Molecular prognostic markers in breast cancer

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Summary

Based on the scientific literature, there are several molecular markers which might be used for the prognosis of breast cancer. Possible molecular prognostic markers are: BRCA-1, BRCA-2, p53, erbB oncogenes, loss of heterozygosity (LOH), chromosomal aberrations, microsatellite instability, transforming growth factor alpha (TGFRα), and the multiple drug resistance (MDR) gene. In this chapter, we discuss the possible role of these prognostic markers in breast cancer.

Introduction

Breast cancer is a complex disease in which numerous genetic aberrations occur. It is unclear which, if any, of these abnormalities are causative of breast tumorigenesis. However, on the basis of the currently accepted view of breast cancer as a multistep process, it is possible that specific abnormalities may be required in the progression from a normal breast epithelial cell to an invasive tumor cell [1].

The knowledge of specific genetic changes and their biological consequences is critical to an understanding of the natural history of breast tumors and the development of rational means to prevent and treat them. A number of genetic changes have been identified in breast tumors. Some of these involve specific genetic loci that directly contribute to one or more attributes of transformation, i.e., dysregulated proliferation and invasion, while other changes confer genetic instability that increases the possibility of acquiring subsequent, specific genetic lesions relevant to tumorigenesis. Many of these changes have been correlated with an adverse prognosis, and attempts to integrate these in comprehensive multifactorial prognostic models are in progress [2].

There are several possible molecular markers which can be used for the prognosis of breast cancer. In this chapter, we have summarized the most recent work in the field of molecular prognostic factors in breast cancer such as BRCA-1, BRCA-2, p53, erbB oncogenes, loss of heterozygosity (LOH), chromosomal aberrations, microsatellite instability, transforming growth factor α (TGFRα), and the multiple drug resistance (MDR) gene.

BRCA-1 and BRCA-2 genes

A family history of breast cancer has long been recognized as an important risk factor contributing
to about 10% of all breast cancer cases. Case control studies have shown that breast cancer aggregates in familial patterns along with uterine and ovarian cancers. There is even the suggestion that families exist with increased risk of prostate or ovarian cancer [3]. Molecular studies of these familial syndromes have so far identified several defective tumor suppressor genes as being the inherited defects associated with familial breast cancer. One such is the BRCA-1 gene at 17q21, a tumor suppressor gene, where a single gene mutation in BRCA-1 dramatically increases a woman's risk for developing breast or ovarian cancer [4]. In addition to BRCA-1 there are two other breast cancer associated genes, BRCA-2 (centromeric to the Rb gene) and BRCA-3 (located on 16q) [5].

With regard to BRCA-1, each of the 1 in 200 women who carry a mutation in this gene will have an estimated 85% life time risk of developing breast cancer. Of intense interest to researchers is not only the mechanism by which a mutated BRCA-1 initiates breast cancer, but why up to 15% of women who carry such a defect never develop breast cancer. BRCA-1, a potential tumor suppressor gene, encodes a predicted 200 kDa protein. Genetic susceptibility to breast cancer results from the inactivation of one BRCA-1 allele in the germ line, followed by the loss of the remaining allele in somatic breast tissue [4,6,7]. Clinical features that suggest a genetic predisposition include bilateral breast cancer, bilateral premalignant lesions, such as lobular carcinoma in situ, and unusually young age at presentation.

Studies by Fitzgerald, et al [8] showed that only BRCA-1 mutations that cause premature chain termination and missense mutations previously documented in familial breast and ovarian cancer should be considered definite mutations. Also, in contrast to the varied BRCA-1 mutations in the non-Jewish population, a specific BRCA-1 mutation (185th codon) was found frequently among young Jewish women with breast cancer. Genetic testing is therefore likely to be most effective in young Jewish women with breast cancer, among whom it may open the possibility of cancer prevention, early detection of secondary tumors, and genetic counseling for the women and their first and second degree relatives.

BRCA-1 associated breast cancers are highly proliferating tumors [9]. A study by Stratton [10] shows that cancers arising in the presence of familial BRCA-1 mutations are of higher grade, exhibiting more mitoses, more nuclear polymorphism, and less tubule formation than sporadic breast cancers.

p53 and breast cancer

Advances in methodology have allowed us to more precisely determine the approximate chronology of some of these aberrations and the possible roles each plays in the formation of malignancy. Simplistically, one could speculate that it is the early loss of cell cycle control in the presence of a mitogenic stimulus that allows a cell to divide unchecked. Such uncontrolled proliferation, occurring for example in the absence of wild type p53, would yield a high level of genomic instability. As proliferation continues, numerous additional chromosomal abnormalities occur, and increased tumor heterogeneity would be observed as distinct subpopulations emerge in the evolution toward a progressively more aggressive phenotype. However, much still remains to be learned to gain a full understanding of the key players behind the genetic evolution of breast cancer. Only by analyzing preinvasive and putative early stages of breast cancer will we be able to characterize the most probable sequence of genomic abnormalities [1].

Several studies have shown that alterations of the p53 gene may be involved in breast cancer etiology. Recently, Valgardsdottir et al [11] reported mutations in 17% of the samples, using polymerase chain reaction (PCR) and constant de-naturant gel electrophoresis (CDGE) on exons 5-8 of the p53 gene, and these were confirmed by sequencing. Abnormal p53 protein staining was found in 55% of the primary samples, using the