Abstract. The genome of breast tumour cells is considered to be unstable, as reflected by multiple chromosomal and gene abnormalities. The molecular mechanism of genomic instability progression in breast cancer is poorly understood, but recent data suggest that mutated or overexpressed proteins affect the genome in several ways, including an abnormal number of centrosomes, inefficient DNA repair and unwanted telomere maintenance. Among these proteins are p53, Brca1, Brca2, Aurora kinase A, Myc and telomerase. The involved molecular networks include co-regulation with cell cycle checkpoints. p53 has been relatively well studied and is considered to be a guardian of the genome integrity. Myc seems to affect tumour pathogenesis in several ways, including increased proliferation and immortalisation of the cancer cells and induction of genomic instability. Aurora kinase A has been shown to control the centrosome number of cells and the segregation of the correct chromosomes to the daughter cells during mitosis. Genomic instability is high in some hereditary breast cancer, particularly in tumours of Brca1- and Brca2-mutation carriers, a finding that is in line with their role in DNA repair.

Breast cancer has all the hallmarks of a multigenic disease. Although germline mutations in several genes are well known to be involved in breast tumour progression, it is largely a consequence of somatic evolution. Tumours in the breast have several characteristics of the abnormal genome, like most other cancer types. The number of chromosomes is frequently abnormal, as is the amount of DNA.

Genetic instability is typically seen in cancer cells, as predicted by Boveri, who theorized that tumours may become malignant as the result of abnormal chromosome numbers (1). Later, it was postulated that tumour progression is facilitated by genomic instability, with five to ten essential mutations to establish the malignant phenotype in most solid tumours (2). It has been demonstrated that the normal mutation rate is unable to allow for the accumulation of mutations essential for cancer progression, suggesting a need for genomic destabilisation (3). Therefore, genomic instability can be considered the underlying mechanism of tumour evolution. It also provides a means to generate the heterogeneous subpopulation of cells that typifies many solid tumours. Such heterogeneous tumours can be subpopulations of biologically-aggressive metastatic and therapy-resistant cancer cells, whose outgrowth can lead to poor clinical outcome. It has been pointed out that, for tumour progression, sufficient genomic instability is required, but it has to be within certain limits, since circumstances causing overwhelming genomic instability probably result in non-viable cells (4). Hence, "moderate" genomic instability facilitates tumour development.

The molecular basis of genomic instability in breast tumours is mostly unknown, but some recent developments have cast light on some of the pathways and networks involved. The proteins involved participate in cell growth control, cell cycle checkpoints and genome integrity (Table I). Various mechanisms have been described which lead to their deregulation or dysfunction. An epigenetic mechanism could also be of importance. Evidence for the involvement of hypomethylation in genomic instability comes from an animal model, as global reduction in methylation was shown to increase chromosomal instability in DNA methyltransferase knockout mice (5). Chromosomal instability events also correlate with the extent of global hypomethylation and the expression of MBD2/demethylase in breast cancer cell lines (6). This review, on breast cancer progression and genomic instability, is focussed on the proteins involved in DNA repair, centrosome control and telomere maintenance.

Chromosomal Instability in Breast Cancer

Genomic instability in tumours can be classified as chromosomal instability (CIN) or microsatellite instability (MIN). MIN is, in general, less frequent in tumours than CIN,
but is quite frequent in some tumours of the digestive tract. A possible explanation for this is the special turnover of cells in the digestive tract as well as exposure to the "environment", i.e., food and food digestion. MIN is mainly due to germline mutations in mismatch repair genes associated with the HNPCC syndrome, but can also be due to somatic mutations and epigenetic mechanisms. Frequent mutations are seen within short repetitive sequences in tumours with MIN, which can be within genes that might have a role in tumour progression (7). CIN is demonstrated in the majority of breast tumours (70%) by aneuploidy, deletions, amplifications and rearrangements, while MIN is rare (8).

There is a difference in genomic alterations in the two histological types of breast cancer, ductal and lobular. In general, the genome is more stable in lobular than in ductal breast cancer, with the exception of loss at chromosome arm 16q, which is detected with higher loss in lobular breast cancer (9). This may be relevant with respect to the rather frequent mutation rate of E-cadherin in lobular breast cancer, not seen in ductal breast cancer.

Alterations at certain chromosome regions are frequently detected in breast tumours with an unstable genome, while alterations at other chromosomes seem to be unrelated to genomic instability. Frequent losses at certain chromosome regions not associated with genomic instability presumably involve a tumour suppressor gene, a loss which gives growth advantage to the cell, resulting in clonal expansion. When losses at certain chromosome regions are associated with genomic instability, tumour suppressor gene involvement is not as probable. Loss at these chromosome regions could reflect the unstable nature of the breast cancer genome and, therefore, these losses could serve as markers for genomic instability. However, this does not exclude the growth advantage of the breast tumour cells, due to tumour suppressor gene elision, being of importance for the clonal selection of these chromosomal losses. We have shown that chromosome arms 3p, 6q and 8p are the regions most frequently altered in breast tumours with an unstable genome (10-18). In contrast, loss at chromosome 16q is not associated with an unstable genome, even though this is the chromosome region most frequently altered in sporadic breast cancer (18). Chromosome 16q loss also differs from chromosomal losses associated with genomic instability with regard to clinicopathological factors, i.e., while chromosome 3p, 6q and 8p losses are associated with aneuploidy, high S-phase and reduced patient survival, chromosome 16 loss does not show this association but is, in contrast, associated with low S-phase and elevated patient survival (10, 11, 17-19). No definitive answer has yet been found to the question of whether losses of 3p, 6q, 8q and some other chromosomes are only markers for genomic instability, or whether true tumour suppressor genes of importance for the malignant progression of breast cancer are located there.

The 3p region is not only frequently altered in breast cancer, but is also among the most frequently lost regions in many types of cancer (20). However, it has been a difficult region in which to find a definite tumour suppressor gene, and it has been hypothesized that combined functional loss of several tumour suppressor genes located at 3p contributes to tumour pathogenesis (21). The FHIT gene is located at the most common fragile site in the human genome at 3p14.2, FRA3B, and is frequently altered in breast cancer, particularly

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**Table I. List of proteins that are known to be involved in genomic instability in breast cancer. See further details and references in the main text.**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Biochemical function</th>
<th>Cellular function</th>
<th>Function in tumour progression</th>
<th>Abnormalities in breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aurora A</td>
<td>Kinase</td>
<td>Chromosome separation in mitosis</td>
<td>Oncoprotein</td>
<td>Gene amplification</td>
</tr>
<tr>
<td>Brca1</td>
<td>Multifunctional, including DNA repair</td>
<td>Genome integrity</td>
<td>Tumour suppressor</td>
<td>Mutation*, methylation</td>
</tr>
<tr>
<td>Brca2</td>
<td>Multifunctional, including DNA repair</td>
<td>Genome integrity</td>
<td>Tumour suppressor</td>
<td>Mutation*</td>
</tr>
<tr>
<td>Myc</td>
<td>Transcription factor</td>
<td>Cell turnover</td>
<td>Oncoprotein</td>
<td>Gene amplification</td>
</tr>
<tr>
<td>p53</td>
<td>Transcription factor</td>
<td>Genome integrity, cell turnover</td>
<td>Tumour suppressor</td>
<td>Mutation and other</td>
</tr>
<tr>
<td>Telomerase</td>
<td>Reverse transcriptase</td>
<td>Telomere maintenance</td>
<td>Cell immortalisation</td>
<td>Overexpression</td>
</tr>
</tbody>
</table>

*Germline mutations (somatic mutations are rare).
if it is of hereditary origin where DNA repair genes are mutated (22, 23). This could merely reflect the unstable nature of the fragile site in the breast tumour cell, but it is also possible that FHIT plays a tumour suppressor role. Specific Fhit pathways have not been identified, but a recent study suggested a role in homologous recombination repair (24). The question may be asked, whether the fragile sites in the genome are more sensitive to alterations in a background of germline mutations where DNA repair is dysfunctional. This could be part of the story, but not the only explanation. When comparing losses from chromosomes that carry the most common fragile sites in the genome, FRA3B, FRA16D and FRA6E, only chromosomes 3p and 6q show elevated loss in tumours associated with DNA repair dysfunction, compared to sporadic breast tumours, but not chromosome 16q (25). There is also higher loss at chromosome 8p in hereditary tumours with mutated repair genes than in sporadic tumours, even though this chromosome region does not contain a defined fragile site (17).

**DNA Repair Proteins and p53**

BRCA1 is a familial breast and ovarian cancer susceptibility gene (26). Brca1 is involved in diverse cellular events and functions, including homologous recombination DNA repair, transcriptional regulation, chromatin remodelling, cell cycle checkpoint control and ubiquitin ligation (27-30). BRCA2 is also a familial breast cancer susceptibility gene that is structurally unrelated to BRCA1, but its protein product plays a partial role in the same pathways (31). The main function of Brca2 is in homologous recombination DNA repair. Both Brca1 and Brca2 bind to Rad51, a protein implicated in recombination and double-stranded DNA repair (32). The Brca1 and Brca2 proteins participate in the BASC (Brca1-associated genome surveillance complex). They are multifunctional proteins involved in complex protein-protein interactions. The factors binding to Brca1 are both specific transcription factors and factors involved in chromatin remodelling. Brca2 is involved in loading of Rad51 to damaged DNA. Mainly active in the S- and G2-phases of the cell cycle, Brca1 and Brca2 are essential for preserving chromosome structure, suggesting that, in their role as tumour suppressors, they behave as caretakers, suppressing genomic instability. While the role of Brca1 and Brca2 in homologous recombination repair of double-strand DNA breaks is well established, more work is needed to clarify how they act as regulators of cell cycle events independently of their role in DNA repair.

Even though BRCA1 and BRCA2 are the major genes involved in hereditary breast cancer, they explain less than 10% of breast cancers. The majority of breast cancers are considered to be sporadic, where somatic mutations play a major role, or are due to the combined effects of low-penetrance sequence variants and genetic background. The mechanism of BRCA1 or BRCA2 inactivation in tumours is considered to be a double hit, a germline mutation and a somatic deletion (33, 34). However, there is a lack of experimental data to clarify whether losses of the wild-type chromosomes are a prerequisite for the non- or abnormal function of the proteins, or whether dominant negative or haplo-insufficient mechanisms can explain the original pathogenesis (35). Since germline mutations of BRCA1 and BRCA2 are relatively frequent in relation to familial breast cancer, the rarity of somatic mutations has been regarded as surprising (36, 37). This situation is different from the TP53 mutation case, where somatic mutations are relatively common and germline mutations are rare. It is not clear whether there is some disturbance of the molecular mechanism leading to somatic mutations of BRCA1 and BRCA2, or whether the mutations do not offer growth advantage to the cells. There could be a particular time-frame in normal tissue maturation, after which somatic BRCA1 and BRCA2 mutations are not selected during sporadic breast tumour development, although gene silencing mechanisms and large rearrangements and deletions can influence tumour progression. Even though somatic mutations are rare in BRCA1, it is frequently deleted and its expression is decreased in breast tumours, although not always by a known mechanism (38, 39). Hypermethylations at the promoter region may partly explain the BRCA1 down-regulation in sporadic breast tumours (40, 41).

Molecular and pathological data suggest not only a difference between BRCA1- and BRCA2-associated tumours, but also between these two and sporadic tumours. BRCA1 and BRCA2 tumours are more aggressive than sporadic tumours, as indicated by the S-phase, mitosis, aneuploidy, genomic instability and pathological appearance (42). Other characteristics of BRCA1 tumours are low ER content, elevated lymphocyte infiltration and appearance of the medullary phenotype (43, 44). The gross genomic instability detected in BRCA1 and BRCA2 tumours fits well with their documented function in DNA repair (45, 46). Moreover, the chromosome aberration profiles of BRCA1 and BRCA2 tumours differ from each other and from other breast cancers, suggesting that specific genetic pathways operate in the progression of genomic instability in these inherited tumours (45, 46). Functional support of the discrimination between BRCA1, BRCA2 and sporadic breast tumours is also evident from genome-wide gene expression profiles (47).

It can be hypothesised that, in the early stage of BRCA1 and BRCA2 pathogenesis, cells progress through a preliminary crisis phase with massive apoptosis due to the accumulation of genetic changes. Further gene alterations, for instance in TP53 or CHK2, rescue the cell from this senescence phase and progression is towards
Reduced apoptosis, enhanced cell growth and a fully malignant phenotype (48-50). Even though TP53 mutations are not as frequent in BRCA2- as in BRCA1-associated tumours, the overexpression of p53 is detected suggesting that, in BRCA2 mutation carriers, the p53 pathway is deregulated by some other mechanisms in addition to mutation (49, 51-53). Mouse knockout experiments support the hypothesis of a preliminary crisis phase and it has been shown that inactivation of p53, or other checkpoint proteins like Bub1 and Mad3L, is of importance in tumour progression in mouse cells lacking Brca (54).

TP53 is somatically mutated in about 25% of breast tumours, and germline mutations have been described in the Li-Fraumeni Syndrome, where one of the increased susceptibility disease phenotypes is breast cancer (55, 56). p53 is a quite well-defined transcription factor and its role in cell cycle checkpoint is generally accepted. In the case of DNA aberrations or other defined stress on the cell, the increased amount of p53 due to stabilization of this otherwise unstable protein is responsible for blocking the cell cycle and inducing apoptosis. Several molecular mechanisms have been described, including the promoter-directed elevated expression of p21, a protein that can block the cyclin-dependent kinase/cyclin function, resulting in halting of the cell cycle at the G1-checkpoint. Interaction of p53 with Brca1 and other proteins important for DNA repair has been reported, but functional evidence for the role of p53 in DNA repair is still limited (57). 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 inducing apoptosis if the damage is overwhelming. With failure of p53 normal function due to mutation, there is a risk of accumulation of genomic instability and mutations in additional genes.

The majority of TP53 mutations are missense, in contrast to mutations in several other tumour suppressor genes, where the majority of mutations result in a truncated protein. Some of the TP53 mutations are dominantly negative, presumably due to incompetent transcription factors, if one or more mutant copies of the protein are included in the p53 tetrameric form. The germline mutation spectrum is slightly different from the somatic pattern, in line with endogenous mutagenic processes (58). A high frequency of codon 163 mutation of TP53 is detected in breast tumours, particularly in a BRCA1 mutational background (48, 49, 51). The mutation spectrum of TP53 in BRCA1- and BRCA2-carriers is different from that of sporadic tumours, which is consistent with a repair function of Brca1 and Brca2 (49). The p53 mutants are presumably selected during malignant progression in the genetic background of BRCA1- and BRCA2-associated tumours.

Somatic and germline mutations in the CHK2 gene have been described in relation to breast cancer, suggesting that loss of Chk2 is functionally equivalent to TP53 mutations, while CHK2 mutation frequency is lower than that of TP53 mutation (50, 59, 60). Germline mutations of CHK2 have been found in Li-Fraumeni and Li-Fraumeni-like families, and by population screening of breast cancer patients (50, 59, 60). The germline variants of CHK2 analysed so far by population screening seem to be low penetrance alleles conferring susceptibility to breast cancer (60, 61). A population-based analysis of a mutation that abolishes kinase activity indicated a 5% frequency in individuals with breast cancer and a two-fold and ten-fold increased risk of breast cancer in females and males, respectively (61). Tumours in BRCA1 carriers have a relatively high frequency of somatic CHK2 mutations, as well as tumours in patients with medullary carcinoma (50). This is of particular interest, since TP53 somatic mutations are also found at a high level in BRCA1 tumours (48, 49, 51). These findings of somatic mutations in cell-cycle-checkpoint genes, like TP53 and CHK2, are in line with the theory that they increase the rate of tumourigenesis in BRCA1-associated tumours.

**Centrosome Amplification**

A defect in centrosome maturation has been described in several cancer types, including breast cancer (62). Centrosome defects are believed to affect the normal segregation of chromosomes and produce aneuploid cells. One of the contributing factors for CIN in breast cancer cells is the presence of more than two centrosomes during mitosis, usually called centrosome amplification. Breast cancer cells frequently display an excess number of centrosomes (63, 64). Precisely two centrosomes are required for accurate chromosome segregation into daughter cells. Cells are equipped with a mechanism controlling the duplication of DNA and centrosomes in every single cell cycle and these two events are co-ordinated, probably to ensure that the two cellular components duplicate only once. The coupling of the initiation of DNA and centrosome duplication is, at least in part, achieved by specific activation of cyclin-dependent kinases and their corresponding regulation partner, cyclins (65). It has been shown that centrosome amplification is an early event in the development of breast cancer and increase of centrosome amplification size and number correlates with CIN (64). Centrosome amplification is seen in a subset of breast cancer cells harbouring mutations in tumour suppressor proteins such as p53, Brca1 and Brca2, or overexpression of oncoproteins such as aurora kinase A.

As p53 is a cell-cycle-checkpoint protein in DNA-damaged cells, it is not surprising that cells that lack
functional p53 accumulate genomic defects, even though not all the target genes of this transcription factor and protein networks have been fully characterised. Tp53 mutations have been implicated as a cause for CIN in breast cancer in some studies, but not all (64, 66). Mouse knockout experiments support the association of dysfunctional p53 and genomic instability (67). It has also been suggested that p53 inactivation induces CIN through centrosome amplification, and a putative mechanism is through loss of transcriptional activation of p21 and subsequent activation of cyclin-dependent kinase 2/cyclin E complexes controlling the centrosome duplication cycle (68). Of interest is the finding that p53 loss induced centrosome amplification and CIN in human cells, in concert with cyclin E overexpression (69). This may explain some of the discrepancies between different studies, but needs further analysis in breast cancer. The mechanism for centrosome amplification associated with loss of p53 is poorly understood, but some additional clues come from an experimental system, in which centrosomes undergo multiple rounds of duplication in rodent cells exposed to DNA synthesis inhibitors (70). This occurs only if p53 is mutated or lost. In the presence of wild-type p53, centrosome re-duplication is blocked. The increased levels of p21 block the initiation of centrosome duplication via the inhibition of cyclin-dependent kinase 2/cyclin E. In hydroxyurea-treated cells with mutant p53 there is an abnormal centrosome accumulation, whereas cells with wild-type p53 arrest centrosome duplication under these conditions (71).

In addition to the role of Brca1 and Brca2 in DNA repair, the proteins have multiple functions, one of which seems to be the regulation of centrosome number. Brca1 can bind γ-tubulin, which is one of the major centrosomal proteins (72). It has been shown that embryonic fibroblasts derived from mice deficient in a full-length wild-type BRCA1 contain amplified centrosomes (73). Similarly, loss of BRCA2 resulted in centrosome amplification (74). The Brca1 and Brca2 proteins are participants in large protein complexes and, as described earlier, one of the proteins is considered to be of major importance is Rad51. This refers both to the DNA repair function and to centrosome amplification. The functional inhibition of Rad51 by expression of dominant negative Rad51, or conditional repression of Rad51, results in centrosome amplification (75, 76). This may imply a link between DNA repair and numeric homeostasis of centrosomes. In support of this, centrosome amplification is induced by irradiation, which is otherwise a well-known inducer of DNA breaks (77). There seems to be a link between Brca1 and aurora A kinase, since the former is phosphorylated by the latter, an event considered to be important for the regulation of the G2-M transition in the cell cycle (78). A recent report suggested that Brca1-dependent ubiquitination activity in concert with Bard1 marks the centrosomes and inhibits their reduplication (79, 80). Mutations of BARD1 are found at low frequency in breast cancer (81, 82). The role of Bard1 in the Brca1 and Brca2 pathways and genomic stability has been further established in knockout mouse experiments (83).

Aurora kinase A is overexpressed in a subset of breast cancer (84, 85). This overexpression can partly be explained by gene amplification, but also by dysregulation at the transcriptional or translational level (86, 87). Genetic variants of the aurora kinase A gene have more recently been implicated in cancer risk, including breast cancer (88, 89). Aurora kinase A is important for cell- cycle regulation and is believed to be involved in a checkpoint network. Aurora kinase A participates in ensuring that the two daughter cells receive identical copies of the genome in cell cycle progression. It is located at centrosomes and microtubules at the spindle poles and the kinase activity is involved in the maturation and separation of centrosomes and the assembly and stability of the spindle (90). The deregulation of aurora kinase A led to defects in centrosome separation and spindle defects (91). It has been defined as an oncoprotein, based on an ectopic expression in immortalised fibroblast cell lines resulting in cell transformation (86, 92). Aurora A mutants with defective kinase activity did not induce cell transformation, indicating that the active kinase is oncogenic.

Several small molecule inhibitors have been designed from the aurora crystal structure (93). Protein kinase inhibitors are currently one of the top new mechanisms for cancer therapy development, that are under investigation with significant progress.

Additional proteins involved in mitotic checkpoints and possibly in centrosome amplification are MAD1 and MAD2, both found to be mutated in breast cancer (94, 95). A recent study described the prolyl isomerase Pin1, overexpressed in breast cancer, as a regulator of centrosome duplication (96).

**Myc and Telomerase**

Another pathway of CIN induction in breast tumours involves telomere maintenance and release from cell senescence, presumably due to elevated expression of the enzyme telomerase. Telomerase maintains cell viability and chromosomal stability through the addition of telomere repeats to chromosome ends. The reactivation of telomerase through the up-regulation of TERT, the telomerase protein subunit, is an important step during cancer development, yet TERT protein function and regulation remain incompletely understood. Telomerase is of importance for cell immortalisation and it can establish genomic instability that favours a growth advantage for
tumour cells. Telomerase overexpression is detected in the majority of breast cancers (97). In mouse models, where telomerase is lacking in a p53 heterozygous background, end-joining and unequal translocations between chromosomes are frequent, but these were not detected in mice with long telomeres (98). The analysis of the genome in mouse tumours lacking telomerase shows that uneven translocations lead to a high number of aberrations on chromosome regions, which are not seen in tumours with normal telomeres (99).

The well-defined oncoprotein Myc has elevated expression in a subset of breast cancer cells. It is a transcription factor involved in cell growth and cell turnover control. The effects of Myc on increased CIN in breast cancer have been documented (100). Myc can bind to the promoter of the TERT gene and activate transcriptional expression, resulting in elevated telomerase (101). Myc seems to affect tumour pathogenesis in several ways, including increased proliferation and immortalisation of the cancer cells and induction of CIN. It is also of interest that aurora A kinase up-regulates Myc and thus, indirectly, telomerase expression (102). This is further support for the postulated cross-regulation between different pathways leading to genomic instability.

Conclusion

CIN is frequent in breast tumour cells and some chromosome regions are more unstable than others, particularly in hereditary breast cancer. Why would a cell with elevated CIN be viable? This must be due to selective pressure of genes involved in cell turnover such as cell proliferation, cell cycle checkpoints, apoptosis etc. Indeed some experimental data support this for breast cancer, with information from both human tumours and mouse models, such as knockout mice. An example of such an explanation comes from the work on Brca1 and Brca2. As genomic instability can result in an increased number of gene abnormalities by growth selection, some of these gene abnormalities can induce the development of further genomic instability. Perhaps an autonomous loop of events is induced in breast cancer, as well as in some other cancer types, where gene abnormalities induce CIN and the induced instability gives rise to further gene abnormalities. There must be some equilibrium in the amount and speed of such events to favour appropriate growth selection for the cancer cell; too much instability could result in poor cell survival. Clarification is emerging about the networks involved in genomic instability in breast tumours, but the molecular pathways need to be studied further. Presumably there is some sort of synergism between the progression of genomic instability and tumour suppressor dysfunction/oncoprotein activation, to facilitate breast tumour development. It is generally accepted that global DNA hypomethylation leads to genomic instability and increased tumour progression, but the role of epigenetics in genomic instability of breast tumour cells has been poorly studied (103). Is it possible to restore genomic stability by affecting global DNA methylation? Further studies will doubtless elucidate the role of global DNA methylation in genomic instability of breast cancer progression, and possibly give some clues to therapeutic intervention. Recent developments in our understanding of the molecular networks involved in genomic instability are already giving some clues to therapy strategies. Can the function of a tumour suppressor protein be restored, as has been suggested for p53, by blocking the degradation pathways or using small molecules that reactivate the protein (104)? To restore Brca1 or Brca2 activity seems more complicated; it may be more relevant to induce further genomic damage to make the cells less viable, as has been suggested using PARP inhibitors (105). Emerging data on the role of aurora kinases in genomic instability and breast cancer pathogenesis are opportune and could give some clues for novel kinase inhibitor treatment.

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