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p53, genetic instability and ras overexpression

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Introduction

Human solid tumours undergo a variety of genetic alterations in the progression from normal to malignant cells. These changes may occur in specific sequential patterns underlying tumorigenesis. Previous studies using multiparameter flow cytometry have determined an adverse prognostic factor for tumours containing aneuploid cells that also overexpressed Her-2/neu and ras in the same cells. Overexpression of epidermal growth factor receptor (EGFR) and/or Her-2/neu almost always preceded ras overexpression. Numerous studies have demonstrated relationships in breast cancers between p53 abnormalities and aneuploidy and Her-2/neu amplification/overexpression, as well as Her-2/neu amplification/overexpression and aneuploidy and ras overexpression within individual tumours.

Aims

To examine the relationship between p53 abnormalities and previously studied intracellular patterns of Her-2/neu overexpression, ras overexpression, and aneuploidy in individual breast cancers.

Comments

Human solid tumours, including breast cancer, are thought to arise viamultiple genetic pathways, although the elucidation of such pathways iscomplicated by the heterogeneity of breast carcinomas.

This paperdemonstrates the approach of multiparameter flow cytometry, supplemented byfluorescent *in situ* hybridisation (FISH), to perform multiple quantitativemeasurements on individual cells.Identification of early events in breast cancers by this method will help to delineate the different pathways by which tumours evolve in the breast, and the application of this approach to putative precursorlesions such as ductal carcinoma *in situ* and atypical ductal hyperplasia iseagerly awaited.

Methods

Fifty-six freshly-obtained primary breast cancers were used in this study. Multiparameter flow cytometry measurements for cell DNA content, p53 protein, Her-2/neu protein and ras protein were carried out, along with FISH determination of *p53* allelic loss and Her-2/*neu* amplification.

Results

Simultaneous overexpression of p53, Her-2/neu and ras in the same cells occured in 45 of the 56 tumours. ras overexpression in the absence of p53 abnormalities and/or Her-2/neu overexpression was rare. Simultaneous p53 and Her-2/neu overexpression occurred frequently in the absence of ras overexpression in the same cells. The levels of abnormally expressed proteins were found to increase progressively as new abnormalities were acquired. Overexpression of all three proteins, together with chromosomal aneuploidy, was found to be a prominent feature of infiltrating ductal, but not lobular, breast carcinomas.

Discussion

Cells showing few and consistent abnormalities were reasoned to contain early events in the evolution of the tumour, whilst late-developing alterations would not be found alone, but together with the early changes inherited by the same cells. On this assumption, infiltrating ductal carcinomas exhibited characteristic phenotypic patterns in which *p53* allelic loss and/or p53 protein overexpression, Her-2/neu amplification and/or overexpression, aneuploidy, and ras overexpression accumulated progressively within individual cells. Lobular carcinomas appear to arise via a different evolutionary pathway, as aneuploidy, p53 abnormalities and Her-2/neu amplification are not prominent features in these lesions.

References

1. Smith CA, Pollice AA, Gu L-P, Brown KA, Singh SG, Janocko LE, Johnson R, Julian T, Hyams D, Wolmark N, Sweeney L, Silverman JF, Shackney SE: Correlations among p53, Her-2/neu, and ras overexpression and aneuploidy by multiparameter flow cytometry in human breast cancer: evidence for a common phenotypic evolutionary pattern in infiltrating ductal carcinomas. Clin Cancer Res. 2000, 6: 112-126.