Molecular Genetics in Breast Cancer — minisymposium

Chromosome 11q13 markers and D-type cyclins in breast cancer

Gordon Peters¹, Vera Fantl², Rosalind Smith², Sharon Brookes¹, and Clive Dickson²
Molecular Oncology¹ and Viral Carcinogenesis² Laboratories, Imperial Cancer Research Fund, 44 Lincoln’s Inn Fields, London WC2A 3PX, United Kingdom

Key words: breast cancer, chromosome 11q13, cyclin D1, gene amplification, oncogene

Summary

One in six primary human breast cancers has DNA amplification centered on the cyclin D1 gene (CCND1) on chromosome 11q13. This genetic abnormality is preferentially associated with estrogen-receptor positive tumors and may define a sub-class of patients with an adverse prognosis. Although CCND1 has the credentials of a cellular oncogene, being a target for chromosomal translocation and retroviral integration, the 11q13 amplicon encompasses several other markers and CCND1 is not the only candidate for the key gene on the amplified DNA. To assess their relative importance, we have constructed a physical map of the amplified DNA and compared the extent and frequency of amplification across the region. Since it is likely that the gene providing the selective force for amplification will be expressed at elevated levels, we have also examined expression of both RNA and protein. By these criteria, cyclin D1 remains the strongest candidate for the key oncogene on the amplicon and we are currently investigating the functional consequences of its over-expression.

Introduction

The conversion of a normal somatic cell to one with neoplastic potential is generally thought to involve an accumulation of genetic alterations, some of which impinge on genes that regulate cell growth and differentiation. Thus, many cancer cells contain structurally abnormal chromosomes resulting from the loss, rearrangement or duplication of particular regions of the genome. Charting these abnormalities in specific tumors is important for two reasons. The first is that the patterns of genetic aberrations within specific cancers may help to refine their classification, by identifying new sub-types, and may provide prognostic information. This information can have value in the clinical management of disease without knowing the precise molecular details or consequences of each abnormality. The second reason, however, is that by identifying the genes involved and gaining insights into their function, it might be possible to develop novel or more

Presented by Gordon Peters at the 16th Annual San Antonio Breast Cancer Symposium, San Antonio TX, USA, November 4, 1993; Minisymposium on "Molecular Genetics in Breast Cancer".
Address for correspondence and offprints: Gordon Peters, PhD, Imperial Cancer Research Fund Laboratories, 44 Lincoln’s Inn Fields, London WC2A 3PX, United Kingdom; Tel: (44) 71 269 3049; Fax: (44) 71 269 3479.
rational therapies. This paper will review the status of a particular abnormality that is common in human breast cancer, namely the amplification of markers on 11q13. Although it is not yet certain which of the several genes on the amplified DNA provides the selective force in tumor development, the most likely candidate is CCND1/cyclin D1. Recent progress in characterizing the cyclin D1 protein raises interesting prospects in unravelling the workings of a tumor cell as well as offering an improved and simplified procedure for detecting this abnormality.

Chromosome band 11q13 is amplified in specific cancers

Since the original reports, some five years ago [1-7], the amplification of DNA markers on chromosome 11q13 has been extensively documented and reviewed [8-10]. The earliest studies were prompted by the fact that the mouse homologue of FGF3/INT2 is a frequent target for activation by mouse mammary tumor virus [11, 12], and by the observation in several laboratories that the FGF4/HST1 gene behaves as a dominant oncogene in DNA transfection assays [1,13,14]. As discussed in more detail below, these two members of the fibroblast growth factor family are encoded by adjacent genes on human chromosome 11q13 [1,6,15,16]. Because of the connection with mouse mammary tumor virus, breast cancer has been the natural focus for the amplification studies, but the same probes have of course been used to survey a wide variety of malignancies (summarized in Figure 1).

Amplification of the 11q13 region has now been reported in breast cancers from many different geographical locations, with a frequency ranging from 5% to 23% [reviewed in 10]. This variability is likely to reflect differences in the techniques and criteria used to score DNA amplification rather than in the study population, and most of the larger surveys are consistent with an average incidence of approximately 15%, close to that in our own survey in London. As discussed below, we now consider this figure to be an underestimate, since the degree of amplification can be relatively modest and we have always been conservative in interpreting marginal cases. Moreover, measurement of DNA amplification only gives a tissue-averaged figure and can be influenced by the stromal content of the original tumor biopsy.

The other major tumor type in which 11q13 amplification is particularly common is squamous cell carcinoma (SCC), of the head and neck region, esophagus, and lung (Figure 1). The specificity of the association with SCC is emphasized by the fact that other categories of lung cancer rarely show the amplification [17]. The frequency of the amplicon in SCC is even greater than in breast cancer, with estimates for esophageal tumors as high as 50% [18]. In contrast, the amplification of 11q13 is remarkably rare in other tumor types (summarized in Figure 1). The significance of 11q13 amplification in single cases or in some metastatic lesions remains unclear, but the fact that the abnormality is confined to specific cancers suggests that it contributes to the phenotype of the tumor cell and is not simply a random feature generated by chromosome instability.

11q13 amplification is associated with ER-positive tumors

Several of the studies cited in Figure 1 have tried to correlate 11q13 amplification with breast cancer phenotype or with other clinicopathological parameters, such as patient age and menopausal status, lymph node involvement, and tumor size or stage. In general, the conclusions drawn are rather inconsistent. Nevertheless, one clear association that has emerged in independent surveys is that amplification of 11q13 markers is much more prevalent in estrogen receptor (ER)-positive tumors [24,26-28,39], although not all studies agree about the statistical significance of this association [21,25]. It is therefore possible that the presence or absence of amplification may