Chapter 1

The Critical Role of Signaling Pathways in Breast Cancer Treatment

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Abstract

Nowadays, the burden of cancer is rising, particularly in developing and developed nations (1). One of the first five cancers that cause the death of women worldwide right after lung cancer is breast cancer (1). Cell transduction is a critical stage in the formation and growth of cancer (2). Many signaling pathways that promote tumor growth, invasion, and metastatic capabilities have been found in breast cancer, as they have been in other cancer types. Cyclin-dependent kinases, Notch, NF-kB, PI3K, JAK/STAT, Hedgehog, Hippo, TGF-β, Wnt/ β-catenin, PARP are among the signaling pathways related to breast cancer (1). In this review, the importance of focusing on key signaling pathways targeted in the treatment of breast cancer is explained in detail. We hope that the information in this publication will help guide preclinical and clinical research in the creation of effective drugs and improve the treatment of breast cancer patients with further studies in this area.

Introduction

One of the biggest causes of death worldwide is cancer (3). With an average annual incidence of 1.4 million cases and a legal-standardized incidence rate of 39.0 cases per 100,000 people and throughout the world, breast cancer is the second most frequent type of cancer (4).There are numerous breast cancer subtypes, and each one has a unique prognosis and course of treatment (5). The most frequent kinds of breast cancer are ductal carcinoma in situ and lobular carcinoma in situ, respectively (6). Depending on whether the ER, PR, and HER2 receptors are present or not, there are numerous subtypes of breast cancer. As a result, a triple negative or basal-like subtype, an ER/ PR+ luminal subtype, a Her2+ subtype with overexpressed Her2, and a

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Her2+ subtype with low expression may all be identified (TNBC). The luminal subtypes that result from this classification are luminal A, which is differentiated by ER/PR+, HER2+, and low Ki67 expression, and luminal B, which is distinguished by ER/PR+, HER2+, and high Ki67 expression. The lack of both receptors is shown by Her2+ subtypes that are ER/PR negative and triple negative (7-9).

Hormonal variables, early menarche or late menopause, aging, infertility, family history, and lifestyle factors like alcohol intake, obesity, and physical inactivity are among those who have the highest risk of developing breast cancer (10, 11). Breast cancer can be sporadic or hereditary. The DNA damage repair (DDR) genes, which are mutations in the BRCA1, BRCA2, and TP53 genes, are among the most frequent mutations linked to hereditary breast cancer (12). Sporadic occurrences of breast cancer make up about 85% of all cases, and they are linked to the particular risk factors we previously stated. Reflect further out that breast cancer may also be influenced by exposure to carcinogens like DDR gene preservation (13), organ radiations (14), and air purifiers (15).

To treat cancer, which is regarded as a challenging disease, one must have a thorough understanding of the biology of both healthy and malignant cells. It has been established that numerous signaling pathways connected to the cell, cell cycle, angiogenesis, and metastasis are linked to the development of cancer (16). There are several different treatment modalities used to treat breast cancer, including chemotherapy, surgery, radiation therapy, hormone therapy, and immunotherapy (17–20). The hazards and toxicity issues associated with chemotherapeutic drugs (21) need the development of novel antineoplastic medicines with fewer side effects, even if side effects can be detected in any therapy plan (22).

Breast cancer cells have a lot of changes that impact cell signaling pathways. In fact, differences in cellular mechanisms underpinning apoptosis as well as responses mediated by calcium-sensitive receptors or hypoxia-inducible factor (23, 24) have been reported (25, 26). In addition, the ER and human epidermal growth factor type-2 receptors (HER2/Neu or c-ErbB2) drive the most researched alterations related to the genesis and progression of breast cancer pathways (26). According to Hanahan and Weinberg (27), tumor cells have several characteristics or indications, such as unchecked proliferative behavior, genetic instability, and aversion to apoptosis. As a result, changes to several cell signaling pathways influence the growth, development, and survival of tumor cells (28). Mutant proteins with uncontrolled activity, mutated oncogenes that overexpress particular proteins, or inactivation of

tumor suppressor genes that enable these processes are the causes of these illnesses (29). To improve early tumor identification and cancer prevention in cancer patients, it is crucial to comprehend the molecular foundation of breast cancer, including the dysregulated genes and linked pathways associated with this illness (30). In this review, we tried to identify the important cellular pathways such as Cyclin-dependent kinases, Receptor Tyrosine Kinases, Breast Tumor Kinase, Notch, NF-kB, PI3K, JAK/STAT, Hedgehog, Hippo, TGF-β, Wnt/ β-catenin, PARP etc. connected to breast cancer that affect breast tissue cell hormone balance, cell proliferation, and apoptosis. In our review, we explore many signaling mechanisms and disease-related networks that may help create novel therapeutic strategies and prognostic indicators.

Breast Cancer Related Signaling Pathways and Targeted Therapies:

a) Cyclin Dependent Kinases (CDKs):

Three main families of molecules—cyclins, cyclin-dependent kinases (CDKs), and cyclin-dependent kinase inhibitors (CDKIs)—are involved in controlling the cell cycle (31). Dysregulation of the interaction between cyclins and associated CDK partners has been discovered to affect one of the features of cancer, the unabated proliferation of tumor cells (32). According to a study, CDK4 and cyclin D1 levels are noticeably higher in breast cancers. Given this, it has been proposed that CDK4 serves as an effective therapeutic target. This is especially true given that CDK4 promotes the suppression of breast cancer cells while protecting other healthy cells (33, 34).

According to the results of the investigations, CDK4/6i has been found to be able to control the host immunological response as well and can thus be utilized in conjunction with immune checkpoint inhibitors (35, 36). Drug resistance to RTK-based treatments and endocrine therapies can be successfully overcome by CDK4/6 inhibition. Preventing CDK4/6 was found to prevent RB phosphorylation from increasing the proliferation of ER+ luminal cancer and HER2+ cancer cell lines in a study that screened 47 breast cancer cell lines. It's significant to note that palbociclib and tamoxifen have been shown to re-sensitize resistant MCF7 cells to tamoxifen (37).

b) Receptor Tyrosine Kinases (RTKs):

Under physiological conditions, RTKs can transmit signals into the cytoplasm that promote cell growth. Growth signals are constantly conveyed even when there are no upstream stimuli because RTKs are amplified, changed, and constitutively active in cancer. Monoclonal antibodies and

specific inhibitors have been created to prevent the action of this mechanism (38).

RTK ecto domains are targeted by monoclonal antibodies (mAbs), which impede agonist binding and interaction. The first monoclonal antibody licensed by the FDA for the treatment of metastatic colorectal cancer is cetuximab, a mAb that binds EGFR (39). It works by assisting the receptor in being dimerized and internalized, which lowers the overall concentration of EGFR protein on the plasma membrane. Several tyrosine kinase inhibitors (TKIs) that target the cytoplasmic domain of EGFR have also been developed because of the incidence of EGFR activation in cancer. There are now three generations of TKIs being used in therapeutic settings. Gefitinib and erlotinib are first-generation TKIs that compete with ATP for the kinase domain of the EGFR; afatinib and dacomitinib are second-generation TKIs with improved affinity for the kinase domain; third generation TKIs, such osimertinib, which binds covalently to the cysteine residue in EGFR, are also known as these (40, 41).

b) Breast Tumor Kinase:

Breast tumor kinase (BRK) overexposure has been linked to several cancers, including metastatic melanoma, prostate, ovarian, and colon cancer (42-45). About 60% of human breast cancers, the nonreceptive tyrosine kinase known as BRK is overexpressed. Its lack of expression in healthy malignancies and the normal human mammary gland reflect this (46, 47). Although aggressive cancer exhibits a high level of BRK, HER2 and HER4 also considerably express it (48, 49). In a distinct version, it has been shown that BRK is drawn to the up-protectors of p38 mitogen-activated protein (MAP) kinases and extracellular signal-released kinase 5 (ERK5) as well as epidermal growth factor receptor (ErbB) drive downstream (50).

Although the functions of BRK in definitive cells in breast cancer have not yet been fully established (51).

c) Phosphatidylinositol 3-kinase (PI3K):

The phosphatidylinositol 3-kinase (PI3K)-protein kinase B (PKB/AKT)-mammalian target of rapamycin (mTOR) axis controls vital cellular activities and physiological processes, such as cell proliferation, growth, survival, motility, and metabolism (52). Breast cancer disrupts the PI3K/AKT/mTOR signaling system in several ways. First, it has been discovered that approximately one-third of early breast cancer tumors had activating mutations in the PIK3CA, Helix, or Kinase area (53-55). The clonal nature of this mutation is supported by a separate file listing comparable mutation

rate in research on metastatic breast cancer (MBC) (56). Second, the tumor suppressor genes dense PTEN, PIK3R1, INPP4B, TSC1, TSC2, and LKB1 may experience inactivating events following this line (54, 57, 58).

AKT gene mutations and PIK3CA amplification have also been documented (56, 59-61). It is currently unknown how these molecular anomalies affect the results. Although recent molecular profiling data from MBC patients seem to suggest that a PIK3CA mutation would likely result in some chemo resistant behavior and a poor outcome in advanced hormone receptor positive (HR)/HER2- breast cancer, a PIK3CA mutation is associated with a better recurrence-free survival (DFS) (62) and a better DFS in early hormone receptor positive (HR)/HER2- breast cancer (62, 63). A worse prognosis seems to be associated with PIK3CA mutations in both the early and late stages of HER2-positive breast cancer (64, 65). Additionally, it has been demonstrated that secondary endocrine resistance in HR-positive breast cancer may be impacted by the PI3K/Akt/mTOR pathway (66). Long-term tamoxifen use and estrogen deprivation boost the PI3K pathway in preclinical models, phosphorylating and activating the ER by signaling through the mTOR complex 1 (mTORC1)/S6K1 axis in a ligand-independent manner (66, 67).

The PI3K inhibitors Wortmannin (68, 69) and LY294002 were used in early preclinical investigations to show that comprehensive inhibition of all PI3K isoforms can result in a therapy response that is acceptable for PIK3CA mutant tumors (70). After this discovery, several pan-PI3K inhibitors were created and have also entered clinical trials, including buparlisib (71), pictilisib (72), pilaralisib (73) and copanlisib (74). Most of them have been discontinued due to their unintended, off-target side effects, except for copanlisib, which is FDA-approved for the treatment of B-cell lymphomas with an increasing PI3K pathway (75).

Some preclinical and early trials have showed significant potential for clinically addressing the PI3K-Akt pathway in cancer-related illnesses (76). Inhibiting the PI3K pathway has been linked to the following factors that influence tumor angiogenesis and elevated antitumor T-cell response: PTEN-deficient cancers show p110 activity, p110 α controls angiogenesis, p110γ, p110δ and p110β significantly influence inflammatory cells in the tumor microenvironment, and p110δ and mTOR are identified as crucial adaptive immune regulators, including lymphocyte activation and differentiation (77, 78). Both wortmannin and LY294002 are first-generation PI3K inhibitors with undesirable side effects for specific PI3K isoforms and a lack of selectivity. Furthermore, other drugs that non-selectively inhibit

PI3K/mTOR have been studied in preclinical or clinical studies, including BEZ235, BKM120, and BGT226, XL765 and XL147, SF1126. Additional drugs that reduce Akt activity include PX316, GSK690693, Akti1/2 and MK2206, and XL418. The anticancer drugs rapamycin, CCI779, AP23573 and RAD001 disrupt the mTOR node, which is another potential target in the PI3K pathway (79).

d) TGF β:

Although there is a link between transforming growth factor- β1 (TGF-β1) and the growth and spread of breast cancer, its therapeutic value in relation to the levels of TGF- β1 in breast cancer patients has not been proven (80). Transforming growth factor beta (TGF- β), a member of the growth reproductive family, can appear in the mammary gland in both benign and cancerous forms. This pleiotropic cytokine plays an important role in rebuilding healthy breast tissue and controlling apoptosis (81). The most prevalent isoform of TGF-β, TGF- β1, has a tumor suppressor-controlling function in the normal breast. Yet, in breast cancer patients, this cytokine exerts tumor-promoting effects, which circumvent TGF-β1-regulatory features in the metastatic progression process (82). TGF- β's participation in mammary tumorigenesis has been proven over time both in situ by research on patient tumors that have been removed and in vitro (83-85), particularly in metastatic situations (86-88).

About this cytokine in human breast cancer, some significant information has been presented. Analysis shows that early TGF- β signaling progression, particularly in individuals with positive tumors, predicts the expansion of many chemokines and is linked to a bad prognosis (89). Because of these disparities, researchers have investigated and examined how anti-TGF-beta therapy affects cancer (90-95). TGF- β has both tumorigenic and tumor-suppressive actions, which gives it a dual function in cancer cells. TGF- β is meant to operate as a tumor suppressor by preventing breast cancer cell line proliferation (96). Hyperplastic breast ducts lacking TβRII are susceptible to turning into invasive breast cancer in the early stages of the disease (97). On the other hand, later cancer cells exhibit direct pro-tumorigenic activities through TGF- β, activation of invasion, tumor migration, and orifices of tumor stroma (98, 99). TGF- β initially inhibits development, but it is thought to disappear as tumors grow due to genetic and epigenetic processes that turn off certain downstream TGF- β mediators (100, 101). Several approaches have been used to investigate the prognostic value of TGF- β ligands and downstream signaling mediators of aggression. High blood TGF- β1 levels are linked to advanced breast cancer stages (102), but

high tissue TGF- β1 levels are linked to a poor prognosis (103). In a high proportion of patients with the formation of distant metastases and overall survival (OS), the complete absence of TβRII tissue in breast tumors was found (104). Walker et al., on the other hand, describe the dissemination of positive TGF- β results and the impact of lymph node metastases in breast cancers (105).

The absence of phosphorylated-Smad2 (p-Smad2) is associated with favorable prognostic features, such as signs of TGF-β, tumor size <2 cm, positive recipient (ER) positivity, and differentiation of good to moderate results if it has a distinct residue TGF-β signaling are intended to be positive nodal state transmissions. The presence of phosphorylated-Smad2 (p-Smad2) is canonically active (106).

The TGF-β signaling pathway is a growing target for therapeutic development in the treatment of cancer. Clinical trials looked at two treatments for metastatic breast cancer. Radiation and fresolimumab, a humanized inhibitory antibody to the TGF ligand, are both administered in a Phase II trial (NCT01401062). The TGF- β1 receptor is the target of the medication LY2157299, which was created by Eli Lilly (107). Furthermore, taken with radiation, this small molecule inhibitor is already enrolling patients (NCT02538471). In a mouse model of glioblastoma generated from humans, TGF signaling, and consequent tumors were both inhibited by LY2157299 (108).

Researchers are looking into using TGF- β inhibitors to chemotherapeutically stop the in vivo spread of the tumor-inducing cells (TIC) in TNBC patients (109). TGF- β induces breast cells to undergo an epithelial-mesenchymal transition (EMT), which results in tumor-like properties. Mammary epithelial cells treated with TGFBR1/2 inhibitors undergo reversible mesenchymal-epithelial differentiation (109, 110). TGF-β ligands have been shown to advance quickly in the tumor microenvironment of TNBC, according to reports (111).

e) JAK/STAT:

Because of the huge number of cytokines and growth factors that the JAK/STAT system is activated by, gain-of-function, loss-of-function, and polymorphisms in the JAK and/or STAT genes have been connected to a range of human disorders. Numerous mechanisms have been demonstrated to mediate the constitutive activation of this pathway, including the production of autocrine/paracrine cytokines that activate STATs later, activating mutations of receptors (point mutations that result in amino acid substitution), JAKs, and/or other upstream oncogenes (112). The majority

of JAKs and STATs either function as tumor suppressors or oncogenes in the development of malignancies in breast tissues, and they are crucial in the control of inflammation, cell survival, and proliferation (113).

The members of the JAK-STAT pathway are therapeutic targets, according to mounting evidence of the pathway's significance in immune system disorders and many cancers. In clinical trials with patients who had solid tumors, it was noted how crucial it was to target the JAK-STAT signal. In vitro and in vivo growth of recurrent leukemia B-cells was reported to be inhibited by JAK inhibitors in early research (e.g., tyrphostin AG490) (114). Another JAK inhibitor with action (pyridone 6) was launched to the market in the early 2000s. This substance has not been found to have any major effects in vivo, despite being effective against every JAK family member in vitro (115).

Pyridone 6 interacts with the adenosine triphosphate pocket in the JH1-kinase domain of the active conformation of JAK2 according to an analysis of its crystallographic structure. The development of the many JAK inhibitors that have been discussed so far has been made easier by this information (116). For the treatment of solid tumors, numerous selective JAK inhibitors are now being studied in clinical trials. These inhibitors mainly target the JAK family members JAK1 and JAK2. Ruxolitinib, a medication that blocks JAK1 and JAK2, is used to treat many solid tumors. For the treatment of pancreatic, colon, and lung malignancies, JAK1 and JAK2 inhibitor momelotinib is also being studied. The JAK1 inhibitors INCB047986 and INCB39110, which block JAK1's phosphorylation, are also moving forward in their clinical trials (117).

f) PARP:

The discovery of the poly (ADP-ribose) polymerases (PARPs), a family of nuclear enzymes, and their roles in DNA damage repair pathways resulted in the creation of PARP inhibitors (PARPi), a new class of antineoplastic medications with the ability to impede cancer's DNA damage repair mechanisms. Homologous recombination (HR), one of the primary DNA damage repair mechanisms, is characterized by suboptimal or impaired function in BRCA-mutated malignancies. The base excision repair pathway (BER) was once assumed to be the target of synthetic lethality of PARP inhibitors; disruption of both pathways causes cell death in tumor cells without a specific DNA repair process. Since tumor cells exhibit faulty homologous recombination repair, preferential susceptibility of BRCA-associated breast and ovarian malignancies has been shown. Moreover, there

have been reports of significant developments in PARPi, BRCA-related breast, ovarian, and other malignancies (118, 119).

Two techniques were the focus of PARPi's clinical development in 2003. Whether used in conjunction with other medications to treat a variety of solid tumors or for certain cancers that largely benefit from PARPi alone, these techniques have been expected to be extremely responsive to PARP inhibition. Ongoing PARPi testing with cytotoxic medicines has demonstrated the viability of this strategy, with good tolerability generally but minimal activity in non-pregnant women (120). On the other hand, promising organs have been found to treat patients with breast and ovarian cancer, the two cancers most frequently linked to BRCA mutations (121, 122). Negative results from the phase III trial of iniparib, which was mistakenly referred to as PARPi, initially delayed down clinical testing of PARPi (123). The clinical development of real PARPi has given it additional power after it was discovered that iniparib and its metabolites do not inhibit PARP in intact constructs (124).

g) Hedgehog (Hh) Pathway:

The Hh signaling system, which serves as a morphogen, mitogen, and inducer of developing organs, mediates several fundamental processes in embryonic development (125-127). The transmembrane receptors Patched (Patched1 and Patched2), Smoothened (Smo), the transcription factor Gli genes (Gli1, Gli2, and Gli3), and the Hh proteins Sonic Hh, Indian Hh, and Desert Hh make up the majority of the Hh pathway (125-127). Glis forms a large protein complex with the serine-threonine kinase Fused and other proteins, such as the kinesin-like Costal2, when Sonic Hh (Shh) is lacking (125, 128, 129).

One of Glis' target genes is Gli1 (130). Gli1 is a sign of the activation of the Hh pathway as a result (128, 131, 132). Data also implies that some adult organs require correctly controlled Hh signaling for stem cell maintenance or tissue repair (133, 134).

The Patched1 (Ptch1) or Gli2 genes are disrupted in the mouse model, where the Hh pathway is crucial for ductal formation in the mammary gland (131), and this causes significant problems in ductal morphogenesis such as ductal hyperplasia that is like certain human hyperplasia (132).

The Hh pathway controls the development and induction of the mammary gland in the developing embryo (133). Mammary development and proliferation are known to be protected by this signaling pathway (134, 135). Hh proteins that bind to the Patched (PTCH) cell surface transmembrane

receptor are known as Hh ligands (Sonic-SHH, Indian-IHH and Desert-DHH). PTCH inhibits smoothed protein-like transmembrane receptor retention (SMO), but when it binds to ligands (SHH, IHH, or DHH), SMO is released, providing possibilities for posttranslational transcription of the zinc-finger GLI (glioma-operated oncogene homolog). There are currently three GLI proteins that are widespread in mammals: GLI1 and GLI2 generally work as transcriptional activators, but GLI3 serves as a repressor of transcription (130).

The capacity to block the Hh pathway can be achieved through a variety of techniques, including as the blockage of SMO, the inhibition of GLI, and antibodies to Hh ligands (136, 137). Cyclopamine, a naturally occurring chemical with a high affinity for SMO, was one among the first compounds that helped researchers understand the Hh pathway in cell lines and animal models (138).Cyclopamine's practical use has been constrained by its poor solubility and ineffectiveness. Sonidegib (139), an SMO inhibitor, has been given FDA approval for the treatment of metastatic or advanced basal cell carcinoma. Additional SMO inhibitors, including glasdegib (140), taladegib (141, 142) and saridegib (140), are being tested in clinical trials (143). Basal cell carcinoma has been documented to have SMO mutations that result in secondary resistance to SMO inhibitors (144). It has been noted that drug-resistant SMO mutants can still be inhibited by the antifungal medication itraconazole, an SMO inhibitor with a distinct method of action from other SMO antagonists (145, 146).

h) Notch Signaling (NS) Pathway:

One of the important regulators controlling cell fate and cell differentiation in the developing mammary gland is the highly conserved Notch signaling system (147-149). Recent studies have shown that Notch signaling is frequently upregulated during the development of therapeutic resistance as well as the progression of various breast cancer subtypes (150-155).

As it amplifies and inhibits vital communication signals via a variety of signaling pathways involved in the oncogenesis process, including WNT, ERK, β -catenin, and Her2/VEGFR, among others, NS has been assigned a clear function in the biology of breast cancer formation (156).

NS-regulated genes, cell transplantation, apoptosis, cell reproduction, and metabolism (157, 158) all send these officials directly. Around 20% of mammary gland tumors are known to be brought on by abnormalities in the Notch4 gene's functioning, while more than 50% of instances are known to be brought on by the Notch1 aberrant gene's functioning (159, 160).

A signaling system that evolved to regulate cell fate is the Notch signaling pathway. It aids in the proliferation, self-renewal, survival, and differentiation of stem cells. Deregulation of the Notch signaling system protects against targeted or cytotoxic treatments by concentrating resistant cells on the small side. Inhibiting the Notch system could block or reverse resistance by stopping the regrowth or removal of breast cancer stem cells, according to a preclinical study. Despite this, Notch inhibitors have not been clinically proven to be successful in the treatment of breast cancer (161).

The treatment resistance occurs in about 80% of breast cancers treated with anti-estrogens, and it is thought that the Notch pathway is involved in this (162). Targeting both signal pathways simultaneously can therefore aid in overcoming or delaying this undesirable resistance. Certain Notch homologues, however, can impede the growth of cancer cells. According to O'Neill et al. (163), Notch-2 inactivates Notch-1 and Notch-4's pro-oncogenic actions in human breast cancer cells.

It was shown that Notch-1 expression was up in breast cancers with poor differentiation while Notch-2 expression was elevated in tumors with well differentiation. Furthermore, one study hypothesized that Notch-1 would have tumor-promoting characteristics whereas Notch-2 might have tumor-suppressing ones (164). Looking more closely at the function of these homologs can assist create a promising therapy strategy since interactions between various Notch homologs can result in varied cancer treatment outcomes.

1) Wnt/β-Catenin Pathway:

Like the Notch signaling network, this signaling system is a possible target for TNBC therapy because, when it is aberrantly activated, it can affect both embryonic and malignant growths. TNBC has been found to abnormally overexpress the Wnt protective-low-density protein 6 (LRP6) and Wnt receptor frizzled-7 (FZD7) proteins (165, 166). The study's findings explain why Wnt/ β -catenin signaling is active in TNBC, where the Wnt receptor frizzled-7 (FZD7) and the Wnt co-receptor LRP6 are especially up-regulated (167).

In the absence of Wnt ligands, Axin, Adenomatous Polyposis Coli (APC), and glycogen synthase kinase 3 (GSK3) work together to maintain the levels of β -catenin. As a result, β -catenin's amino-terminal region is regularly phosphorylated. The multiple ubiquitination (Ub) of phosphorylated catenin is then influenced by the 26S proteasome. Hence, a Wnt ligand's engagement with its receptor on the cell surface upregulates Wnt/ β -catenin

target genes and starts and spreads cancer by uncontrollably controlling cell growth and death (165, 166). Recent investigations on the anticancer effects of the medication Gigantol, which is derived from medicinal orchids, show that cytosolic -beta catenin significantly reduces total LRP6 and phosphorylated LRP6 levels, resulting in low levels of Axin2 and Survivin (Wnt-targeted genes). Wnt/ β -catenin inhibitors that cause the degradation of LRP6 include salinomycin and nigericin, which also influence breast cancer stem cells (phase I/II clinical trial) (168, 169).

i) NF-κB Signaling:

The NF-κB signaling was shown to be crucial in controlling mammary epithelial reproductive proliferation during pregnancy in a genetically modified animal using a fee model. It has also been discovered that at least six NF-κB pathway structures, including RANKL and RANK, are controlled by a cascade of beams. CyclinD1, IKKa, IkBa, p50/p65 (170). Additionally, a growing body of data suggests that the NF-κB pathway's constitutive development or dysregulation may contribute to the development of breast cancer (171, 172). Given the numerous disorders for which the NF-κB pathway has been implicated, including breast cancer, targeting this signaling system looks to be a viable technique. Many clinical trials have previously employed combinatorial therapies that target components of the PI3K/Akt and MAPK pathways that activate NF-κB. (173). Other medications, such as certain IKK inhibitors, are the subject of continuing research. Cellular senescence has been linked to the medication TBK1-II, which slows the growth of human HER2+ breast cancer cells. Some breast cancer cell lines are susceptible to the cytotoxic effects of doxorubicin when IKKs are suppressed (174, 175).

Additionally, inhibiting NF-κB DNA binding is a plausible strategy for decreasing NF-κB activity since it would very specifically block the transactivation of downstream targets that are prosurvival and antiapoptotic. Combinatorial therapy for breast cancer uses more than 780 substances that have been acknowledged to have NF-κB inhibitory activity (176). Clinical trials involving breast cancer patients have been conducted on drugs like the proteasome inhibitor bortezomib, with modest results (177, 178).

j) Hippo Signaling:

The Hippo Signaling Pathway is described as a newly found developmental signaling mechanism in Drosophila melanogaster. The Hippo tract organs, tissue regeneration, wound healing, and maintenance of tissue stem cells are all under the direction of the mammalian body (179, 180). By a variety

of pathways, an aberrant Hippo pathway promotes the spread of breast cancer (181). For invasive breast tumor colonization inside or outside of breast tissue, YAP, TAZ, and MST1 are required (182). Relevant data from supplementary research showed that in a genetically designed mouse model of breast cancer, YAP deficiency lowers the risk of lung metastases. Ski substantially lowers breast cell lung metastases after TAZ overexpression (183, 184). In order to promote metastasis in bone cancer, phosphorylated HER3 Tyr1307 can cause MST1 to methylate at the lys59 area and cause active YAP/TAZ to be produced in tumor cells (185). According to a study, TAZ's nuclear expression in bone metastases was substantially higher than its cytoplasmic expression in primary tumors. Another crucial element in the invasion of malignancies is a hypoxic microenvironment in the bone marrow. When the oxygen level is low, a protein known as hypoxia inducing factor (HIF)-1a is present. Studies have demonstrated that the interaction between HIF-la and TAZ in a hypoxic environment causes bone metastases in breast cancer (186, 187). MST1/2 and LATS1/2, two Hippo pathway upstream kinases, have the capacity to regulate YAP phosphorylation as tumor suppressors. Hence, LATS1/2 may offer great potential as a target for breast cancer anticancer therapy (181).

MST and LATS, two essential kinases in the hippo pathway, have been shown to be often hypermethylated in BC. Although there are no known direct activators of MST and LATS, these indirect activators of MST and LATS may one day lead to the development of drugs that specifically target the cells that cause breast cancer (188). Recently, it was discovered that Raf-1 is upregulated by MST2, and ISIS 5132 is an antisense oligonucleotide that is made to hybridize with both Raf-1 and c-Raf mRNA (189, 190). By cleaving MST2 into an inert molecule, Raf-1 can prevent BC cell death. ISIS 5132 was put on hold despite preclinical studies demonstrating anti-tumor advantages in breast cancer and other solid xenograft mouse models indicating success in patients with colorectal, ovarian, or prostate cancer (191).

Future Directions:

Understanding the therapeutic options available to us requires a close examination of the cellular events that take place throughout oncogenic processes. It is also crucial to comprehend that carcinogenesis entails a variety of adjustments in tumor cells that enable their transition into malignant ones (192). Therapy for early-stage breast cancer necessitates a complex strategy to completely remove the illness and stop it from returning. For breast

cancer to be effectively treated, mechanisms that support or maintain the proliferation and invasion of carcinoma cells must be targeted (193, 194).

Treatment options for breast cancer are currently moving steadily in the direction of powerful, non-toxic targeted medicines that can be customized to the tumor of each patient. Today, nearly all breast cancer subtypes can be treated with targeted therapies that take advantage of the various carcinogenesis-promoting factors present in each tumor type (195).

Today's oncology drug development is fraught with difficulties. To choose the best dose of a targeted medication for phase II clinical trials, we need to better understand the molecular biology of signaling pathways and find new biomarkers (196).

The discovery of numerous genes in the human genome, the advancement of sequencing technology, and whole genome gene expression research have created new prospects for choosing the proper patient for an effective medication. To better match the active drug(s) with the unique molecular characteristics of the cancer patient, numerous research has been carried out and are continuing in progress (197-199). By additional research, it should deliver urgently required information on maximizing patient benefit, identifying causes of resistance to such medicines, and predicting responsiveness to targeted therapies (200).

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