GENETICS OF BREAST CANCER

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Summary
Breast cancer has all the hallmarks of a multi-step genetic disease. Somatic and germ-line mutations have been described in several tumor suppressor genes, and oncogenes are found to be amplified. Genes in the ATM-CHK2-TP53 cell-cycle checkpoint pathway are mutated in relation to breast cancer, particularly TP53 at the somatic level. Germ-line mutations in BRCA1 and BRCA2, in which DNA repair function is interrupted, account for the majority of familial breast cancers. The mechanism behind the frequent instability of the genomes of breast cancer cells has been poorly understood, but recent functional findings on oncogenes and tumor suppressor genes have provided substantial information on the matter. Some recent developments in drug therapy are based on molecular and genomic findings about breast cancer pathogenesis. © 2004 Prous Science. All rights reserved.

Introduction
The genome of breast cancer cells is characterized by genomic instability, abnormal number of chromosomes, multiple losses of several chromosome parts and amplification of several other chromosome parts (reviewed in ref. 1). In breast cancer, this is generally classified as chromosome instability. The regions where definite losses are detected are presumed to carry tumor suppressor gene(s). Some of these genes have been characterized, but additional tumor suppressor genes will presumably be defined in relation to breast cancer pathogenesis in the future (Table I).
Several germ-line sequence variants of tumor suppressor genes are related to breast cancer pathogenesis. The majority of familial and about 5–10% of all breast cancers are associated with mutations in the BRCA1 and BRCA2 autosomal-dominant genes. In addition, a minority of hereditary breast cancers are due to germ-line mutations in TP53, CHK2, ATM and PTEN. Germ-line mutations of TP53 and CHK2 are linked to Li-Fraumeni cancer syndrome, ATM to ataxia-telangiectasia and PTEN to Cowden’s disease; in all cases breast cancer is one of the diseases detected. Somatic mutations in some of these genes are also found within breast tumors. For example, TP53 is mutated in about 25–30% of tumors. Germ-line mutations in these genes are not full-penetrance breast cancer sequence variants. However, some of them, such as BRCA1 and BRCA2, are considered to be high-penetrance variants, at least in a certain genetic background, while others, such as ATM and CHK2, are low-penetration variants.

At the somatic level, several oncogenes are amplified in breast tumors, i.e., MYC, CCND1, HER2, ESMY and STK15 (Table I). The frequency of these amplifications is rather low, about 15–25%. The detection of amplification and overexpression of HER2 is a good example of how information from molecular biology has become useful in cancer therapy, since today there are existing antibodies against the protein product (2). In addition, strict dependence on cyclin D1, the protein product of CCND1, for development of certain breast tumors argues for a role of cyclin D1 antagonists in the treatment of this disease (3). The frequent genomic instability in breast tumors can be explained partly by some of the above-mentioned tumor suppressor gene mutations in genes responsible for genome integrity, such as BRCA1, BRCA2 and TP53, and also by amplification and overexpression of the MYC gene, which encodes a transcriptional factor important for cell proliferation, immortalization and apoptosis, and of the STK15 gene, which encodes serine threonine protein kinase, important for chromosome segregation. This review will focus on genome instability in breast cancer and on mutations in tumor suppressor genes.

**BRCA1 and BRCA2 and autosomal-dominant familial breast cancer**

Germ-line mutations in the BRCA1 and BRCA2 genes markedly increase the risk of developing breast cancer (4, 5). These mutations are an excellent example of Mendelian inheritance of susceptibility to a common, genetically complex, adult-onset disease. Initial risk estimates in carriers of predisposing mutations are based on high-risk families that are not representative of all carriers; if calculated by age 70 years, breast cancer risk is 84% and 87% in BRCA1 and BRCA2 carriers, respectively (6). A definite breast cancer risk figure for carriers of BRCA1 or BRCA2 mutation among women who have at least one relative with breast cancer was provided recently by the New York Breast Cancer Study Group (7). The relatives were genotyped directly, and analysis was based on genetically confirmed carriers with validated diagnoses. These data show that female carriers have an 82% lifetime risk of developing breast cancer, a risk which is similar to that observed in families with many cases. In addition, cancer risk for BRCA1 and BRCA2 carriers has increased markedly in recent generations, suggesting that nongenetic factors can affect risk, even in the context of a significant inherited predisposition (7). These findings have clinical relevance to women carrying BRCA1 and BRCA2 mutations. In contrast, studies in less selected popula-
tions show substantially lower incidence of breast cancer. Many studies identified BRCA1 and BRCA2 families through genetic testing of index breast cancer cases, regardless of whether the patients had a family history of cancer. A meta-analysis of such studies estimated the risk of breast cancer by age 70 years as 65% in BRCA1 carriers and 45% in BRCA2 carriers (8). It seems clear that precise risk with respect to an individual is difficult to estimate, since both genetic background/modifyng genes and environmental factors are involved. Nonetheless, knowledge of penetrance within a given family would be helpful when estimating the risk in each case.

Studies on founder mutations provide the opportunity to estimate risk in groups of individuals carrying a single mutation within the same gene. The 999del5 mutation in BRCA2 is a truncation mutation; it is defined as a founder mutation and is found in 7% of Icelandic breast cancer patients (9, 10). In addition, this mutation is frequent in male breast cancer (40%) and in other cancer types such as ovary and prostate cancer (9, 10). This founder mutation, like founder mutations found in the BRCA1 gene in Ashkenazi Jews and other populations, gives an excellent opportunity to study risk and penetrance. The risk estimate of the Icelandic BRCA2 999del5 mutation is 17% at the age of 50 years and 37% at 70 years (10), and the relative risk of breast cancer in a first-degree relative is 7.55 (11). Risk in different breast cancer patient subgroups has also been analyzed (12).

BRCA1 and BRCA2 genes are rarely mutated at the somatic level in sporadic breast cancer. BRCA1 is frequently deleted and expression is decreased in breast tumors, although not always by a known mechanism (13, 14). Nevertheless, alternative downregulation mechanisms of the genes in sporadic breast cancer have been reported, such as hypermethylation at the BRCA1 locus and amplification of EWSY, a negative regulator of Brca2 (15–18). EWSY has functions associated with DNA repair and transcriptional regulation (18). The EWSY gene, located at chromosome 11q13.5, is amplified in 13% of breast cancers, and this amplification is associated with worse patient survival, particularly in node-negative breast cancer (18).

The Brca1 and Brca2 proteins are multifunctional proteins involved in complex protein–protein interactions, DNA repair, DNA recombination, transcription and cell-cycle checkpoint control. They participate in BASC (Brca1-associated genome surveillance complex). The factors binding to Brca1 are both specific transcriptional factors and factors involved in chromatin remodelling, suggesting both positive and negative regulation of transcription. Brca1 is phosphorylated by several kinases upon DNA damage (19). Mainly active in the S and G2 phases of the cell cycle, the Brca1 and Brca2 proteins are essential for preserving chromosome structure, suggesting that, in their role as tumor suppressors, they behave as caretakers, suppressing genome instability. While the role of Brca1 and Brca2 in homologous recombination repair of double-strand DNA breaks is well established, less is known about whether they are regulators of cell-cycle events independently of their role in DNA repair. Intensive studies have been carried out on Brca1 and Brca2 loss of function in breast tumor pathogenesis, but more work is needed to clarify their role in the biology of epithelial tissues.

Molecular and pathological data suggest a difference between BRCA1- and BRCA2-associated tumors, and also between them and sporadic tumors. BRCA1 and BRCA2 tumors are more aggressive than sporadic tumors, as indicated by S phase, mitosis, aneuploidy, genomic instability and pathological appearance (19, 20). Other characteristics of BRCA1 tumors are low estrogen receptor content, elevated lymphocyte infiltration and appearance of medullary phenotype (21, 22). The gross genomic instability detected in BRCA1 and BRCA2 tumors is consistent with their documented function in DNA repair (23, 24). Moreover, the chromosome aberration profiles of BRCA1 and BRCA2 tumors differ from each other and from other breast cancers, suggesting that specific genetic pathways operate in the progression of these inherited tumors (23, 24).

Functional support of the discrimination between BRCA1, BRCA2 and sporadic breast tumors is also evident from genome-wide gene expression profiles (25). Extensive studies in knockout mice have been helpful in understanding the role and function of Brca1 and Brca2. In general, multiple genetic alterations occur in mammary tumors of the mice, similar to those detected in human breast cancer (26).

Cell-cycle checkpoint genes ATM, CHK2 and TP53 mutated in breast cancer

The biochemical pathways of Atm, Chk2 and p53 overlap. Atm and Chk2 are kinases involved in stabilizing the p53 transcriptional factor (27, 28). Atm can also induce a homodimer formation and activation of Chk2. Mutations in ATM, CHK2 and TP53
are associated with family syndromes where breast cancer is one of the phenotypes that can appear in individuals.

Ataxia-telangiectasia is an autosomal-recessive disease. The penetrance of different ATM sequence variants, and the exact magnitude of breast cancer risk, are still a matter of consideration. Penetrance of defective ATM in heterozygotes is manifested by sensitivity to ionizing radiation and radiomimetic chemicals in cells in culture, and increased risk of cancer, including breast cancer (29, 30). Ataxia-telangiectasia cells are defective in cell-cycle checkpoints that are usually activated by DNA damage, as demonstrated by radioresistant DNA synthesis and lack of normal radiation-induced arrest. The data on elevated breast cancer in ATM mutation carriers have been controversial. An association of breast cancer with the truncation mutations of ATM that predominate in ataxia-telangiectasia has not been confirmed, but recent data suggest an association of breast cancer with ATM missense mutations (31, 32). This finding is further supported by functional studies, since the missense mutants of ATM show dominant-negative effects (31). Although conclusive data on the risk of breast cancer in mutation carriers are lacking, a recent study suggests that the attributable risk of mutations in the ATM gene is 13% in women with breast cancer (32).

TP53 is somatically mutated in many tumor types and in about 30% of breast tumors (33). Germ-line mutations have been described in Li-Fraumeni cancer syndrome, where one of the increased susceptibility disease phenotypes is breast cancer (34, 35). TP53 encodes the p53 transcription factor important for cell-cycle checkpoints and induction of apoptosis. One well characterized pathway in G1 cell-cycle checkpoint activation involves transcriptional activation and subsequent expression of the cyclin-dependent kinase inhibitor p21. Upon DNA damage or other environmental stress in the cell, p53 accumulates and transactivates the gene encoding the p21 inhibitory protein, and the cell halts in the G1 phase of the cell cycle. A well known pathway of p53 induction of apoptosis is by transcriptional activation of several genes inducing cell death, including one which encodes Bax. A feasible model is that p53 is important for blocking the cell from entering the S phase of the cell cycle upon cell damage and for inducing apoptosis if the damage is overwhelming. With failure of p53 normal function due to mutation, there is a risk of accumulation of genetic instability and mutations in additional genes.

TP53 somatic mutations have been associated with reduced survival of breast cancer patients (36). The majority of TP53 mutations are missense, in contrast to mutations in several other tumor suppressor genes, where the majority of mutations result in a truncated protein. Some of the TP53 mutations are dominant negative, presumably due to incompetent transcription activity, if one or more mutant copies are included in the p53 tetrameric form. About 1,400 TP53 mutations in relation to breast cancer are listed in the IARC database. The germ-line mutation spectrum is slightly different from the somatic pattern, in line with endogenous mutagenic processes, such as methylated cytosins or polymerase errors (33). The somatic mutation spectrum of TP53 in breast tumors is similar to that found in other cancers, with the exception of lower frequency of certain transversions known to be strongly associated with environmental carcinogens, as well as a higher frequency of transitions (33). Given the differing mutation patterns observed in different populations, environmental factors seem to affect the mutation pattern of TP53 in breast cancer (33).

Chk2 is a recent member in the increasing number of proteins that have a role in cell-cycle checkpoint signalling, and it has been demonstrated that germ-line and somatic mutations are associated with breast cancer. Although germ-line mutations in the CHK2 gene are not frequent, several have been described and many of them are associated with breast cancer in addition to other cancers. We and others have found such sequence variants to be associated with hereditary breast cancer and have concluded that these are low-penetration breast cancer susceptibility alleles with a high degree of statistical significance (37–39). Variants are common in families predisposed to combined breast, colon and stomach cancer (38, 40, 41). Population-based studies of the 1100delC mutation in CHK2 indicate that it is found in 1–5% of different populations, with a 2-fold and 10-fold increased risk of breast cancer development suggested in females and males, respectively (39–41). Recent publications on the involvement of CHK2 defects in breast cancer indicate distinct modes of action for different genetic variants of this tumor suppressor, pioneering examples of low-penetration breast cancer predisposing genes, of which CHK2 probably represents only the tip of the iceberg. Since these are low-penetration breast cancer variants, testing for them alone would probably have little predictive value for individual patients. However, it may even-
tually allow risk assessment for breast cancer at the population or even individual level as a part of a broader panel of analogous variants suitable for profiling and screening, thereby proving useful for chemoprevention or lifestyle counselling.

Somatic mutations of CHK2 in breast cancer are rare, but they are more frequent in a BRCA1 germ-line mutation background than in sporadic cases. This pattern is similar to the elevated p53 somatic mutations in the same patient group (42). A high frequency of codon 163 mutation of TP53 is detected in breast tumors, particularly in a BRCA1 mutational background (43–45). The mutation spectrum of TP53 in BRCA1 and BRCA2 carriers differs from that of sporadic tumors, which is consistent with a repair function of Brca1 and Brca2 (46). Even though TP53 mutations are not as frequent in BRCA2 mutation carriers, the p53 pathway is deregulated by another mechanism in addition to mutation (44–47).

It is reasonable to expect that the p53 pathway is activated in the DNA-damaged background of cells due to deficient Brca1 or Brca2 function. Also, reduced expression of FHIT due to deletions has been reported to be high in familial, as opposed to sporadic, breast cancer (48, 49). The relevance of these FHIT alterations for breast cancer pathogenesis is not clear, but they have been associated with reduced patient survival and genome instability (49).

It can be hypothesized that in the early stage of BRCA1 or BRCA2 pathogenesis, cells progress through a preliminary crisis phase with massive apoptosis due to accumulated genetic changes (Fig. 1). Additional gene alterations, for instance in TP53, CHK2 or FHIT, rescue the cell from this senescence phase, and progression is towards reduced apoptosis, enhanced cell growth and malignant phenotype. The p53 and Chk2 mutants and Fhit deletions are presumably selected during the malignant progression in the genetic background of BRCA1- and BRCA2-associated tumors (Fig. 1). In line with the biochemical function of p53 and Chk2, downregulation of their activity would give cells with DNA damage, normally targeted for apoptosis, a growth advantage. How the biochemical function of Fhit is linked to DNA damage checkpoints is not as well known, but the suggested role of Fhit in cell growth and apoptosis is consistent with the idea that its downregulation may result in growth advantage and escape from apoptosis (52).

Mouse knockout experiments support the hypothesis of preliminary crisis phase, and it has been shown that inactiva-

![Fig. 1. Theoretical scheme of breast cancer progression in individuals carrying BRCA1 or BRCA2 germ-line mutation. The deactivation of BRCA1 and BRCA2 is by a two-hit mechanism in which deactivation of the second copy of the gene is somatic (refs. 50 and 51). Presumably, this leads to a preliminary phase with induction of genomic instability and activation of cell-cycle checkpoints and apoptosis. Additional somatic defects (TP53, CHK2 and FHIT in human tumors and p53, Bub1 and Mad3L in mouse tumors) could rescue the cells from checkpoint control and apoptosis phase, resulting in growth advantage for the breast tumor cell (see text for references and details).](image)

**Opportunities for targeted therapy**

The central role of the DNA damage checkpoint and p53 pathways in tumor suppression makes these pathways prime targets for improved cancer therapy. Conventional radiotherapy and much chemotherapy is known to function via the p53 pathways. Therefore, these pathways should be considered in the development of novel therapeutic strategies that could have synergistic effects when used in conjunction with conventional therapy.
Several types of therapeutic strategies would affect the dysfunctional signalling pathways of cell-cycle checkpoint control in breast cancer, i.e., restoration of tumor suppressor gene stability and activity, inhibition of tumor suppressor gene activity in order to trigger apoptosis of the cancer cell due to increased genomic instability, and inhibition of the tumor suppressor gene in order to increase sensitivity to radiation and DNA-damaging drugs. Defects in apoptosis and cell-cycle checkpoint control not only affect tumor development but also contribute to multidrug resistance (55, 56). Many tumors respond poorly to conventional cancer therapy (i.e., chemotherapeutic drugs, radiotherapy). This may in many cases be due to inactivation of critical DNA damage checkpoints, e.g., p53 and Chk2. Restoration of such checkpoint proteins may increase the sensitivity of tumor cells to currently used cancer therapy. Multiple types of cells lacking CHK2 function show resistance to radiation-induced apoptosis (27, 28). Since several therapies are based on induction of apoptosis in cancer cells, therapeutic alternatives could be considered in cases with ATM, CHK2 and TP53 mutations. Further exploration is also required to determine whether chemical inhibition of Chk2 during radiation may protect sensitive tissues from the side-effects of chemotherapy or drugs that cause double-stranded breaks in DNA. It is important to define suitable inhibitors of Chk2 and to test whether this strategy can be applied without increasing the incidence of tumors. Identification of new small-molecule inhibitors of Chk2, and design and validation of novel strategies of checkpoint modulation, combined with the traditional radiation and chemotherapy modalities, hold promise for improved treatment of breast cancer. The well regulated degradation pathway of p53 can be altered in order to stabilize it as a drug treatment strategy. In addition, post-translational modifications can enhance the binding of p53 to DNA, presumably by interfering with folding. Such conformational changes can be achieved by antibodies, peptides and drugs. Some recent developments in novel anticancer drugs restore DNA damage checkpoints and p53 tumor suppressor function (57). Small molecules have been developed that can either reactivate mutant p53 or activate wild-type p53 in human tumor cells, thereby triggering cell death (57). For both types of molecules, antitumor effects in vivo have been demonstrated with systemic administration, but improvements have to be developed on targeting delivery to the breast cancer cells in patients. These molecules could be optimized by screening and testing structural analogs, with subsequent testing in clinical trials. However, the use of small molecules presents a formidable challenge because of the extensive interfaces that underlie their molecular interactions.

Due to the radiosensitivity of ATM patients, it is expected that radiotherapy or radiomimetic chemotherapeutic agents may be particularly effective. The response to different therapeutic agents of tumors with somatic deletions of ATM, or tumors in individuals with ATM sequence variants, should also be addressed.

Genomic instability in breast tumor cells

Both chromosome instability and microsatellite instability have been demonstrated in breast tumors. Microsatellite instability is only detected in a minority of breast tumors, or fewer than 2% (58). Microsatellite instability seems to be mainly due to occasional somatic events, but has also been found in breast tumors of individuals in HNPCC families (58, 59).

Chromosome instability is demonstrated in the majority of breast tumors (about 70%) by aneuploidy, deletions, amplifications and end-to-end fusions. Alterations at chromosome regions are frequently detected in tumors with an unstable genome, while alterations at other chromosomes seem to be unrelated to genetic instability. One would expect frequent losses of certain chromosome regions which are not associated with genetic instability to involve a tumor suppressor gene, a loss which gives growth advantage to the cell, resulting in clonal expansion. The situation is not as clear when losses at certain chromosome regions are associated with genetic instability. Losses at these chromosome regions may reflect the unstable nature of the breast cancer genome and could therefore serve as markers for genetic instability. This does not exclude the growth advantage of the breast tumor cells, due to tumor suppressor gene elision, from being of importance for the clonal selection of these chromosomal losses.

We analyzed the genome of breast tumors using microsatellite markers (1). It is of particular interest that deletions of chromosomes 3p, 6q and 8p are associated with unstable genome and aneuploidy, together with elevated S phase and reduced patient survival (60–62). The genome of lobular breast cancer seems to be more stable in general.
than the genome of ductal breast cancer, with the exception of chromosome 16q, where the CDH1 gene is located, encoding E-cadherin (63, 64). Somatic mutations in this gene are specific to the lobular type of breast cancer (63, 65).

Although the reasons for chromosome instability in breast tumors are not well understood, explanations can partly be obtained from deficient control of genes controlling cell proliferation, apoptosis, DNA repair or chromosome segregation (Fig. 2). Among these genes are TP53, MYC, STK15, BRCA1 and BRCA2. Since TP53 is considered to be the guardian of genome integrity, it is not surprising that genome instability is associated with TP53 mutations. This is confirmed by some, but not all, studies (47, 66, 67).

Telomerase is of importance for cell immortalization, and it can establish genetic instability that favors growth advantage of tumor cells. Overexpression of telomerase is detected in a majority of breast cancers (68). In mouse models in which telomerase is lacking in a p53 heterozygous background, end-joining and unequal translocations between chromosomes are frequent, but these are not detected in mice with long telomeres (69). The analysis of the genome in mice tumors lacking telomerase shows that uneven translocations lead to a high number of aberrations on chromosome regions not seen in tumors with normal telomeres (70). Aneuploidization in breast cancer is considered to be a late genetic event, and it is preceded by oncogene amplifications and chromosomal rearrangements (71). The effects of MYC on increased chromosome instability have been documented (72). MYC can bind to the promoter of the hTERT gene and activate transcriptional expression, resulting in elevated telomerase (73). MYC seems to affect tumor pathogenesis in several ways, including increased proliferation and immortalization of the cancer cells and induction of chromosome instability. As genomic instability can result in an increased number of gene abnormalities by growth selection, some of these gene abnormalities can induce development of further genomic instability. Perhaps an autonomous loop of events is induced in breast cancer, as well as in some other cancer types, with gene abnormalities inducing chromosome instability and the induced instability giving rise to further gene abnormalities (Fig. 2). There must be some equilibrium in the amount and speed of such events to favor appropriate growth selection for the cancer cell; too much instability could result in poor cell survival.

The STK15 gene encodes Aurora A serine/threonine kinase, which has been shown to bind to centrosomes and is important in controlling their number and the segregation of correct chromosomes to the daughter cells during mitosis (74). Amplification of STK15 and overexpression of Aurora A increase centrosome number, chromosome instability and
Table II: Frequency of loss of heterozygosity of sporadic and BRCA2 tumors at several aphidicolin-sensitive fragile sites and one stable site (chromosome 8p). The numbers in parentheses (1, 2 and 3) denote how common the fragility is in the human genome, in order of frequency. Information in the table is based on results from refs. 23, 49, 60-62 and 64.

<table>
<thead>
<tr>
<th>Fragile site</th>
<th>Chromosome location</th>
<th>Loss of heterozygosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRA3B (1)</td>
<td>3p14.2</td>
<td>24%/76%</td>
</tr>
<tr>
<td>FRA6E (3)</td>
<td>6q26</td>
<td>37%/75%</td>
</tr>
<tr>
<td>Stable</td>
<td>8p</td>
<td>50%/78%</td>
</tr>
<tr>
<td>FRA16D (2)</td>
<td>16q23</td>
<td>60%/61%</td>
</tr>
</tbody>
</table>

progression towards breast cancer phenotype (75, 76). Chromosome instability values are elevated in breast tumors in relation to STK15 expression (76). Furthermore, STK15 expression is associated with histological grade and steroid hormone receptors, an observation which suggests that STK15 may serve as a marker of poor prognosis and resistance to endocrine therapy (76).

Genomic instability is high in some hereditary breast cancers, particularly in tumors of BRCA1 and BRCA2 mutation carriers, a finding which is in line with the role of the gene products in DNA repair (23, 24). Relatively high frequency of alterations at FHT, located at FRA3B, which is the most common fragile site in the genome, is detected in sporadic tumors, and at a much higher frequency, in BRCA2 tumors (49). This could merely reflect the unstable nature of the fragile site in the breast tumor cell, but it could also be that FHT plays a tumor suppressor role. Another possibility is that the fragile sites in the genome may be more sensitive to alterations in a BRCA1 and BRCA2 mutation background, due to the DNA repair role of Brca1 and Brca2. This explanation could be part of the story, but not the whole story. When comparing our loss of heterozygosity data from chromosomes that carry the most common fragile sites in the genome, FRA3B, FRA16D and FRA6E, only chromosomes 3p and 6q, but not chromosome 16q, show elevated loss of heterozygosity in BRCA2-associated tumors compared to sporadic breast tumors (Table II). Furthermore, there is higher loss of heterozygosity at chromosome 8p in BRCA2-associated tumors compared to sporadic tumors, even though this chromosome region does not contain a defined fragile site (62).

Conclusions

In breast cancer, the somatic changes are distributed among several genes, whereas the frequency of single-gene alterations is low. Breast cancer is mainly a sporadic disease. Highly penetrant alleles only explain a small fraction of breast cancer and the role of low-penetration alleles in a certain genetic background remains a puzzle. Transgenic and knockout mouse models have been used to study the progression of breast cancer in relation to genetic defects, and recent information on tumor reversibility or regression has been obtained from conditional gene expression models (77, 78). These new models provide an excellent opportunity for developing new drug strategies affecting different steps in tumor progression and regression. Some therapeutic intervention strategies include disarming or activation of genes in order to restore activity or affect cell turnover. However, before these strategies can be used, it is crucial to establish the conditions governing these factors.

Even though TP53 alterations only partly explain the malignant phenotype in the breast, in a fraction of tumors, the mutations are well characterized and the role of p53 as a tumor suppressor is well documented. An exciting development in progress concerns restoring p53 stability and activity using small molecules. Germ-line mutations are detected in several genes, where BRCA1 and BRCA2 are the major breast cancer susceptibility genes. TP53 is to a lesser extent, and germ-line variants of CHK2, the newest member of tumor suppressor genes in breast cancer pathogenesis, seem to be of low penetrance. The estimation of breast cancer risk of individuals with germ-line mutations has been controversial, and both environmental factors and genetic background are of importance. Further studies will doubtless elucidate new genes of interest in normal and transformed cells of the breast epithelium and reveal the function of their protein products in normal and malignant growth. The clinical importance of this genetic information is emerging. Molecular pathways of cell-cycle checkpoint regulators in normal cells should be studied further, and it should be determined to what extent these checkpoints are inactivated in tumor cells. The type of lesion can be correlated to the response of tumor cells to chemotherapeutic drugs and irradiation. Improved understanding of the gene function in relation to tumor cell turnover and resistance to therapy will be important for effective breast cancer management. Molecular and genetic data have
recently become useful in breast cancer treatment, and this field is already approaching pharmacogenomics. With increasing new knowledge on the gene mutations and genomics of breast cancer cells, further development in this direction should be expected in the near future. One application of genomic data as a marker of response to breast cancer therapy is represented by gene expression analysis using microarray methodology (79). Patient outcomes can be compared to the microarray profiles before and after treatment. The relative expression of several genes in candidate subjects for clinical trials can be used as a marker of sensitivity or resistance to chemotherapeutic drugs, kinase inhibitors or other novel strategies, allowing only sensitive tumors to be treated.

References


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