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The prognostic significance of transcripts for transforming growth factor alpha and fetal and epidermal growth factor receptor in primary breast cancer

R C Coombes, P Murray, Y Luqmani

Medical Oncology Unit, St George's Hospital Medical School, Cranmer Terrace, London SW17

We have now examined 129 primary breast carcinomas for the presence of TGFB mRNA. Some degree of expression was observed in all of these; high levels (>3+ on an arbitary scale from 0-5) were inversely related to the presence of nodal metastases (p=0.042). The patients in this category were also found to have a longer median survival and a significantly longer relapse free survival probability at 72 months (p=0.012) compared with those patients whose tumours had <3+ level of TGFB mRNA. However log rank analysis over the whole study period of 120 months fell short of statistical significance (p=0.07). No differences in overall survival were seen between the two groups. The presence of TGFB transcripts in 53/104 carcinomas had no relationship with survival or other clinical features such as T stage, nodal or menopausal status or pathological node stage.

We also looked at EGFR and found some level of expression in 55/107 tumours. The presence of EGFR message was inversely related to the expression of estrogen receptor as determined by immunocytochemistry (p=0.002). Statistically there was no difference in survival between EGFR positive and EGFR negative groups or TGF-alpha positive and TGF-alpha negative groups.

The results with TGFB look promising and we plan to extend that study with tumours from another 50 patients selected from our tumour bank.

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GENETIC REARRANGEMENTS IN BREAST CANCER

A.H.Bootsma, A.de Klein and S.W.J.Lamberts
Erasmus University. Dept. of internal medicine III and dept of genetics. Rotterdam, the Netherlands.

Oncogenes and tumor suppressor genes are involved in the etiology of human cancer. Since breast cancer is pathologically a heterogeneous disease it is interesting to investigate whether certain genetic changes can be correlated with specific subgroups of these tumors. Thus far amplification of neu, int-2 and the myc genes and loss of p53 and retinoblastoma genes have been reported. Overexpression of the neu gene was found to occur mainly in comedo type ductal carcinomas. Twenty percent of all breast tumors express the somatostatin receptor. It has been shown by Reubi et al. that this group overlaps with breast tumors that have neuroendocrine characteristics. In small cell lung carcinoma, a neuroendocrine tumor it was demonstrated that in 60% the retinoblastoma gene was inactivated. We have investigated whether loss of retinoblastoma sequences, which are found in 25% of all breast tumors, correlates with the neuroendocrine subgroup. To this end 49 primary breast cancers were analysed for expression of the somatostatin receptor, neuroendocrine characteristics and deletions of the retinoblastoma gene. The tumorspecimens were also used to investigate genetic alterations and/or amplification of the neu, int-2 and myc genes.

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VITAMIN D: A MODULATOR OF TUMOR CELL PROLIFERATION AND DIFFERENTIATION

J.P.T.M. van Leeuwen, J.C. Birkenhäger and H.A.P. Pols
Dept. Internal Medicine III, Erasmus University Medical School, Rotterdam, The Netherlands.

The steroid hormone 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) is involved in the regulation of calcium homeostasis and bone metabolism. Recently, receptors for $1,25(OH)_2D_3$ have been shown in tissues and cells not directly related to calcium homeostasis, as tumor cells, cells of the immune and hematopoetic system, and keratinocytes. In the leukemia cell line HL-60 it has been shown that besides inhibition of proliferation $1,25(OH)_2D_3$ stimulates differentiation. The induction of phenotypical differentiation is preceded by a changed oncogene expression. Also, $1,25(OH)_2D_3$ reduces growth of human breast cancer cells. $1,25(OH)_2D_3$ reduces the number MCF7 and T47D cells in the S-phase of the cell cycle. In various cell types interactions between growth factors and $1,25(OH)_2D_3$ have been reported. Important in vivo data are that high doses of $1,25(OH)_2D_3$ prolongs the survival of mice injected with leukemia cells and inhibits the growth of human malignant melanoma an colonic cancer xenografts in immune suppressed mice. The data up to now point to a role for $1,25(OH)_2D_3$ in the control of cell growth and differentiation. However, an important drawback at the moment is the necessity of high doses $1,25(OH)_2D_3$ with its concomittant hypercalcaemic effect.