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HOXA5 regulation of p53 in breast tumours

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Chris Jones,[Aff1]

Aff1 Royal Free and University College Hospitals, London, UK

Keywords

Breast cancer, HOX genes, p53, transcriptional regulation

Introduction

Mutational inactivation of p53 occurs in only around 20% of human breast cancers, suggesting other mechanisms for loss of p53 function in these tumours. Although much work has been performed on the control of p53 degradation, information is lacking regarding factors which regulate p53 synthesis.Class I homeobox (*HOX*) genes are a family of regulatory genes encoding transcription factors that primarily play a crucial role during development. Several indications suggest their involvement in the control of cell growth and, when dysregulated, oncogenesis.

Aims

To identify and investigate potential regulators of *p53*transcription.

Comments

Mutations in the p53 gene which inactivate its cell cycle checkpoint functions have been observed in over 50% of all human tumours. In up to 80% of sporadic breast cancers, however, no p53 mutations are found. This important paper indicates that the homeobox gene product HOXA5 may be a positive regulator of p53 transcription and function, and that loss of *HOXA5*expression by methylation of the promoter region (resulting in loss of p53 expression) may be a critical step in breast tumorigenesis.

Methods

p53 mRNA levels were found to be 5- to 10-fold lower in tumour cells than in normal breast epithelium. Six putative HOX-core binding sequences were identified within the human *p53* promoter, and HOXA5 mRNA levels were markedly reduced in breast cancer cells. There was a tight correlation of HOXA5 with p53 mRNA levels in 10 cell lines tested for both genes. Transient transfection with HOXA5 activated the *p53* promoter in ZR75.1 breast cancer cells. Expression of *HOXA5* in epithelial cancer cells expressing wild-type p53, but not in isogenic variants lacking the *p53* gene, led to apoptotic cell death. Concurrent loss of p53 and HOXA5 protein expression was observed in 20 out of 30 primary breast tumours, although HOXA5 mutations were absent. The *HOXA5* promoter region was found to be methylated by methylationspecific PCR of sodium-bisulphite-treated DNA in 16 out of 20 p53-negative breast tumour specimens, but not normal human mammary epithelial cells, with strong correlations between methylation and gene silencing in these tumours.

Discussion

p53 and HOXA5 mRNA levels were found to be markedly reduced in breast cancer cells, with HOXA5 seemingly activating p53 expression. An increase in HOXA5 levels in breast cancer cells appeared to increase p53 levels, which in turn resulted in apoptosis. Primary breast tumour samples showed concomitant loss of HOXA5 and p53 protein levels, and preliminary evidence suggests that methylation of the *HOXA5*promoter region may be responsible for silencing of gene expression.

References

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