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*Tpl-2*overexpression in breast cancer

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breast carcinoma, gene amplification, quantitative RT-PCR, *Tpl-2/Cot*

Introduction

The proto-oncogene *Tpl-2/Cot* encodes a serine/threonine kinase which is activated by provirus insertion in Moloney murine leukemia virus (MoMuLV)-induced rat T cell lymphomas and mouse mammary tumor virus (MMTV)-induced mouse mammary carcinomas. *Tpl-2* kinase activates the mitogen-activated protein kinases (MAPK) and the stress-activated protein kinase (SAPK) pathways, which play an important role in the transduction of signals generated by growth factors produced in mammary epithelial neoplasms.

Aims

To investigate *Tpl-2/Cot* mRNA expression in human breast carcinomas.

Comments

Tpl-2 was originally identified as an oncoprotein in rats, and is more than 90% identical to the human oncoprotein Cot, which was identified as a new component of mitogenic signalling cascades, activating both the classic cytoplasmic cascade and the SAPK stress pathway. Activation of these pathways contibutes to cell transformation and proliferation.

This is the first report linking the *Tpl-2/Cot* oncogene to human breast cancer, with a significant proportion of tumours showing mRNA overexpression, possibly due to gene amplification, associated with early stages of the disease. This work provides insights into a new and potentially important oncogenic pathway involved in the pathogenesis of breast cancer.

Methods

A total of thirty-five primary breast cancer specimens were analysed in this study. *Tpl-2/Cot* mRNA levels were detected by semi-quantitative reverse transcriptase polymerase chain reaction(RT-PCR). Gene amplification was investigated by PCR amplification of the 5' untranslated region of exon 1 of the *Tpl-2* gene. Allelic imbalance at the *Tpl-2* locus on chromosome 10p11.2 was examined using two highly polymorphic microsatellite markers flanking the *Tpl-2* gene. Estrogen receptor (ER) and progesterone receptor (PR) expression was also determined.

Results

Of the 35 human breast tumours 14(40%) showed increased *Tpl-2* expression levels as compared to their corresponding adjacent normal tissue. Overexpression was not associated with histological subtype, tumour grade or age of the patients, but correlated significantly with stage I tumours. Of the 14 specimens that exhibited overexpression, eight showed amplification of the *Tpl-2* gene locus and also exhibited allelic imbalance at the two markers used. Allelic imbalance was not seen in the samples with an absence of gene amplification. No significant correlation was seen between *Tpl-2* and ER overexpression, although an association was found between tumours overexpressing *Tpl-2* and PR.

Discussion

The *Tpl-2* oncogene was found to be overexpressed in 40% of breast tumour samples tested and correlated significantly with stage I tumours, suggesting a role in the early stages of breast cancer development. Gene amplification was seen in more than half of the samples showing *Tpl-2* overexpression, indicating a possible mechanism for the up-regulation seen in these tumours. Overexpression was also associated with positive PR status in the patients investigated. The molecular mechanisms through which *Tpl-2* contributes to the development of breast cancer remains to be determined.

References

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