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 (TGFα), 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 (TGFα), 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 in-
herited defects associated with familial breast
breast. 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 (loca-
ted 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 develop-
ing breast cancer. Of intense interest to re-
searchers 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
ever develop breast cancer. BRCA-1, a potent-
tial 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 pre-
viously 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 poly-
morphism, and less tubule formation than sporad-
ic breast cancers.

p53 and breast cancer

Advances in methodology have allowed us to
more precisely determine the approximate chron-
ology 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 gen-
omic 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 aggres-
sive 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 puta-
tive 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] re-
ported mutations in 17% of the samples, using
polymerase chain reaction (PCR) and constant
denaturant 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