Molecular genetics of breast cancer progression

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Somatic changes in the genome of breast cancer cells include amplifications, deletions and gene mutations. Several chromosome regions harboring known oncogenes are found amplified in breast tumors. Despite the high number of chromosome regions deleted in breast tumors the functional relationship to known genes at these locations and cancer growth is mainly undiscovered. Mutations in two tumor suppressor genes (TSG) have been described in a subset of breast carcinomas. These TSG are the TP53, encoding the p53 transcription factor, and the CDH1, encoding the cadherin cell adhesion molecule. Breast tumors of patients with a germ-line mutation in the BRCA1 or BRCA2 gene have an increase of additional genetic defects compared with sporadic breast tumors. This higher frequency of genetic aberrations could pinpoint genes that selectively promote tumor progression in individuals predisposed to breast cancer due to BRCA1 or BRCA2 germ-line mutations. Accumulation of somatic genetic changes during tumor progression may follow a specific and more aggressive pathway of chromosome damage in these individuals. Although the sequence of molecular events in the progression of breast tumor is poorly understood the detected genetic alterations fit the model of multistep carcinogenesis in both sporadic and hereditary breast cancer. This review will focus on the genetic lesions within the breast cancer cell.

Key words: breast cancer / tumor progression / oncogene / tumor suppressor gene / amplification / deletion / mutation / loss of heterozygosity

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Introduction

A complex and heterogeneous set of genetic alterations is involved in the etiology of breast cancer.1,2 It is believed that breast cancer, like most other cancers, has its origin in one cell which through a number of different events becomes malignant. Later additional events lead to the development of different clones with different characteristics. Few genes have been found mutated in breast tumors but large numbers of chromosome arms with so far unidentified genes are affected. These aberrations include both DNA amplifications and deletions (Table 1). The detected genetic abnormalities in breast tumors are amplification of oncogenes (MYC, ERBB2 and CCND1), mutation of the TSGs TP53 and CDH1 and loss of heterozygosity (LOH) at chromosomes 1, 3p, 6q, 7q, 8p, 9p, 10q, 11, 13q, 16q, 17, 18q, 22q and X. The LOH may correspond to losses or inactivation of TSGs. Several genetic defects have been detected in premalignant breast tissues, suggesting that TSGs might have a role in their pathogenesis. The sequential steps of molecular lesions during breast tumor progression are poorly understood.

Detection of chromosome abnormalities in breast tumors is based on several methods, such as; flow cytometry, cytogenetic studies, FISH, LOH loss of heterozygosity, CGH comparative genome hybridization. These methods have both advantages and disadvantages. Frequently used markers in LOH studies can give problems in distinguishing between deletions and amplifications. This is especially difficult if the method is based on PCR, but PCR has other advantages, such as utilization of a small sample, and a huge number of highly polymorphic markers tightly distributed over the genome, allowing dense mapping. The CGH and some other methods allow the genome to be screened in a single experiment with respect to losses and gains of genetic material in the tumors, but the resolution power is less than by using molecular markers with well defined locations.

DNA amplification in breast tumors

Several chromosome regions have been documented to carry a gene amplification in breast tumors. These are chromosome 1q, where no strong gene candidate
Table 1. Sites of deletions, amplifications and gene mutations in breast neoplasia

<table>
<thead>
<tr>
<th>Chromosomal locations</th>
<th>Deletion/amplification</th>
<th>% Of tumors</th>
<th>Mutated/amplified gene</th>
<th>Possible TSG</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p</td>
<td>Deletion</td>
<td>36–54%</td>
<td></td>
<td></td>
<td>3–7</td>
</tr>
<tr>
<td>1q</td>
<td>Deletion/amplification</td>
<td>50–67%</td>
<td></td>
<td></td>
<td>4,6,8</td>
</tr>
<tr>
<td>3p</td>
<td>Deletion</td>
<td>34–45%</td>
<td></td>
<td></td>
<td>9,10</td>
</tr>
<tr>
<td>6q</td>
<td>Deletion</td>
<td>19–62%</td>
<td></td>
<td>FHT</td>
<td>11–15</td>
</tr>
<tr>
<td>7q</td>
<td>Deletion</td>
<td>0–84%</td>
<td></td>
<td></td>
<td>16–19</td>
</tr>
<tr>
<td>8p</td>
<td>Deletion</td>
<td>47–58%</td>
<td></td>
<td></td>
<td>20,21</td>
</tr>
<tr>
<td>8q</td>
<td>Amplification</td>
<td>15%</td>
<td>MYC*</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>9p</td>
<td>Deletion</td>
<td>38–58%</td>
<td></td>
<td></td>
<td>23,24</td>
</tr>
<tr>
<td>10q</td>
<td>Deletion</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>11q</td>
<td>Deletion/amplification</td>
<td>23–59%</td>
<td>CCND1*</td>
<td></td>
<td>26–31</td>
</tr>
<tr>
<td>13q</td>
<td>Deletion</td>
<td>33–75%</td>
<td>BRCA2†</td>
<td>BRCA2, RB1</td>
<td>32–35</td>
</tr>
<tr>
<td>16q</td>
<td>Deletion</td>
<td>57–85%</td>
<td>ECDH†</td>
<td></td>
<td>36–39</td>
</tr>
<tr>
<td>17p</td>
<td>Deletion</td>
<td>41–73%</td>
<td>TP53†</td>
<td></td>
<td>40–42</td>
</tr>
<tr>
<td>17q</td>
<td>Deletion/amplification</td>
<td>30–70%</td>
<td>BRCA1††/ERBB2*</td>
<td>BRCA1</td>
<td>43,44</td>
</tr>
<tr>
<td>18q</td>
<td>Deletion</td>
<td>15–65%</td>
<td></td>
<td></td>
<td>45–48</td>
</tr>
<tr>
<td>20q</td>
<td>Amplification</td>
<td>5–26%</td>
<td></td>
<td></td>
<td>49–52</td>
</tr>
<tr>
<td>22q</td>
<td>Deletion</td>
<td>40%</td>
<td></td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td>48%</td>
<td></td>
<td></td>
<td>54</td>
</tr>
</tbody>
</table>

*Amplified gene.
†Mutated gene.
‡Germ-line mutations, somatic mutations are rare.

has been detected, chromosome 8q24, harboring the MYC oncogene, chromosome 11q, harboring the CCND1 gene, chromosome 17q, harboring the HER2 gene and chromosome 20q, where no strong gene candidate has been detected.8,22,40,50,55 In general only a subset of invasive breast cancer shows amplification at these regions, ranging from 15 to 20%. Nonetheless, elevated expression of CCND1 and HER2 is detected in primary breast carcinoma, when examined immunohistochemically, in a larger proportion of cases.58–62 The myc oncoprotein is a transcriptional regulator and its expression is strongly associated with cell proliferation and cell differentiation. The CCND1 gene encodes the cyclinD1, an important regulatory molecule of the cell cycle. The Her2 protein is a transmembrane receptor with homology to the epidermal growth factor receptor and contains intrinsic tyrosine kinase activity. Although the biochemical role of these oncoproteins is fairly well characterized, their exact role in breast cancer is poorly defined.

**Mutated genes in breast tumors**

**Tp53**

The TP53 gene encodes a transcription factor, p53, that binds as a tetramer to a specific DNA sequence. The spectrum of TP53 mutations detected in breast tumors with respect to epidemiology has recently been reviewed.63 This TSG is the most frequently mutated gene in human tumors; approximately 50% of tumors have a mutation in this gene. In breast cancer this frequency is slightly lower; 15–34% of tumors have a mutation in the TP53 gene in most ethnic groups, but a higher proportion in certain regions of Japan, or 56–71%.63 The majority of TP53 mutations are missense, in contrast to mutations in several other TSGs, where the majority of mutations result in a truncated protein. Some of the TP53 mutations are dominant negative. The p53 protein is important in the G1 checkpoint of the cell cycle and one described pathway involves the cyclin-dependent kinase inhibitor (CDK) p21.64–67 Upon DNA damage or other stress environment in the cell, p53 accumulates, transactivates the gene encoding the p21 inhibitory protein, and the cell halts in G1 phase of the cell cycle. P53 can even induce apoptosis, and one known pathway is by transcriptional activation of the gene encoding Bax1, an inducer of apoptosis.68 Interaction of p53 with proteins important for DNA repair has been reported, but functional evidence for a role in DNA repair is still lacking. 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 induces apoptosis if the damage is over-
whelming. By failure of \( p53 \) normal function due to mutation there is a risk of accumulation of genomic instability and mutations in additional genes. Germ-line mutations are found in family members of the Li–Fraumeni syndrome, and individuals within these families have inherited elevated risk of several cancer types, including breast cancer.\(^{69}\)

**E-cadherin and lobular breast carcinoma**

The \( E\text{-cadherin} \) gene, \( CDH1 \), has been found mutated in a large portion of lobular breast tumors.\(^{70–72}\) The gene is located on chromosome 16q22.1, a region frequently deleted in breast tumors. The \( CDH1 \) behaves like a typical TSG in lobular breast cancer, with one copy of the gene deleted, while the other copy is mutated. No mutations have been detected in the \( CDH1 \) gene in tumors of the ductal histological type. This is the clearest evidence of molecular difference in the two histological types of breast cancer although \( TP53 \) mutations are predominantly in tumors of the ductal histological type and other differences are also detected at chromosome level (see later). Reduced expression of \( E\text{-cadherin} \) has been found in both lobular and ductal breast cancer.\(^{73,74}\) Deletions of chromosome 16q22.1 are frequent in ductal carcinoma and this is the highest documented loss of a chromosome region in sporadic breast cancer.\(^{38}\) It seems that the \( CDH1 \) gene does not behave like a typical TSG in ductal breast cancer with respect to the Knudson’s two-hit model.\(^{75}\) Two explanations of this difference are possible: (1) either a gene other than \( CDH1 \) is the target of the 16q22.1 deletions in ductal compared to lobular carcinoma of the breast; or (2) the progression of ductal carcinoma is more sensitive to loss of one copy of the \( CDH1 \) gene, and corresponding reduction of expression, than lobular breast cancer, where both copies need to be knocked out for further progression to malignant invasive growth.

The \( E\text{-cadherin} \) protein is a calcium-dependent cell adhesion molecule, involved in homophilic cell–cell interactions. Loss of function of \( E\text{-cadherin} \) seems to facilitate malignant invasive growth of breast cancer cells. Other cancer types of epithelial origin, like colon cancer also exhibit reduced expression of \( E\text{-cadherin} \). Germ-line mutations in the \( E\text{-cadherin} \) gene are found in hereditary gastric cancer.\(^{76}\)

**The estrogen receptor gene**

Mutations and abnormal transcripts of the estrogen receptor gene (\( ESR \)) have been reported in tumors of the breast (recently reviewed by Murphy \textit{et al}, 1997 and Dowsett \textit{et al}, 1997).\(^{77,78}\) The majority of the work on variant mRNA has concentrated on their expression in malignant tissues, but it has become apparent that many of them also exist in normal tissues.\(^{79,80}\) Several reports are consistent with the involvement of variant \( ER \)s in the establishment of certain pathological phenotypes of the breast and it has been suggested that some of the variant \( ER \)s have a role in breast tumorigenesis.\(^{81–83}\) Still, the physiological and pathological function of variant \( ER \) proteins remains unclear. Although it has been suggested that \( ER \) mutants may contribute to hormone resistance, direct evidence of an association of \( ER \) mutants in breast carcinomas with hormone resistance does not exist.\(^{82,85}\) The studies of germ-line mutations of the \( ESR \) gene do not support the hypothesis that \( ER \) alterations are a major factor in breast cancer risk.\(^{84}\) The fundamental question if \( ER \) mRNA variants have physiological or pathological significance remains conclusively unanswered. Although point mutations in \( ER \) can have profound effects on protein function in model systems, their relevance to breast cancer appears to be slight, in terms of risk of development and phenotype of established tumors.

**The PTEN gene**

The \( PTEN \) gene encodes a protein tyrosine phosphatase with homology to tensin. Somatic mutations in the \( PTEN \) gene are rare in breast tumors.\(^{85,86}\) Germ-line mutations in the \( PTEN \) gene are responsible for Cowden disease (CD).\(^{87}\) Germ-line mutations in the \( PTEN \) gene predispose to breast cancer in association with CD.\(^{87}\)

**BRCA1 and BRCA2 genes**

Mutations in the \( BRCA1 \) and \( BRCA2 \) genes are rare at somatic level but germ-line mutations in these genes predispose to breast cancer.\(^{88–91}\) An elevation of deletions and amplifications at several chromosome arms in tumors of \( BRCA1 \) and \( BRCA2 \) carriers compared to tumors from individuals without this mutation have been reported.\(^{92–95}\) A genome-wide search for the chromosome changes in tumors of \( BRCA1 \) and \( BRCA2 \) carriers by CGH demonstrated a higher frequency of aberrations at several chromosome arms compared to sporadic tumors.\(^{95}\) These results suggested a specific tumor progression path-
Figure 1. Major somatic changes in sporadic tumors (A), tumors from individuals carrying a germ-line mutation in the *BRCA1* gene (B), and tumors from individuals carrying germ-line mutations in the *BRCA2* gene (C). Alterations found at higher frequency in *BRCA1* or *BRCA2* tumors are characterized by bold numbers and letters. This figure is based on results from refs 92–98,104,105,108. The order of chromosome alterations is mostly unknown but some of them have been reported to appear in premalignant tumor growth (see text). In the case of *BRCA1* and *BRCA2* it is not clear if loss of wild-type 17q and 13q, carrying the corresponding genes, respectively, must be prior to enhanced rate of losses and gains at other chromosome regions.

Figure 1. Somatic loss of the wild-type chromosome in tumors of *BRCA1* and *BRCA2* mutation carriers suggests that both alleles of the corresponding gene are inactivated in cancer, a pattern expected of a TSG. Accordingly a high frequency of loss at chromosome 17q (where the *BRCA1* gene is located) is found in tumors of individuals carrying a *BRCA1* germ-line mutation, and a high frequency of loss at chromosome 13q (where the *BRCA2* gene is located) is found in tumors of individuals carrying a *BRCA2* germ-line mutation. Earlier findings based on the loss of wild-type chromosome 13q suggested a strong selection of tumor cells with both alleles of the *BRCA2* gene being mutated. It has been shown that the loss at 13q involves the *BRCA2* gene in the majority of tumors. So far it is not clear if loss of the wild-type chromosome carrying the *BRCA1* or *BRCA2* genes, respectively, is prerequisite to enhanced risk of further chromosome alterations.

The 3p chromosome region showing elevation of 3p LOH in *BRCA2* tumors involves the *FHIT* gene at 3p21.1-p14.2. Several reports have described abnormalities in the *FHIT* gene in breast carcinomas. Furthermore, the *FHIT* gene has been shown to suppress tumorigenicity of cancer cells. The *FHIT* gene encompasses the carcinogen sensitive common fragile site, *FRA3B*.

Crook *et al* has documented an elevated proportion of *TP53* mutations in tumors from *BRCA1* carriers compared to sporadic tumors. These results suggest that loss of cell cycle checkpoint due to somatic *TP53* mutation may increase the rate of *BRCA1* tumorigenesis. Furthermore, the region at chromosome 17p harboring the *TP53* gene shows a significant elevation of LOH in *BRCA2* tumors in comparison to sporadic tumors. Knockout mouse experiments have suggested that *p53* protein is accumulating in *Brc2* defective mice and that a cell cycle checkpoint mechanism is activated due to defective *BRCA2* protein and corresponding DNA damage.

It has been suggested that accumulation of *p53* protein can reduce the malignant behavior of *BRCA2* defective tumors due to cell cycle checkpoint activation. Still, no significant elevation of *TP53* somatic mutations is detected in tumors from individuals carrying *BRCA2* germ line mutation. The growth advantage of *BRCA2* defective tumors may be enhanced if only one copy of the *TP53* gene is deleted. The association of both *Bra1* and *Bra2* proteins with the *Rad51* protein establishes a direct link between these proteins and the control of genomic integrity and stability since *Rad51* is required for meiotic and mitotic recombination events and the repair of double stranded DNA breaks. Furthermore, fibroblasts from *Bra2* knockout mice show defects in DNA repair of double stranded breaks. Defects in chromatid exchange during mitotic recombination result in numerous spontaneous chromosomal abnormalities in fibroblasts from *Bra2*
The increased number of somatic alterations at chromosome level may reflect the inability of mutated \textit{Bra}1 or \textit{Bra}2 proteins to participate in the \textit{Rad51} mediated repair. A putative model of LOH selection might be that due to improper fidelity in mitotic recombination and corresponding DNA repair, the tumors with \textit{BRCA1} or \textit{BRCA2} mutation follow a more aggressive pathway of chromosome damage than tumors without this mutation. Whether loss of additional genes is involved in the tumor progression of \textit{BRCA1} and \textit{BRCA2} carriers compared to sporadic tumors remains unsolved.

The architecture of the LOH is different in \textit{BRCA2} and sporadic tumors at some chromosome regions, as the \textit{BRCA2} tumors involve larger regions. In tumors showing loss at a given chromosome arm, specific regions can be preferably affected in \textit{BRCA1} or \textit{BRCA2} tumors in comparison to sporadic tumors. These findings may pinpoint candidate loci for the search of genes that when inactivated promote tumor progression in individuals predisposed to breast cancer due to a germ-line \textit{BRCA1} or \textit{BRCA2} mutation.

The large number of abnormal chromosomes observed in tumor cells in \textit{BRCA1} and \textit{BRCA2} individuals supports the belief that their protein product is involved in maintaining appropriate chromosome segregation and/or chromosomal repair. The high number of genetic defects that are detected in \textit{BRCA1} and \textit{BRCA2} carriers indicates that germ-line mutation of these genes results in an accelerated accumulation of secondary somatic genetic changes in the tumors. This acceleration could explain the aggressive phenotype of tumor growth in tumors from \textit{BRCA2} carriers, as breast cancers associated with the \textit{BRCA2} mutation are high grade tumors with a rapid proliferation rate. The chromosome defects in \textit{BRCA1} and \textit{BRCA2} tumors are likely to be helpful in the understanding of the somatic genetic progression pathways that contribute to the development of malignancy in genetically predisposed individuals.

**Premalignant breast tissue and tumor progression**

The development of breast cancer involves many types of genes that need to be activated or inactivated in order to promote malignancy. This is a complex process, where for most tumor types the steps involved are not known. For breast cancer the sequential steps in gene alterations with respect to tumor progression are not clear, far less understood than what is currently the best example of tumor progression, colorectal carcinoma. Putative precursor stages to invasive tumor growth; such as usual ductal hyperplasia, atypical hyperplasia and cancer \textit{in situ} of the breast have been studied. The detected LOH in hyperplastic disease suggests that hyperplasias are really benign neoplasms and inactivation of TSGs participates in their development. In general the studies on \textit{in situ}, locally advanced and metastatic tumors indicate a complex pattern of alterations. Most of the genetic defects detected in invasive cancer are also detected in \textit{in situ} carcinoma. The large number of alterations that have been identified at the genetic level fit the model of multistep carcinogenesis of breast cancer. No gatekeeper gene has been proposed for breast cancer, in contrast to the \textit{APC} gene deactivation in colon cancer.

Gene amplifications appear to be a late event in tumor progression, being mainly found in tumors that have acquired genomic instability and tolerate its presence. None of the oncogenes located at amplified chromosomal region are amplified in benign breast disease. In ductal hyperplasia with or without atypia, oncogene amplification is detected at only low levels for genes located on 11q. It may be concluded that oncogene amplification is not an early event in the multistep carcinogenesis of breast cancer but emerges in ductal carcinoma \textit{in situ}. The percentage of oncogene amplification varies with the histological subtype of ductal carcinoma \textit{in situ}, for example, \textit{HER2} amplification is lower in the cribriform type compared to the comedo type. The overall rate of \textit{HER2} amplification in ductal carcinoma \textit{in situ} is decreasing towards the development of invasive ductal carcinoma and is absent in lobular carcinoma \textit{in situ} and very rare in invasive lobular carcinoma. This is different for other oncogenes; for example, \textit{CCND1} amplification is similar in ductal carcinoma \textit{in situ} and in invasive ductal carcinoma. All oncogenes show low amplification rate in invasive lobular carcinoma. These findings are consistent with the biological and histological difference between lobular and ductal carcinoma \textit{in situ}. It can be concluded that the oncogene amplification seems to be specific for a certain histological subtype; the oncogene mediated proliferation is predominantly at the intermediate state of breast cancer development and is not of obvious importance in the progression to metastatic disease.
17p, 17q and 18q. O’Connell et al reported that in hyperplasias from noncancerous breast, LOH at any given locus is rare although 37% of usual ductal hyperplasia and 42% of atypical ductal hyperplasias show losses, suggesting that the development of hyperplasias may involve many different TSGs. Apocrine cysts and papillomas of the breast are negative for LOH, while hyperplasias of usual type exhibit LOH at chromosome regions 16q, 17p and 17q and the atypical ductal hyperplasia show LOH at chromosomes 16q and 17p. In ductal carcinoma in situ from non-cancerous breasts, LOH was common, including LOH at loci on chromosome 16q, 17p and 17q, suggesting that inactivation of TSGs in these regions may be important in the development of non-invasive breast cancer. Additional LOH was detected in in situ growth in cancerous breasts, for instance on chromosome 2p, 11p and 17q, suggesting that genetic alterations in these regions may be important in the progression to invasive disease. Certain changes appear to develop early, e.g. loss at chromosome 3p, while other changes, like loss at chromosome 11p and 15, appear late in tumor progression. In a subset of tumors, loss of 11p was only observed in the invasive tumor and not the corresponding cancer in situ. High incidence of loss on chromosome 15 was detected in metastasis from the breast, suggesting that a gene on chromosome 15 contributes to the pathogenesis of metastatic breast carcinoma. In general, these findings support the idea that the putative precursors and the cancers are related. Some of the changes found in the hyperplastic, premalignant and malignant breast epithelium, like LOH of 3p, also exist in apparently normal cells adjacent to the tumor. A model to explain this is that the first mutation may occur early in breast cancer progression before clonal expansion occurs, suggesting that the molecular heterogeneity of the invasive tumor may occur at the earliest detectable stages of progression.

RER and breast cancer

Replication errors (RER) are key features of hereditary non-polyposis colorectal cancer (HNPCC) and an indicator of defects in the DNA mismatch repair genes. Screening of sporadic colorectal tumors has revealed that 12–28% of cases are of the RER+ phenotype. It has been reported that RER+ is also present in significant subsets of common, non-hereditary forms of cancer of the gastrointestinal tract, endometrium and lung and, at a lower frequency, in ovarian, brain and soft-tissue tumors. Breast cancer is rarely associated with the HNPCC phenotype. Still, Glebov et al reported a high frequency of RER+ in breast cancers from individuals with a positive family history of the disease. In their series, RER+ was seen in five of 14 (35%) cases of sporadic breast tumors and 15 of 18 (83%) in the familial tumors. A study performed on 23 invasive lobular breast carcinomas reported RER+ in nine cases (39%). Another study revealed RER+ at a single locus on chromosome 11p15.5 in 20 of 60 (33%) primary breast tumors analyzed. These results are inconsistent with the findings of Peltomaki et al who found no RER+ phenotypes in 86 breast tumors examined. In independent studies RER+ has been reported in 5% (5/93) and 8% (8/100) of primary breast tumors, respectively. Our results indicate that RER exists in 8/419 (1.9%) of primary ductal breast cancer cases at one or more chromosomal loci and that no RER was observed in 40 cases of primary lobular breast cancer. Bergthorsson et al suggested three explanations for the appearance of replication error in sporadic breast cancer. First, the instability observed is not caused by mismatch repair gene defects, but rather reflects the ability of the tumor cell. Secondly, sporadic RER+ tumors could be caused by mild mutations, and perhaps in different genes. Finally, sporadic breast tumors may have a defective mismatch repair system but need an additional environmental or genetic co-factor to result in a strong RER+ phenotype. The breast cancer cases with RER do not seem to be part of a HNPCC syndrome since a family history of colorectal cancer growth is not detected in relatives. It can be concluded that RER is a rare somatic event during human breast carcinogenesis and may be associated with progression of breast carcinomas.

Mutations and prognosis

A large number of molecular markers have been suggested to give prognostic information in breast cancer. Overexpression and/or amplification of the HER2 oncogene generally correlates with poor prognosis for breast cancer patients. The HER2 overexpression correlates with tumor grade, size, relapse rate, and lymph node and distant metastases. In addition to prognosis and prediction of response
to chemotherapeutic drugs, the HER2 oncogene may also have an important role in breast cancer therapy. Baselga et al used weekly intravenous injections of humanized monoclonal antibody against the HER2 protein in patients with overexpressing metastatic breast cancer in phase II clinical trial. Their results were not dramatic, but 11.6% overall response rate in this usually refractory subset of patients was documented.

Other molecular markers have been studied less with respect to prognosis and therapy. It has been suggested that p53 mutation is an important prognostic indicator of short-term survival for breast cancer patients. The TP53 gene mutations could be an important factor to identify node-negative patients who have a poor prognosis in the absence of adjuvant therapy. Furthermore, LOH at chromosomes 1p, 3p, 6q, 11q and 13q have been shown to be of independent prognostic value. It is not clear if this prognostic association is due to inactivation of specific TSGs or reflects the general chromosome instability in the tumor. E-cadherin expression has been shown to be associated with decreased overall survival of breast cancer patients.

Conclusions

Despite intense efforts the question remains unanswered what gene losses are involved in the pathogenesis of breast cancer located at the numerous chromosome arms altered in breast tumors. There can be little doubt that several genes from these chromosome regions are of importance, so far not characterized with respect to breast cancer pathogenesis. Although molecular function of the p53 protein is well documented, mutations in the TP53 gene are only involved in a subset of breast tumors. The E-cadherin gene is mutated in a smaller portion of breast tumors, and only in tumors of the lobular histological type. Breast tumors bear all the hallmarks of multiple gene alterations, where sequence of events is poorly understood. At present it is not possible to establish a complete model of multistep carcinogenesis in the breast. The somatic chromosome alterations are more frequent in tumors from individuals carrying BRCA1 and BRCA2 germ-line mutations than in sporadic tumors, possibly reflecting the putative role of their protein products in DNA recombination and repair. 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.

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