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*neu/erbB-2*oncogene in mouse mammary tumorigenesis

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Keywords

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Introduction

Also known as *c-erB-2* and *Her-2*, *neu* is a proto-oncogene that is amplified and overexpressed in about a quarter of human breast cancers. This study further refines the genetically engineered mouse model of activated Neu and shows that, as in human *erb-B-2*-positive breast tumors, mammary tumorigenesis in this model requires the amplification and overexpression of the *neu* gene.

Aims

To determine whether mice genetically engineered to produce activated Neu under the transcriptional control of the intact endogenous promoter can develop mammary tumours (as *neu* can when driven by strong viral promoters such as mouse mammary tumour virus [MMTV]).

Comments

The use of mice as models for human breast cancer has often been undermined by the fact that many of the genes engineered for expression in transgenic mice are driven by strong viral promoters whose relevance to human disease is questionable. In this study, a murine model transgenic for *neu* has been further refined by producing a conditionally expressed activated Neu protein that uses the intact endogenous *neu* promoter. These mice form numerous lobular side buds and, following a long latency period, develop tumors that are associated with a selective amplification of the activated *neu* allele and elevated levels of *neu* RNA and protein.

Methods

Transgenic mice were generated that conditionally expressed activated *neu* allele. This was achieved initially by constructing a transgenic line of mice that have exon one of *neu* replaced by a *loxp*-flanked cassette containing oncogenic *neu*, generated by an activating mutation in the transmembrane domain region of *neu*. This line was then crossed with a line containing the *Cre* recombinase gene driven by the MMTV promoter. In theory, this should induce *loxp*-mediated excision specifically in the mouse mammary gland.

Results

Transgenic mice were generated that conditionally expressed activated *neu* mainly in the mammary gland. *Cre*-mediated excision of the *neu* cassette was also observed in the spleen and salivary glands, without any apparent ill effects. Nulliparous mice displayed abnormal mammary gland development with numerous lobular side buds composed of acinar structures. No staining for Neu was observed around these highly branched structures. Focal comedo-adenocarcinomas occured in 45% of female mice 1 year or older. These tumours showed membrane and cytoplasmic immunoreactivity for Neu, whereas MMTV-*neu*-induced tumours expressed only membrane Neu. Elevated oncogenic *neu* RNA and protein expression were observed in tumours but not in adjacent normal tissue. Selective amplification of the activated *neu* allele, ranging from 2- to 22-fold compared to the wild-type allele, was observed. Tumour formation did not correlate with parity status.

Discussion

In contrast to the transgenic murine model of MMTV-driven activated Neu, activated Neu driven by its own promoter is not sufficient for the induction of mammary tumours. Mammary tumours eventually developed after a long latency period in these mice. These data suggest that amplification and elevated expression of activated Neu is required for efficient transformation of mammary epithelial cells. This refined mouse model is encouraging in that it mimics human disease in the type of tumour that forms and in the extended latency period needed for tumour formation. It should be a useful system for determining the role of other transcription factors (such as the oestrogen receptor and c-*myc*) in *neu*-mediated tumorigenesis.

References

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