Breast cancer: Molecular basis and therapeutic strategies (Review)

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Abstract. Breast cancer is the most common malignancy among women. It is frequently treated with chemotherapy and hormone therapy. More recently, however, 'targeted therapy' has emerged as an important approach to cancer therapy. Targeted therapy works by interfering with a specific molecular target, though inter-individual variability in drug response often causes treatment failure. Anticancer agents inhibit breast cancer progression by several different mechanisms. The Ras/Raf/MEK/ERK signal transduction pathway regulates cell cycle progression and apoptosis in diverse cell types. Alterations in this pathway are often associated with human cancer, including breast cancer. Understanding breast cancer biology is useful for the identification of appropriate anticancer drugs. This review describes the effect of gene alterations on breast cancer development. In addition, it shows how each anticancer drug used to treat breast cancer may block aberrant cell proliferation. Finally, the mechanisms of resistance to therapy are also discussed.

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1. Introduction

Breast cancer is the most common malignancy among women (1). Over 180,000 new cases are diagnosed in the United States each year, and approximately half of all patients diagnosed die from the disease (2). The incidence of breast cancer presents a wide geographic variability; it is almost 10 times more common in the developed countries of the West than in the third world. The rate of incidence in the US in 2005 was 242,570 new cases (32% of neoplasia diagnosed in women) (3). However, in the last decade, in spite of its increasing incidence, breast cancer mortality has been declining in the majority of developed countries. Undoubtedly, the reasons for this decline are multifactorial: the result of better education, widespread screening programmes and more efficacious adjuvant treatments (4). However, the use of systemic therapies in early disease treatment is commonly regarded as a major contributing factor (5).

An increased knowledge of the regulation of cell growth and the genetic and biochemical changes that lead to malignancy has created many new opportunities for the development of cancer drugs. These new targets include oncogenes, growth factors and their receptors, signal transduction pathways and cell differentiation signals (6).

2. Breast cancer biology

Mutations in a number of genes are now known to cause susceptibility to breast cancer. In high-risk families, the most significant of these are the BRCA1 and BRCA2 genes (7-12,14). Hereditary breast cancer accounts for only ~10% of all breast cancer cases and generally results from the lack of a tumor suppressor gene, as opposed to the gain of an oncogene (13).

BRCA1 and BRCA2 are responsible for 80-90% of genetically determined tumors, codifying nuclear proteins involved in the biochemical mechanisms that control the integrity of the genome. These genes are rarely mutated in sporadic forms, suggesting they play a pathogenetic role in the promotion of carcinogenesis. BRCA genes are also involved in male breast cancer. Men who carry germline mutations in the BRCA2 gene have a higher risk of developing breast carcinoma than men in the general population, and those who carry germline mutations in the BRCA1 gene may also be at a higher risk, though this association is not as well established (15).

Other genes are involved in the genesis of breast cancer as well. These are tumor suppressor genes, p53 and PTEN. The most common route by which the p53 pathway is inactivated in human cancers is by mutation in the coding region of the
proto-oncogene encodes a growth factor receptor that is over-
expression and prognosis in breast cancer (29). The HER2/neu
many studies indicate a close correlation between its expres-
sion and frequency of breast cancer (30). PTEN has a function in tumor
expression is associated with decreased survival and decreased
relapse-free periods. The anti-HER2 antibody is designed to
block this receptor. Epidermal growth factor (EGF), its cognate
receptor (EGFR) and related family members have been shown to
be important in the normal as well as the malignant growth
of many cell types, including glioblastomata, astrocytomas,
medulloblastomata, non-small cell lung carcinoma and breast
cancer (30).

HER2 gene amplification is a complex event including
the coamplification of other potentially oncogenic genes and
the facilitation of the generation of additional genomic aber-
trations (31). It is estimated that amplification of the HER2
gene takes place in roughly 18-20% of breast cancer patients,
resulting in aberrant overexpression of p185HER2 protein.
As a result, HER2 represents an attractive therapeutic target (32).

**Ras/Raf/MEK/ERK pathway.** The Ras/Raf/MEK/ERK cas-
cade couples signals from cell surface receptors to transcription
factors, which regulate gene expression. This cascade also
regulates the activity of many proteins involved in apop-
tosis. The pathway is frequently activated in certain tumors
by chromosomal translocations such as BRC-ABL, mutations
in cytokine receptors such as Flt-3, Kit and Fms, or over-
expression of wild-type or mutated receptors, such as EGFR.
Abnormal activation of the Raf/MEK/ERK pathway occurs
in human cancer due to mutations in the upstream mem-
bane receptors Ras and B-Raf, as well as in genes in other path-
ways (e.g., PI3K, PTEN, Akt) that serve to regulate Raf
activity (33). Mutations at B-Raf are frequently detected in
certain malignancies, including melanoma and thyroid cancer
(34).

The mitogen-activated protein kinase (MAPK) signaling
pathway is a potential target for cancer therapy (35). HER2/
neu overexpression can activate PI3K and the Ras/Raf/MEK/ERK pathway, resulting in the reduction of wild p53 protein expression. This may be the molecular mechanism responsible for the poor prognosis and therapeutic non-responsiveness of patients with HER2/neu-overexpressed breast cancer (36). The Ras/Raf/MEK/ERK and PI3K/PTEN/AKT signaling cascades play critical roles in the transmission of signals from growth factor receptors, regulating gene expression and preventing apoptosis. Components of these pathways are mutated or aberrantly expressed in human cancer (e.g., Ras, B-Raf, PI3K, P, Akt) and mutations occur in genes encoding upstream receptors (e.g., EGFR and Fli-3), while chimeric chromosomal translocations (e.g., BCR-ABL) transmit their signals through the cascades. The pathways interact to regulate growth and, in some cases, tumorigenesis (37) (Fig. 1).

**PI3K/AKT pathway.** PI3K consists of an 85-kDa regulatory subunit containing the SH2 and SH3 domains, and a 110-kDa catalytic subunit (38). The PI3K/Akt signal transduction cascade has been extensively investigated for its roles in oncogenic transformation; uncovering the signaling network spanning the region from the extracellular environment to the nucleus should illuminate biochemical events contributing to malignant transformation. PI3K/Akt signaling plays an important role in regulating the proteins that control cellular proliferation. These targets include cyclins, cyclin-dependent kinases and cyclin-dependent kinase inhibitors (39). PIK3CA mutations are common in invasive ductal carcinomas of the breast (40).

Numerous studies have demonstrated that breast cancer arising in young women is characterized by a higher incidence of negative prognostic factors, higher recurrence rates and poorer overall survival, despite aggressive therapies (41). In fact, breast cancer patients younger than 35 years have a poorer prognosis than older patients (42). The poor prognosis subgroup of young women with breast cancer is characterized by a higher incidence of late relapse. We have identified a gene signature that can predict the selectivity of nitrogrenated mustard. It is an odorless, fine white crystalline powder with a molecular weight of 261.1 and a melting point of 45.9-53°C, and is soluble in water and ethanol, slightly soluble in benzene, ethylene glycol, carbon tetrachloride and dioxane, and sparingly soluble in diethyl ether and acetone. Its log octanol-water partition coefficient is 0.63. Cyclophosphamide reacts with strong oxidizing agents, is sensitive to moisture and light, and is hydrolyzed in aqueous solutions above 30°C. It is a clinically implemented cytotoxic agent that is effective on a wide range of tumor types, including breast and small-cell lung cancers. Many tumoral cells are, in fact, full of phosphamidasis and phosphatases, the enzymatic systems responsible for its activation. The hepatic metabolism converts cyclophosphamide to 4-hydroxycyclophosphamide, the tautomerization of which yields aldophosphamide. Acrolein and N,N-bis-2-(2 chloroethyl) phosphorodiamidate are produced by the spontaneous cleavage of aldophosphamide. N,N-bis-2-(2 chloroethyl) phosphorodiamidate is a bifunctional alkyating agent and is considered to be the true active agent of cyclophosphamide. DNA is alkylated by N,N-bis-2-(2 chloroethyl) phosphorodiamidate at multiple sites. The N7 position of guanine is a site that is particularly susceptible to alkylation by N,N-bis-2(2 chloroethyl) phosphorodiamidate. Alkylation of the N7 position of guanine caused by cyclophosphamide treatment stabilizes the enol tautomer of guanine, which causes guanine to pair with thymine instead of cytosine. The mechanism of action of cyclophosphamide is linked to its interaction with DNA. The most important actions are those which alter the basic mechanisms of growth with mitotic, differentiation and cell functions. The focus on this drug is precisely related to its ability to interfere with the normal mitosis and cell differentiation of all tissues in rapid proliferation.

Cyclophosphamide is used as an adjuvant therapy, often in association with patterns and sequences of combination therapy with fluorouracil and methotrexate (MTX), to treat women who do not have hormone receptors or who are at high risk for relapse. We have identified a gene signature that can predict tumor response to cyclophosphamide and warrants clinical validation (45).

**Methotrexate.** Antimetabolites prevent cell division because they are embedded in the material of nuclear neosynthesis, or because they combine it irreversibly with the enzymes necessary for life, preventing normal cellular mitotic division. MTX belongs to the class of antimetabolites and folate acid analogs. DNA synthesis requires thymidine 5'-triphosphate (TTP), which is synthesized from thymidine 5'-monophosphate (TMP). Thymidylate synthetase generates TMP by catalyzing the transfer of a methyl group from N5,N10-methylene tetrahydrofolate to 2'-deoxyuridine 5'-monophosphate (dUMP). Treatment with MTX blocks TMP synthesis by preventing the synthesis of N5,N10-methylene tetrahydrofolate. MTX contains a single glutamic acid residue. Folinic acid-5'-glutamate synthetase (FPGS) catalyzes the addition of one or more glutamic acid moieties to MTX. MTX and its polyglutamylated derivatives inhibit dihydrofolate (DHF) reductase (DHF). DHFR reduces folate to DHF, which is in turn reduced to tetrahydrofolate. Serine hydroxy-methyltransferase converts tetrahydrofolate to N5,N10-methylenetetrahydrofolate. MTX
treatment reduces TMP production by eliminating a source of N5,N10-methylenetetrahydrofolate synthesis (13).

5-Fluorouracil. 5-Fluorouracil (5-FU) is also an antimetabolite that is part of similar pyrimidine, capable of preventing the biosynthesis of nucleotide pyrimidines. The 5-FU molecule, inactive in both normal and tumor cells, acquires its cytotoxic activity following biotransformation affected within the cell. Treatment with 5-FU prevents the synthesis of TMP. Thymidylate synthetase is irreversibly inhibited by 5-fluoro-2-deoxyuridine 5'-monophosphate (FdUMP), which is produced by 5-FU. Reduction in TMP levels by treatment with methotrexate or 5-FU inhibits TTP production. This blocks cell proliferation by preventing DNA synthesis.

Anthracyclines. Anthracyclines are anticancer agents belonging to the category of cytotoxic antibiotics. They are a group of drugs, for the most part isolated from natural sources, whose antineoplastic action is due to interaction with DNA. The resulting introduction of nucleic damage triggers apoptosis. Anthracyclines are very effective but also very toxic, unable to discriminate between malignant and healthy cells. They are intercalant agents: aglycone intercalate between DNA base pairs, deforming the double helix. Drug intercalation is necessary but not sufficient for topoisomerase II poisoning. Indeed, the operation of anthracyclines is essential to the formation of a stable complex of DNA-topoisomerase II, which determines the inhibition of this enzyme. Several anthracyclines interfere with topoisomerase II functions by stabilizing an intermediate reaction, in which DNA strands are cut and covalently linked to the tyrosine residues of the enzyme (46). Disruption of the DNA structure by anthracyclines inhibits the synthesis of both DNA and RNA. The antitumor activity of anthracycline drugs results from a combination of various intracellular effects. The main mechanisms of anthracycline-mediated tumor cell death involve i) DNA topoisomerase II inhibition, ii) DNA damage through a p53-dependent and/or p53-independent mechanism, iii) induction of apoptosis mediated by cytochrome c release, iv) proteasome interactions, and v) oxidative damage mediated by the generation of free radicals (47).

DNA cleavage likely makes an important contribution to the cytotoxicity of anthracyclines, as reduced expression of topoisomerase IIα is correlated with decreased anthracycline sensitivity (48). These anthracyclines induce apoptotic cell death. In breast cancer, the anthracyclines used are doxorubicin (Adriamycin) and epirubicin.

Taxanes. Microtubule-targeting agents have made significant contributions to cancer therapy over the past fifty years. Taxanes have been used to treat a broad range of malignancies, including leukemias and lymphomas, and many types of solid tumors. They have frequently been used in the treatment of advanced ovarian, breast, lung, head and neck and prostate cancer, and are increasingly being used in early-stage disease (49).

Taxanes comprise a group of drugs which includes paclitaxel (Taxol) and docetaxel (Taxotere), used in the treatment of cancer. They have a unique way of preventing the growth of cancer cells, by affecting cell structures called microtubules that play an important role in cell functions. In normal cell growth, microtubules are formed when a cell starts dividing. Once the cell stops dividing, these microtubules are broken down or destroyed. Taxanes, however, stop the microtubules from breaking down. Thus, cancer cells become so clogged with microtubules that they cannot grow and divide (50).

Epothilones are a novel class of antineoplastic agents possessing antitubulin activity. They induce tubulin polymerization and enhance microtubule stability. Epothilone-induced stabilisation of microtubules has been shown to cause arrest at the G2/M transition of the cell cycle, as well as apoptosis. The compounds are active against cancer cells that have developed resistance to taxanes resulting from the acquisition of β-tubulin overexpression or mutations, and are active against multidrug-resistant cells that overexpress P-glycoprotein or multidrug resistance-associated protein. Thus, epothilones represent a new class of antimicrotubule agents with low susceptibility to key tumor resistance mechanisms (51).

4. Hormone therapy

Aromatase inhibitors. Many breast cancers rely on supplies of the hormone oestrogen to grow. In women who have been through menopause, oestrogen is mainly acquired through the changing of androgens (sex hormones produced by the adrenal glands) into oestrogen. This is carried out by an enzyme called aromatase, with the conversion process, known as aromatisation, taking place mainly in the fatty tissues of the body. Aromatase cytochrome P450 (CYP19) converts androgen to estrogen (52). Enzyme aromatase, which catalyzes the reaction of estrogen synthesis starting from androgens, in particular by the conversion of androstenedione estrone and estradiol to testosterone, is inhibited by aromatase inhibitors.

Aromatase inhibitors prevent the proliferation of breast cancer cells by blocking estrogen production. There are two classes of aromatase inhibitors, which differ in chemical structure and their mechanism of action. Type 1 inhibitors (enzyme inhibitors and steroids), such as exemestane, bind irreversibly to aromatase. Type 2 inhibitors (non-steroidal enzyme inhibitors), such as anastrozole and letrozole, reversibly bind to aromatase. In one comparative study conducted in 2000, anastrozole satisfied the predefined criteria for equivalence to tamoxifen (TAM). Moreover, both a significant increase in thymidine 5’-triphosphate (TTP) and a lower incidence of thromboembolic events and vaginal bleeding with anastrozole was observed (53). Aromatase inhibitors provide an alternative to TAM as an adjuvant therapy for post-menopausal, hormone-receptor-positive breast cancer patients (54).

Tamoxifen. Hormonal intervention as a means to treat breast cancer has been implemented since the late 1800’s, when Beatson (55) was able to treat this cancer by ovarioectomy. By 1900, Boyd (56) had reported that 37% of breast cancer patients studied responded to ovarioectomy. Many years later, the mechanisms underlying this response were demonstrated to be related to the fact that a large subset of breast cancers are hormonally responsive due to their dependence on signaling via the estrogen receptor (ER) (57). TAM, a non-steroidal anti-estrogen, is currently used to treat post-menopausal breast cancer patients. In estrogen-sensitive breast cancer cell lines, TAM and some of its metabolites display, for the induction
of estrogen-regulated proteins, a partial agonist/antagonist activity. They also totally inhibit the proliferation of these cells (58). The observed clinical efficacy of TAM has been attributed to both growth arrest and the induction of apoptosis within breast cancer cells. Although its primary mechanism of action is believed to be related to the inhibition of estrogen receptor (ER), research over the years has indicated that additional, non-ER-mediated mechanisms exist. These include the modulation of signaling proteins, such as protein kinase C (PKC), calmodulin, transforming growth factor-β (TGF-β), and the proto-oncogene c-myc. Recent studies have implicated the role of caspases and MAPK, including c-Jun N-terminal kinase and p38, in TAM-induced apoptotic signaling. Oxidative stress, mitochondrial permeability transition, ceramide generation, as well as changes in cell membrane fluidity may also play important roles in TAM-induced apoptosis (59). TAM has significantly decreased the mortality rate of both premenopausal and postmenopausal women with hormone receptor-positive breast cancer (60).

5. Antibody-based therapy

The term ‘targeted therapy’ refers to a new generation of cancer drugs designed to interfere with a specific molecular target, typically a protein, believed to play a critical role in tumor growth or progression. Over the last several years, multiple definitions for the term targeted therapy have emerged. First, the US Food and Drug Administration (FDA) considers targeted therapy to be a drug with an approved label with a specific reference to a simultaneously- or previously-approved diagnostic test that must be performed before the patient can be considered eligible to receive the drug (61). For many scientists and oncologists, targeted therapy is defined as a drug with a focused mechanism that acts specifically on a well-defined target or biologic pathway which, when inactivated, causes the regression or destruction of the malignant process. Many investigators consider anticancer antibodies an additional type of targeted therapy, especially when they are conjugated with cytotoxic radioisotopes, cytotoxic drugs or cellular poisons that seek out and kill malignant cells bearing the target antigen (62).

Genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors and other drug targets have been linked to inter-individual differences in response to the efficacy and toxicity of many medications. Pharmagenomic studies are rapidly elucidating the inherited nature of these differences in drug disposition and effect, thereby enhancing drug discovery and providing a stronger scientific basis for optimizing drug therapy on the basis of the genetic constitution of each patient (63).

Trastuzumab. Trastuzumab is the first example of a novel approach to genetic and biologic research concerning neoplastic cell growth; it is a rare example of a success story of clinical and translational medicine moving from bedside to bench to bedside (64). Trastuzumab (Herceptin®, Genentech Inc., San Francisco, CA) is a recombinant humanized monoclonal antibody directed against the extracellular domain of the human epidermal growth factor receptor 2 (HER2 or ErbB-2) protein. Currently, trastuzumab is the only HER2-targeted therapy approved by the FDA for the treatment of metastatic breast cancer (65). Signal transduction research has shown the importance of members of the human epidermal growth factor receptor (HER) family of transmembrane tyrosine kinases in a number of solid tumors. One member of this family is HER2 (ErbB-2). HER2 is normally expressed in all epithelial cells but, in a percentage of breast cancer cases ranging from 10 to 30%, was amplified, with a consequent membrane glycoprotein overexpression. In a small percentage of cases, ranging from 3 to 10%, hyper-expression of glycoprotein without gene amplification was observed. The mechanism behind this is still unknown. The gene for this receptor is amplified in up to 30% of breast cancers, leading to aggressive behavior and an unfavorable prognosis. Amplification of the HER-2/neu gene is a significant predictor of both overall survival and time to relapse in patients with breast cancer (66). However, the overexpressed HER2 receptor protein also serves as a target for anti-HER2 antibody (trastuzumab) therapy. The presence or absence of amplification can be used to differentiate patients who may have a response to the antibody from those who will not have a response (67). Unlike most pathologic testing, which serves as an adjunct to establishing a diagnosis, the results of HER2 testing stand alone in determining which patients are likely to respond to trastuzumab, a monoclonal antibody against HER2. Given the significant clinical impact of testing results on subsequent patient management, the accuracy, precision and reproducibility of HER2 testing are critical. At present, several pre-analytic factors, including the time from tissue removal to tissue fixation, are underappreciated as important variables that have the potential to negatively impact the consistency and reliability of HER2 testing. Rigorous quality control and standardization of the testing process, from the handling of tissue samples to the interpretation and reporting of results, are essential for achieving accurate and reproducible assay results (68).

The principal adverse event associated with trastuzumab therapy among patients with prior exposure to anthracycline is cardic dysfunction (CD). Patients treated with trastuzumab appear to be at an increased risk of developing cardiomyopathy, reminiscent of the cardiomyopathy associated with anthracyclines. The pathophysiologic basis of trastuzumab-associated CD is poorly understood. It remains unknown whether trastuzumab exacerbates previous damage caused by anthracyclines or acts through an independent mechanism to directly affect the cardiac myocyte. It has been suggested that p185HER2 may play a role in myocyte survival. However, the molecular mechanisms underlying trastuzumab-associated cardiomyopathy are obscure. The greatest risk for the development of CD was observed in patients receiving concomitant trastuzumab and anthracycline. Risks for patients treated with concurrent paclitaxel and trastuzumab and patients treated with trastuzumab as a single agent seem to be substantially lower than those associated with the concurrent administration of anthracycline and trastuzumab (69). Trastuzumab is generally well tolerated by most patients, the most significant adverse effects being acute fever and/or chills and the potential to cause CD. Serious adverse events, including anaphylaxis and death, have occurred in 0.25% of patients. Symptomatic or asymptomatic CD has occurred in 27% of patients receiving anthracycline and cyclophosphamide treatment combined with
trastuzumab. Thus, combination therapy with anthracyclines is not recommended. Symptomatic or asymptomatic CD occurred in 13% of patients receiving trastuzumab plus paclitaxel and in 4.7% of patients receiving trastuzumab alone (70).

6. Mechanisms of resistance and the RAF/MEK/ERK pathway

Inter-individual variability in drug response and the emergence of adverse drug reactions are the main causes of treatment failure in cancer therapy. Recently, membrane transporters have been recognized as important determinants of drug disposition, thereby affecting chemosensitivity and resistance. Genetic factors contribute to inter-individual variability in drug transport and targeting. Pharmacogenetic studies of membrane transporters can therefore lead to new approaches to optimizing cancer therapy (71). MAP-kinase activity and expression may be increased in some human breast cancers, independently of EGFR or HER2, rendering these tumors less sensitive to anticancer approaches targeted to HER receptors (72). A potential mechanism by which resistance to targeted antibodies might develop is via the disruption of the therapeutic agent in binding to the target protein (65). The membrane-associated glycoprotein mucin-4 might mask HER2, preventing it from binding effectively to trastuzumab (73). An important study provided compelling evidence supporting a role for the PI3K/Akt pathway in trastuzumab resistance. The authors essentially showed that, in patients with HER2-overexpressing breast tumors, the absence of PTEN expression was associated with a poorer response to trastuzumab-based therapy than in those patients with normal PTEN. Furthermore, it has been demonstrated that, in PTEN-deficient cells, PI3K inhibitors rescue trastuzumab resistance in vitro and in vivo (74). These results suggest that PTEN loss could serve as a predictor of trastuzumab resistance, and that PI3K inhibitors should be explored as potential therapies in patients with trastuzumab-resistant tumors expressing low levels of PTEN protein (65).

A study performed to investigate which pathway plays a major role in Ras-induced drug resistance to chemotherapeutic agents in breast cancer cells demonstrated that, although inhibition of MEK/MAPK or PI3K/Akt can enhance the cytotoxicity of paclitaxel, doxorubicin or 5-FU, inhibition of the PI3K/Akt pathway seems to have a greater effect than inhibition of the MEK/MAPK pathway in reversing Ras-mediated drug resistance. The results indicate that the PI3K pathway may play a more important role in receptor tyrosine kinase-mediated resistance to chemotherapy, and suggest that PI3K/Akt may be a critical target molecule for anticancer intervention in breast cancer (75). Therefore, MAP-kinase may be an additional target that anti-EGFR and anti-HER2 interventions may have to disable in order to exert an anti-tumor effect (76).

7. Conclusions

The biologic heterogeneity of breast cancer has been elucidated through genome-wide profiling technologies. Several studies have defined the genetic inter-individual differences among breast cancer patients. These differences may affect response to therapy and prognosis. Mechanisms of resistance to therapy may be identified by exploring alterations of genes involved in breast cancer development. Therefore, a better understanding of breast cancer biology may enable oncologists to identify a tailored treatment for these patients.

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