Sustaining Proliferative Signaling in Instances of HER2 Gene Amplification: Contemporary Insights

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The epidemiology of breast cancer and the methods of overcoming the growth of cancer cells are essential research topics in the current age. Considering that cancer cells can sustain division without necessary signals, this ability becomes a significant obstacle in impeding the advancement of various types of cancer. The Human Epidermal Growth Factor Receptor 2, commonly referred to as HER2, has been outlined as a gene the overamplification of which is linked to the emergence of breast cancer tumors in numerous populations (1). As this gene belongs to the membrane tyrosine kinase group and dimerizes on ligand binding, its activation is significant for upholding cell division and apoptosis, regulating the normal flow of cell development (1). Nevertheless, when HER2 is amplified, the created heterodimers become biased, negatively impacting the HER2 signal-transduction network and altering the transmission of growth factors (1). The resulting abnormal kinase activity and incorrect signaling lead to excessive proliferation of breast cancer cells (1). Thus, HER2 amplification can become a crucial factor in the progression of breast cancer tumors.

Although usually coordinated, uncontrolled proliferation caused by the mutation exceptionally harms the normal evolution cycle, contributing to the emergence of malignant tumors and carcinogenic growth. Similar instances of gene overexpression are BRCA1 and BRCA2 gene mutations, which alter the process of DNA repairment (2). In addition, TP53, ER, and CHEK2 gene abnormalities have been found to influence proliferative signaling pathways, as well as activate invasion and metastasis and evade immune destruction, which are also two prominent breast cancer hallmarks (3). Nevertheless, considering that the malfunction in the

expression of HER2 can lead to uncontrolled division of breast cells, finding prominent methods that interrupt such advances and restore normal cell development are essential tasks. It has been reported that 18- 20% of invasive breast cancers are related to the amplification of the HER2 gene, which results in aggressive HER2 protein overexpression (4). An increasing prevalence of this cancer subtype is a significant issue, with incidence rates increasing to 88 cases per 100000 women (4). Thus, evaluating the factors that might decrease the growth rates of these tumors becomes an essential task.

The prognosis for this disease is overwhelmingly negative, leading to severe complications or cancer re-occurrence. Contemporary studies show that blocking the ability of cancer cells to transfer signals, thus limiting proliferation, can substantially decrease the possibility of tumor evolution and promote the effectiveness of chemotherapy (3). In this regard, current treatment options introduce anti-HER2 antibodies, namely trastuzumab and pertuzumab, combined with chemotherapy (1). Other common possibilities include radiation therapy and the administration of kinase inhibitors (5). The current study presents a contemporary scholarly perspective on sustaining proliferative signaling in HER2 gene amplification of breast cancer, highlighting the most recent advances in this area. Given that this cancer subtypes' mortality and prevalence rates remain overwhelmingly high, it is essential to outline the factors contributing to sustaining proliferation in this disorder, examining approaches to countering HER2 influence.

Proliferation as a Common Hallmark of Carcinogenesis

A substantial body of research shows that the sustainability of proliferative signaling is a crucial factor in developing numerous carcinomas, from gastrointestinal to breast cancer formations (6). As such, cancer cells may secrete multiple varieties of molecules that stimulate

the surrounding healthy cells to obtain growth factors or generate such factors themselves, causing the activation of proliferative signaling pathways (6). In the former scenario, a constant loop of cell growth promotion occurs, thus establishing a basis for the subsequent development of carcinogenic masses. Different manifestations of breast cancer are associated with this hallmark, suggesting that sustained proliferative signaling to breast cells, initiated by gene mutations, contribute to the emergence of carcinomas.

The overexpression of the HER2 gene, which leads to abnormal cell growth, is a prominent example of a malignant mutation that disrupts the normal cycle of cell growth and division. These instances are referred to as HER2 positive breast cancers, disorders that possess exceptional proliferative tendencies, manifesting in rapid growth and a highly increased chance of re-occurrence (5). A continuous uncontrolled development of these cells gruesomely affects the human body and requires specific treatment aimed at negating the consequences of amplification.

Primary Factors of Sustained Proliferative Signaling in HER2-Positive Breast Cancer Types

ErBb2 Gene Malfunctions

Mutations in the HER2 gene possess several definitive features that can be outlined using relevant testing methods. It is suggested that utilizing cancer type classifications based on molecular characteristics of the tumor is the most prominent strategy that allows increasing the accuracy of diagnosis, contributing to the most effective therapeutic decision-making (7). In general, the amplification of the *ErBb2* gene is connected with HER2-positive cancer, as this gene encodes the HER2 growth factor (1). The amplification of the gene leads to the abnormal

activation of proliferation pathways controlled by HER2, resulting in increased cell growth in breast cancer tumors (1). Studies report that breast cancer cells overexpressing *ErbB2* are internally resistant to DNA-damaging agents such as cisplatin due to inhibition in their paired transfectants overexpressing ErbB2 (5).

Receptor Tyrosine Kinases Impacting HER2 Overexpression

Concerning the HER2-enriched classification, the overexpression of this gene is also frequently related to genetic aberrations. Although both classes demonstrate mutations on chromosome *17q12*, the molecular structure of the HER2-enriched subgroup is distinguishable from the Luminal B subtype, especially in the high expression of Receptor Tyrosine Kinases (RTKs) (5). For instance, FGFR4 and FGFR2 levels are often significantly expressed in HER2+ cancer cells, proposing that the emergence of aberrant FGFR signaling promotes the development of HER2-positive cancer masses (5). The molecular process behind this mutation includes an altered homo- or heterodimerization process, which leads to the autophosphorylation of tyrosine residues within the cytoplasmic domain of the receptors, causing aberrations in primary signaling pathways. The created ligands bind to FGFRs in an autocrine or paracrine manner using heparan sulfate proteoglycans. Although the specific mechanisms behind the onset of uncontrolled proliferative signaling are still unknown, abnormal alterations in FGFR signals are deemed to be prominent research areas.

TP53 Mutations in HER2+ Conditions

As highlighted by studies on HER2 aberrations, it is possible that TP53 mutations, the amplification of the PI3K pathway, and aberrant FGFR signals might be the factors contributing to maintaining proliferative signaling of breast cancer cells. The majority of investigations

involving HER2-positive patients report that CpG dinucleotides mutate at a rate ten times higher than other nucleotides, leading to a higher load of CpG transitions in cancers (1). It is possible that such genetic aberrations, when combined with the amplification of the HER2 gene, increase the sustained proliferation of cancer cells and disrupt the appropriate functioning patterns for normal cells, which results in a poor prognosis for the individuals.

After that, the PI3K pathway is also closely linked to the amplification of the HER2 gene in HER2-positive tumors. Recent findings indicate that PI3K might be affected by HER2 mutations, strengthening the signals and producing growth factors later used by cancerous masses for subsequent development (1). This pathway contains p110α and p85α subunits; p110α is inhibited by p85α and catalyzes the phosphorylation of the lipid phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-trisphosphate (PIP3) (5). When PIP3 accumulates at the plasma membrane, downstream signaling is activated by the PIP3-binding protein phosphoinositide-dependent kinase 1 (PDK1) and by mammalian target of rapamycin complex 2 (mTORC2) (5). Therefore, it is possible that the abnormal activation of these pathways leads to the carcinomas' proliferation strength, driving this hallmark.

The Role of FGFR System in HER2+ Breast Cancers

The most prominent recent advancement refers to the role of aberrant FGFR signals in the occurrence of HER2-positive cancers. The FGFR system consists of four RTKs, namely FGFR1, FGFR2, FGFR3, and FGFR4, which regulate proliferative signaling and control normal cell growth in breast regions, thus affecting various transduction pathways (5). Alterations in this signaling cascade were found in 32.1% of breast cancer cases, and scholarly findings report that these aberrations can coexist with HER2 mutations, increasing the expression levels of FGFR2

and FGFR4 (5). Furthermore, several investigations indicate that FGFR4 promotes the progress from Luminal B subtype to HER2-enriched one, and suppressing the amplification of this gene is correlated with higher treatment effectiveness and lower cancer recurrence (4). In this regard, targeting both FGFR signaling pathways and HER2 overexpression creates the most productive approach to mitigating the consequences of sustained proliferative signaling.

However, the distinction between FGFR RTKs appears to be a crucial detail in the current research endeavors. Scholars claim that overexpression of FGFR levels can differ based on the FGFR subtype in question, resulting in diverse outcomes in tumor progression (5,8). For instance, elevated levels of FGFR1 were found to increase the individuals' resistance to anti-HER2 therapy, diminishing the possibility of productive recovery (8). Nonetheless, contradictions in the existent findings require additional investigations as HER2-enriched cancer types are less responsive to this type of treatment.

In comparison with FGFR1, FGFR2 is more strongly linked to HER2+ positive treatment outcomes. Given that FGFR2 activation results in HER2 transactivation and elevated resistance to HER2-targeted therapies, inhibition of the FGFR2 gene allows impeding the tumor progression (9). However, it is possible to mitigate this influence by FGFR2 inhibition, which hinders abnormal activation of the HER2 gene and induces apoptosis in cells that are especially resistant to relevant therapies (9). In this regard, supplementing the standard treatment with FGFR2 inhibition strategies appears to establish good response rates.

Considering the involvement of FGFR3 in this cancer subtype, the majority of statistical evidence reports a low possibility of FGFR3 amplification in breast cancer. Although this RTK might influence the individuals' resistance to tamoxifen, thus decreasing therapy efficiency, only

1.1% of relevant cohorts demonstrate the prevalence of FGFR3 overexpression (8). Therefore, FGFR2 is currently considered to be a more prominent approach in contrast with FGFR3.

Finally, FGFR4 may be a potentially significant factor in the progression of HER2-enriched tumors through proliferative signaling. Both Luminal and HER2-positive breast cancer subtypes demonstrate a prevalence of FGFR4 overexpression, which possibly promotes tumor development and can be associated with endocrine resistance, decreasing the efficiency of HER2 targeted therapy (8). Therefore, FGFR4 inhibitors' impact on the management of diverse breast cancer types is an exceptionally prominent strategy, which allows targeting particular biomarkers related to FGFR4 overexpression.

The Prominence of FGFR Family Research

Although the highlighted strategies of accounting for the overexpression of FGFR family RTKs FGFR1, FGFR3, and FGFR4 present positive results, a key detail should also be addressed. As such, it is proposed to include the co-expression of other RTKs related to the erbB family, as well as alterations in signaling pathways affected by FGFR and HER2 genetic aberrations. The previous connection to PI3K pathways appears to be a prominent solution, which, however, necessitates extensive empirical exploration. Multiple studies mention that outlining singular responses might be insufficient to achieve necessary outcomes, especially in the cases of HER2 amplification, which are linked to exceptional tumor invasiveness and speed of growth (1). Considering that therapies combining the inhibition of FGFR RTKs and HER2-targeting demonstrate remarkable productivity, accounting for additional correlating issues might be highly efficient.

In light of the discovered tendencies, the connection between FGFR amplification in

HER2-positive cancer types is a considerable advancement in breast cancer research. Although the specific mechanisms behind the FGFR family's influence on the patterns of tumor emergence are still unknown, their impact on the sustainability of proliferative signaling is a tremendous achievement that could be utilized to manage the development of cancer growths (5). For instance, while the FGFR1 locus might be responsible for aberrations in cell copy numbers, FGFR2 is less connected with this phenomenon and is attributed to increased therapy resistance (8). Altogether, each of the discussed RTKs possesses a unique potential to alter the development of HER2-positive tumor types depending on the carcinoma's attributes, which is an essential accomplishment in diversifying the available treatment options to achieve higher efficacy.

Open Questions Regarding Sustained Proliferative Signaling in Breast Cancer

Even though the results attained present a significant advancement for this clinical area, there are several considerations regarding the sustainability of proliferative signaling in HER2-positive breast cancer types. As such, TP53 mutations and the impact of HER2 gene amplification on the PI3K signaling pathway remain underexplored, and it is still unclear whether healthy manifestations of TP53 can protect individuals from developing particular tumor classes (10). After that, the PI3K pathway, although reported to be significantly affected by the genetic mutations occurring in the HER2 gene, is still to be evaluated based on its connection to HER2-targeted therapy resistance (1). Furthermore, it is vital to ascertain how HER2 inhibitors impact PI3K signaling and whether such downstream inhibition is less toxic for the patients.

Moreover, the involvement of the FGFR family RTKs in the progression of HER2-positive tumors can be considered an exceptionally undiscovered area of investigation, which necessitates further inquiry. Given that the FGFR inhibition approach is relatively novel,

additional studies are required to establish its efficacy for individuals who demonstrate both resistance to HER2-targeted therapy and receptivity towards it. For instance, almost all FGFR RTKs' levels have been observed as increased in HER2+ breast cancer types, but their impact on the prognosis and the development of the tumor is especially diverse (4). It is unknown whether the amplification of FGFR1 is correlated with FGFR inhibition sensitivity, meaning that FGFR1 might be an inappropriate drug target in specific cases.

Concerning the FGFR2 overexpression, although the preclinical data is favorable, the importance of copy number aberrations and their influence on therapy resistance are still not distinguished. Concerning the FGFR3 phenomenon, it is essential to compare its overexpression manifestations to other family RTKs, clarifying whether it positively induces the resistance to tamoxifen (8). Finally, FGFR4 is considered to be a potential therapeutic target, but the mechanisms behind FGFR for fusions and their frequency are still to be established, and its significance for HER-enriched cancer types requires additional supporting findings.

The highlighted questions are especially relevant for contemporary research on breast cancer types demonstrating the amplification of the HER2 gene, primarily due to their connection to maintaining proliferative signaling in the human body. The outlined genes and their mutations significantly affect the production of valuable proteins and cell growth factors, as well as play an imperative role in signaling pathways essential for cell cycling. Considering the preliminary data that suggests positive tendencies in the implementation of combinative approaches targeting both HER2 aberrations and TP53, PI3K, and FGFR family markers, it is vital to answer the proposed prompts and establish the most efficient treatment strategies.

Conclusion

To conclude, over-amplification of HER2 protein mutations in connection to sustained proliferative signaling in breast cancer was discussed in detail in this paper, presenting the most recent scientific advancements in this area. TP53 aberrations, PI3K pathway amplification, and aberrant FGFR signaling appear to be the most prominent advances in the current age, which allows distinguishing prognostic factors in Luminal B and HER2 enriched cancer types. Modifying the functioning patterns of these systems might potentially resolve several significant issues in cancer treatment, specifically the sustainability of proliferative signaling, tumor re-occurrence, and HER2 targeted therapy resistance.

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