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CpG island methylation

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Chris Jones,[Aff1]

Aff1 Royal Free and University College Medical School, London

Keywords

Array, CpG island, epigenetic

Introduction

DNA methylation is a common epigenetic alteration in the tumour genome, which usually occurs by deletion or addition of a methyl group in the fifth carbon position of a cytosine located 5? to a guanine, known as a CpG dinucleotide. A recent array-based technique, known as differential methylation hybridization (DMH), has been described which can scan the tumour genome for methylation alterations. DMH was successfully applied to detect specific methylation profiles in a group of breast cancer cell lines, and hypermethylation of CpG island loci was independently confirmed by Southern blot analysis. Subsequent pattern analysis of the positive loci revealed potential mechanisms governing aberrant methylation in these cells.

Aims

To determine whether DMH alone can be routinely applied to identify CpG island hypermethylation in clinical breast cancer specimens and to correlate hypermethylation with clinicopathological data.

Comments

Methylation of DNA sequences is an important epigenetic event whose critical role in cancer development is still emerging. This paper reports a pilot study investigating the usefulness of CpG island arrays to investigate genome-wide hypermethylation in human breast cancers. The correlation between hypermethylation and poorer histological grade in breast tumours is an intriguing finding, and the development of the technique for population-based studies will be an important step in identifying epigenetic events in breast tumorigenesis.

Methods

Twenty-eight paired primary breast cancer and normal samples were selected and DMH performed (Huang *et al* 1999, *Hum Mol Genet*, **8**:459-470). Amplicons derived from these samples, representing a pool of methylated CpG DNA, were used as hybridization probes in an array panel containing 1104 CpG island tags.

Results

Close to 9% of the CpG island tags exhibited extensive hypermethylation in the majority of breast tumours relative to their normal controls, whereas others had little or no detectable changes. Analysis of 30 hypermethylation-positive CpG island tags revealed 9 that contained sequences identical to those of known cDNAs. CpG island hypermethylation was found to be associated with histological grades of breast tumours, with poorly differentiated tumours exhibiting more hypermethylated CpG islands than moderately or well-differentiated tumours.

Discussion

The results suggest that patients with more advanced disease status are prone to methylation alterations, although some of the patients showed little or no changes of methylation at the loci tested. This indicates that progression of some tumours may be independent of this epigenetic event, or that the alteration could occur in later stages of tumour development in such patients. This pilot study illustrates the potential of DMH for surveying methylation patterns in breast cancer, allowing for the development of population-based analysis of CpG island hypermethylation at the whole genome level.

References

1. Yan PS, Perry MR, Laux DE, Asare AL, Caldwell CW, Huang TH-M: CpG island arrays: an application toward deciphering epigenetic signatures of breast cancer. Clin Cancer Res. 2000, 6: 1432-1438.