heterogeneity generated by genetic instability.

The HER family of growth factors plays an important role in breast development and mammary carcinogenesis. Although HER2 itself has no known ligand, it forms heterodimers with ligand-activated EGF receptor (EGFR), HER3, and HER4. Previous studies using the mouse models of conditional HER2 knockout in the mammary gland have shown that HER2 is required for normal mammary ductal morphogenesis (7).

The *HER2* gene is amplified in approximately 20% of human breast cancers, a molecular subtype associated with an aggressive clinical course with early development of metastasis. The development of HER2 targeting agents such as trastuzumab has led to a dramatic alteration in the natural history of this disease (8). Preclinical studies, as well as clinical trials, have shown that in women with advanced breast cancer, the clinical benefit of HER2-targeted therapies are limited to women whose breast cancers display *HER2* gene amplification. This observation has led to the routine testing of breast cancer samples for HER2 overexpression by immunochemistry and FISH (9). On the basis of the studies in advanced breast cancer showing that the potentiation of tumor regression by HER2 targeting agents was limited to $HER2^+$ breast cancers, entry into adjuvant trials using these agents was limited to this patient population. These adjuvant trials showed that addition of the HER2 blocking agent trastuzumab to cytotoxic chemotherapy resulted in a remarkable 50% reduction in disease recurrence compared with patients receiving chemotherapy alone (10–12). However, the conventional wisdom that only $HER2^+$ patients benefit from adjuvant trastuzumab was challenged by a study published by Paik and colleagues in the *New England Journal of Medicine* in 2008 (13). In this retrospective study, clinical samples accrued to NSABP B31, a pivotal trastuzumab adjuvant trial were reanalyzed for *HER2* gene amplification in a central laboratory. This reanalysis identified 174 cases which although originally reported as $HER2^+$ actually lacked *HER2* gene amplification. Surprisingly, analysis of outcome data revealed that these $HER2^-$ patients benefited as much from adjuvant trastuzumab as did patients whose tumors displayed *HER2* gene amplification. These findings were confirmed in a similar analysis from an independent trastuzumab adjuvant study (14). Although provocative, these studies are limited by their retrospective nature, and a randomized prospective phase III trial, NSABP B47, is currently in progress to determine whether the clinical benefits of adjuvant trastuzumab extend to women whose tumors do not display HER2 amplification. Although the molecular mechanisms that might account for the clinical efficacy of adjuvant trastuzumab in women with $HER2^-$ breast cancer are not known, recent preclinical findings by our group suggest that this clinical observation may be explained by the CSC model.

HER2 and Breast Cancer Stem Cells

Several lines of evidence indicate that HER2 is an important regulator of the CSC population in $HER2^+$ breast cancers (13). We previously showed that HER2 overexpression increases and HER2 blockade decreases the CSC population in breast cancer cell lines and mouse xenografts (15). Furthermore, in human breast cancers, there is a correlation between HER2 amplification and CSC frequency as assessed by expression of the breast CSC marker ALDH-1 (5). In contrast with cytotoxic chemotherapy, neoadjuvant HER2 blockade reduces the CSC population, resulting in a significantly increased complete pathologic response rate compared with chemotherapy alone (16). In addition, in contrast with chemotherapy, administration of the EGFR/HER2 blocker lapatinib in the neoadjuvant setting reduced the breast CSC population (4). In a new study published in *Cancer Research*, we show that HER2 also plays an important role in regulating the CSC population in luminal breast cancers that do not display HER2 amplification and therefore are currently classified as $HER2^-$. In these tumors, HER2 is selectively expressed in and drives the CSC population. As CSCs constitute only a small fraction of the total tumor population, analysis of whole tumors masks this measurement of HER2 expression. A recent report that HER2-expressing cells in luminal $HER2^-$ breast cancers are radiation-resistant provides further evidence for such a model. Our studies also raise questions about current clinical practices for HER2 assessment. Tumors are routinely evaluated by immunohistochemistry on a scale from 0 to 3+, with the latter being considered $HER2^+$. Those that are 2+ are further examined by FISH and if HER2 is amplified they are also considered positive. FISH analysis of *HER2* gene amplification is considered to be the gold standard for classification of breast cancers as $HER2^+$ a designation that has dictated treatment selection.

Our studies suggest that contrary to this dichotomous model, HER2 expression in breast tumors follows a distribution related to molecular subtype, with luminal tumors expressing an intermediate level of HER2 compared with claudin-low/basal (low) and HER2-amplified (high; ref. 17). These data are consistent with previous reports showing a bimodal association of clinical outcomes with HER2 expression levels (19, 20). Those studies indicated that when HER2 expression was quantitated with ELISA or immunofluorescent *in situ* assays, very low and very high HER2 protein levels in patients with breast cancer had a poorer outcome than those with intermediate expression. Consistent with our findings, the HER2-low group was associated with triple-negative, the HER2-high group with $HER2^+$ and the intermediate HER2 group with luminal ER^+ breast cancer. Our preclinical studies predict that women with luminal breast cancer in which HER2 and the CSC marker ALDH1 are coexpressed in the same cells will benefit most from adjuvant trastuzumab. This hypothesis can be directly tested in prospective clinical trials such as NSABP B47.

Regulation of HER2 Expression by the Tumor Microenvironment

If HER2 expression in CSCs does not require HER2 gene amplification, what regulates HER2 expression in these cells? We show that the bone microenvironment at sites of bone metastasis is able to induce expression of HER2 in a process regulated by RANK ligand, which is produced by bone osteoblasts. It has previously been shown that normal breast stem cells are regulated by RANK ligand, which is produced in response to progesterone elevation during pregnancy (21, 22). In triple-negative basal breast cancers, it has been shown that RANK ligand produced by bone osteoblasts is capable of

stimulating self-renewal of CSCs through activation of NF-κB (7). Our studies expand upon this concept by showing that RANK ligand is also able to regulate CSCs in luminal breast cancers through induction of HER2 expression (23). The RANK ligand inhibitory antibody denosumab is currently approved for the treatment of bone metastasis in breast and other cancers. Ongoing randomized clinical trials are in progress to determine whether administration of denosumab in the adjuvant setting reduces recurrence in women with early-stage breast cancer. The ability of RANK ligand to regulate CSC populations in bone micrometastasis suggests a potential mechanism that might produce clinical benefit in this setting. Through a comparison of HER2 protein expression in patient biopsies from primary luminal breast tumors and bone metastasis, we showed a significant increase in HER2 protein expression in the bone metastasis compared with matched primary tumors. Furthermore, as indicated by FISH analysis, this increase in HER2 expression was not due to the selection of clones of HER2-amplified cells (17). These observations are consistent with those from previous studies that reported a significant discordance in HER2 protein expression among primary tumors, circulating tumor cells, and metastatic lesions (9, 24). A number of these studies used FISH to assess HER2 gene copy number and thus may have missed regulation of HER2 protein expression by the tumor microenvironment. However, a recent report showed that 89% of women with $HER2^-$ breast cancer had circulating tumor cells (CTC) that expressed HER2 protein. Furthermore, trastuzumab decreased recurrence in these patients, an effect associated with reduction in HER2-expressing CTCs (25).

Interaction of HER2 and Other Signaling Pathways in the Regulation of Breast CSCs

We have previously reported that HER2 regulates breast CSCs through a cell intrinsic process involving signaling through the phosphoinositide 3-kinase (PI3K), Akt, and Wnt pathways (26). In contrast with the adjuvant setting, the majority of patients with advanced $HER2^+$ breast cancer develop resistance to trastuzumab. Many of these trastuzumab-resistant patients respond to newer HER2 targeting drugs such as pertuzumab or the trastuzumab drug conjugate T-DM1. Furthermore, immunotherapeutic approaches including T-cell therapy targeting HER2 have been developed (27). In addition, loss of expression of the tumor suppressor gene PTEN is frequently associated with resistance to HER2 targeting agents. In preclinical models, we showed that PTEN knockdown in $HER2^+$ breast cancer cells generates trastuzumab-resistant CSCs through activation of an inflammatory loop mediated by NF-κB and interleukin (IL)-6 (28). It has been proposed that the trastuzumab resistance in $HER2^+ER^-$ (basal) compared with $HER2^+ER^+$ (luminal) breast tumors may be related to CSC regulatory pathways (29). In addition, recent studies have shown that HER2-activating mutations may contribute to trastuzumab resistance (30). HER2 may also interact with other CSC regulatory pathways. For example, it has been recently shown that in $HER2^+$ breast cancers HER2 interacts with CXCR1, a receptor for the cytokine IL-8 (31), which has been shown to be selectively expressed in breast CSCs (32). The Notch pathway, another regulator of breast CSCs, regulates HER2 expression (33, 34). Together, these studies suggest that multiple cell-extrinsic and cell-intrinsic pathways, including HER2, interact to regulate breast CSCs. These pathways provide potential targets for therapeutic intervention, as illustrated in Fig. 1. A number of early-stage clinical trials targeting these CSC regulatory pathways are in progress.

HER2 and CSCs in Other Tumor Types

The demonstration that HER2 regulates breast CSCs in the absence of gene amplification suggests the possibility that similar signaling pathways may exist in other tumor types. Indeed, it has been recently shown in hormone-refractory prostate cancer that these CSCs are regulated by a pathway involving α6β4 integrin, which amplifies signaling through the HER2 and c-Met pathways (30). HER2 has also been reported to be expressed in a number of other solid malignancies, including those of the bladder and ovary (35). In these tumors, expression of HER2 protein generally occurs in the absence of gene amplification. Whether HER2 regulates CSCs and thus whether HER2 blockade will be a useful clinical strategy in these tumor types remains to be determined. It will be important to consider the CSC model in the design of clinical trials to assess the efficacy of HER2 blockade in these tumors. Trials using tumor regression as a measure of efficacy may miss important effects of HER2 blockade on CSC populations. Lessons learned from HER2-targeted therapies in breast cancer may prove useful in designing clinical trials for these other cancers.

Implications for Development of Adjuvant Therapies

Although HER2-targeted therapies have shown clinical benefit in breast cancer in both advanced and adjuvant settings, the use of adjuvant trastuzumab has had the greatest impact on breast cancer mortality, reducing tumor recurrence by approximately 50%. Because the natural history of $HER2^+$ breast cancer includes a propensity for early metastasis, the likelihood of cure for patients who remain disease free after 5 years is great. This raises the intriguing possibility that effective targeting of CSCs in the adjuvant setting may have similar dramatic effects in other cancer types. If the lessons learned from development of HER2-targeted therapies in breast cancer apply to other tumor types, we may need to alter the current paradigm for development of adjuvant cancer therapies. This paradigm selects agents based on their ability to cause regression of advanced tumors. These agents are then administered in the adjuvant setting after removal of the primary tumor. The CSC model calls this strategy into question because regression of advanced tumors largely reflects effects on bulk tumor populations whereas growth of tumors from microscopic foci at metastatic sites may be mediated by CSCs. This model posits that only CSCs possess sufficient self-renewal capacity to form clinically significant macrometastasis from these micrometastatic foci. Because CSC and bulk tumor populations may be driven by different pathways, it will be important to use agents

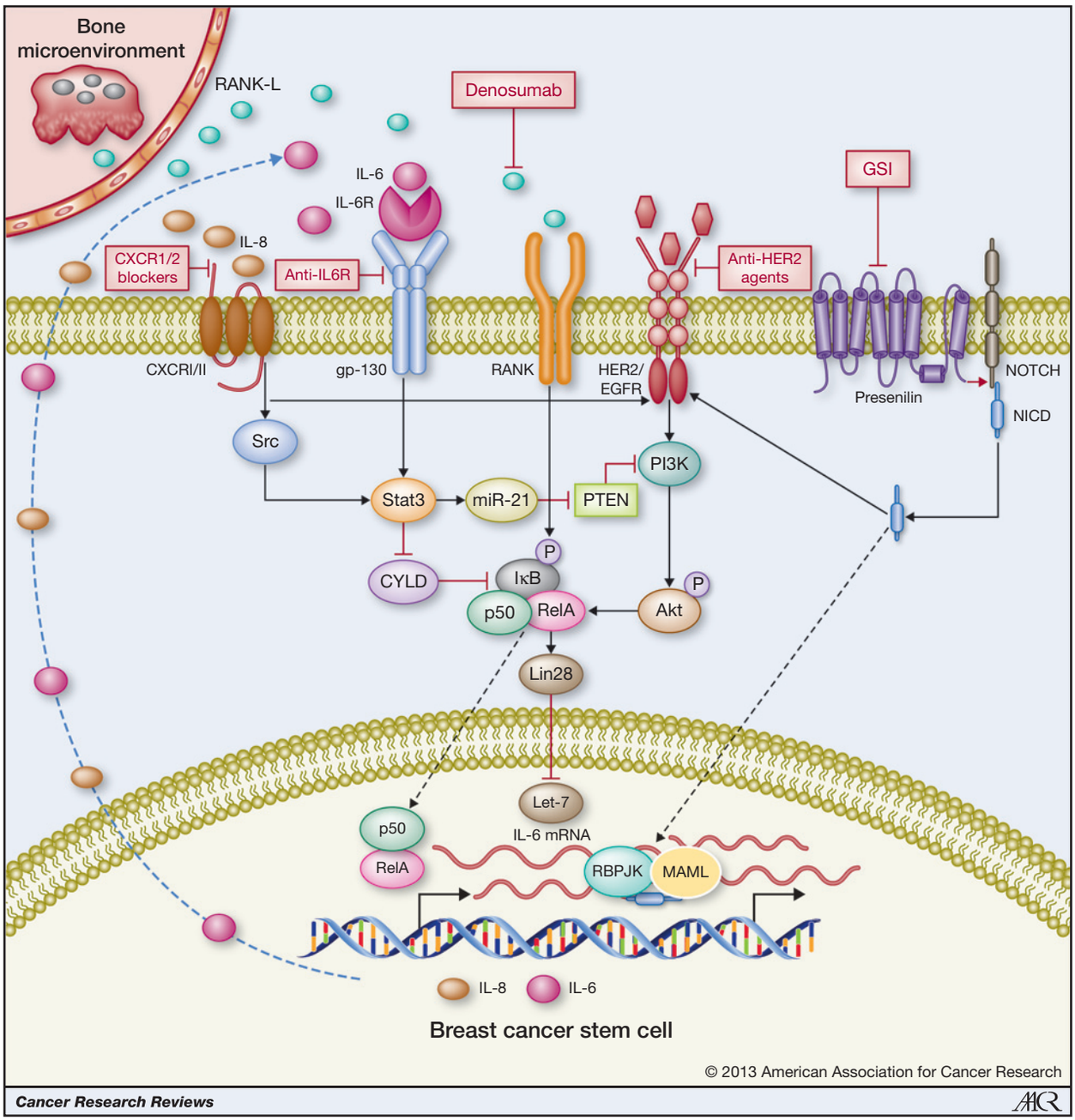

Figure 1. Pathways regulating breast CSCs. Molecular pathways interacting with HER2 regulate self-renewal of breast CSCs. Therapeutic agents inhibiting these pathways are shown.

that target CSC regulatory pathways in the adjuvant setting. If lessons learned from HER2-targeted therapies apply to other tumor types, then administration of effective CSC-targeting therapies in the adjuvant setting should reduce recurrence and improve patient outcomes.

Disclosure of Potential Conflicts of Interest

H. Korkaya has a commercial research grant from MedImmune. M.S. Wicha has a commercial research grant from MedImmune and Dompe; has ownership interest (including patents) from OncoMed; and is a consultant/advisory board member of MedImmune, Verastem, and Paganini.

Authors' Contributions

Writing, review, and/or revision of the manuscript: H. Korkaya, M.S. Wicha
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