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Beta-catenin in breast cancer

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Keywords

Beta-catenin, cyclin D1, prognosis

Introduction

Overexpression of cyclin D1 is found in almost half of all breast tumours. However, amplification of the gene is seen in only 20% of cases, suggesting other pathways are involved in cyclin D1 overexpression. β-catenin was first described as a cell adhesion molecule but was later shown to additionally function as an oncogene when translocated to the nucleus. Within the nucleus, it binds to T cell factor (Tcf) or lymphoid enhancer factor (Lef) and can activate genes containing Tcf/Lef promoters. Reported mechanisms include deletion of the adenomatous polyposis coli (APC) gene, mutation of β-catenin or activation of the Wnt pathway. Expression of Wnt genes has been associated with breast cancer; although APC deletions and β-catenin mutations are common in other cancers (eg colorectal) so far they have not been associated with breast cancer.

Aims

This paper sets out to define the interaction of β-catenin with cyclin D1 in breast cancer progression.

Comments

β-catenin has been identified as a novel prognostic marker in breast cancer, impacting on the cyclin D1 pathway. Although widely studied in colorectal cancers, the precise role of β-catenin in breast cancer is not known. The involvement of β-catenin with other oncogenes more commonly associated with breast carcinogenesis, eg the Wnt family, may also be important and should be studied. Identification of how these pathways interact may allow the identification of novel therapeutic targets.

Methods

Promoter activity was determined by transfection studies using a panel of breast cancer cell lines and the results were confirmed by gel shift analysis. Immunohistochemical analysis of the cellular distribution of cyclin D1 and β-catenin in archival breast tumours was also carried out.

Results

Cyclin D1 promoter activity was significantly upregulated by β-catenin and could be blocked by addition of inhibitors of the β-catenin/Tcf4 pathway such as APC, the β catenin, GSK-3β, and a dominant-negative mutant of Tcf4. Using deletion constructs containing Tcf4 mutations, β-catenin was unable to activate the cyclin D1 promoter, identifying cyclin D1 as the target gene for β-catenin.Expression levels of β-catenin and cyclin D1 were compared in a panel of breast cancer cell lines. MCF-7 cells, which had highest cyclin D1 expression, also had the most significant levels of β-catenin whereas cell lines with no detectable cyclin D1 (HBL100 and BT549) expressed only background levels of β-catenin/Tcf4. Linear regression analysis showed a proportional correlation of cyclin D1 with β-catenin activity.

Immunohistochemical analysis of cyclin D1 and β-catenin in breast tumours revealed that, of the 53 samples positive for cyclin D1, 49 of these were also β-catenin positive. Both nuclear and cytoplasmic β-catenin was observed which is indicative of its activated form. Kaplan Meier and log rank analysis showed overexpression of both cyclin D1 and activated β-catenin were associated with poor prognosis and were negatively correlated with patient survival. Furthermore, high β-catenin activity was a strong independent prognostic factor.

Discussion

This study has identified β-catenin as a marker for poor prognosis in breast cancer. Cyclin D1 has been identified as one of the targets of the β-catenin pathway. Thus, β-catenin may be involved in the progression of breast cancer and has potential as a novel therapeutic target.

References

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