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Molecular cytogenetic analysis of breast cancer cell lines

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Keywords

CGH, FISH, molecular cytogenetics, oncogenes

Introduction

Breast cancer development and progression are associated with genetic changes. Although many chromosomal regions are involved, the genes responsible for these changes are largely unknown. Much of this type of work has been conducted using established breast cancer cell lines; however, as many of these lines do not originate from the primary lesion, they may not be truly representative of breast tumours. Many are poorly characterised, both phenotypically and genotypically. Also, some of these cell lines were established in the 1970s and will probably have undergone considerable genetic drift, making them unsuitable models for cytogenetic studies. Cultures established from primary breast tumours are much better models and are already used by some groups.

Aims

To carry out molecular cytogenetic analysis using comparative genomic hybridisation (CGH) to evaluate genetic changes in 11 newly established breast cancer cell lines.

Comments

Breast cancer is characterised by genetic aberrations. The use of well-characterised novel breast cancer cell lines such as those described herein offers the possibility of identification of new genes which may be responsible for tumour progression. These genetic changes may be correlated with established clinical criteria and allow the future development of a model for breast cancer similar to the Vogelstein model for colorectal cancer.

Methods

Eleven new cell lines were established from either the primary breast tumour (n=4), pleural effusions (n=4), chest wall recurrences (n=2) or skin metastasis (n=1). Nine out of the eleven patients had received prior chemotherapy. All cell lines were immortal and expressed luminal cytokeratins, confirming their luminal epithelial origin. For CGH analysis, tumour and reference DNA were labelled by nick translation incorporating spectrum green (tumour) or spectrum red (normal) and hybridised to metaphase spreads. Images were captured with a CCD camera and the ratio of red to green fluorescence quantified. Dual colour fluorescent *in situ* hybridisation (FISH) was used to detect DNA amplifications of known oncogene loci using centromeric probes for chromosomes 8, 11 and 17 to detect *myc*, *cyclin D1* and *erbB2* genes, respectively. *FGFR1* and *FGFR2* genes were detected by Southern blotting.

Results

All 11 cell lines showed genetic alterations by CGH. An average of 14 genetic changes were observed in each line with a mean of 8 gains and 6 losses. The most common gains occurred at 8q (73%), 1q (64%), 7q (64%), 3q (45%) and 7p (45%), while losses were observed most frequently at 8p (45%), 18q (45%) and the long (54%) and short (45%) arms of the X chromosome.

One third of amplifications were associated with known breast cancer oncogenes. This was validated using specific probes which revealed amplification of *erbB2* at 17q12, *cyclin D1* at 11g13, *FGFR1* at 8p11-p12 and *FGFR2* at 10q25. Although losses and gains affecting 8q were common in all cell lines, these did not appear to involve the *myc* locus located at 8q24.1. The remaining two thirds of amplifications were observed at sites not previously associated with established oncogenes and affected a range of chromosomes including 1q41-q43, 7q21-q22, 7q31, 8q23, 9p21-p23, 11p12-p14, 15q12-q14, 16q13-q21, 17q23, 20p11-p12 and 20q13.

Discussion

This paper has identified several new areas of the genome distinct from those of known oncogenes. Amplification of these areas may be of potential importance in breast cancer development. The new cell lines described in this study may facilitate the identification and characterisation of novel genes responsible for the development and progression of breast cancer.

References

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