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SYMPOSIUM

Breast cancer – from bench to bedside

147 INVITED

Expression of the c-erbB-4/her-4 growth factor receptor in breast cancer

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In order to examine the expression of the c-erbB-4 growth factor receptor protein in normal tissues and in tumours we have made polyclonal and monoclonal antibodies which react in formalin-fixed paraffin-embedded tissues. Using these reagents to detect protein expression by immunohistochemical staining and antisense RNA probes in *in situ* hybridisation we have determined c-erbB-4 expression in a wide range of normal foetal and adult tissues. c-erbB-4 was expressed in the lining epithelia of the gastrointestinal, urinary, reproductive and respiratory tracts as well as the skin, skeletal muscle, circulatory, endocrine and nervous systems. The developing brain and heart notably express high levels of the receptor.

We have also examined the pattern of c-erbB-4 expression in a survey of common solid tumours. Loss of expression was noted in 40–80% of adenocarcinomas and up to 100% of squamous cell carcinomas whereas overexpression was observed in 10–20% of cases.

We are currently analysing a series of 180 breast cancers for expression of c-erbB-4 and whether this has any relationship to clinical or molecular variables.

148 INVITED

Tumour suppressor genes in breast cancer

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Tumour suppressor genes (TSG) codes for proteins normally involved in suppression of cell growth and cell proliferation. Loss of function of TSGs may lead to tumour formation. Both inherited and somatic inactivating mutations in TSGs have been identified in breast cancers. Only a handful of genes have been proved to be classical TSGs. Several genes showing Loss of Heterozygocity (LOH) in tumours as well as germline mutations in hereditary cancer syndromes have been identified. Germ line mutations in the *BRCA1, BRCA2,* and *TP53* genes predispose to breast cancer. Tumours from individuals with such germ line mutations have lost the other copy of the gene leading to total inactivation of the TSG in question. Somatic mutations and LOH leading to inactivation of the Rb, TSG101, p16 as well as the TP53 gene are found in breast carcinomas. So far the most frequently involved gene is the TP53 gene. Mutation in this gene has been shown to be both a prognostic and a predictive marker. Analyses of TP53 mutations in breast carcinomas may give valuable information of prognosis, choice of treatment, and for selection of patients for novel treatment strategies.

149 INVITED

The immune response to breast cancer

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Purpose: Cytokines are produced by breast tumour cells and elevated levels of IL6, VEGF and M-CSF have been associated with cancers of poor prognosis. The question we asked was how the production of large amounts of M-CSF is a macrophage differentiation and survival factor and its presence at high concentrations in the tumour might impair differentiation of dendritic cells and favor macrophage differentiation.

Methods and Results: In vitro studies have confirmed this hypothesis and our results clearly demonstrate that concentrations ranging from 1245–16,600 pg/ml (75–1000 U/ml) were able to dedifferentiate immature dendritic cells to macrophages by both phenotypic and functional analysis. Plasma levels in breast cancer patients showed median levels of 380 pg/ml (range 33 to 2564 pg/ml). In a clinical vaccination program, prevaccination M-CSF levels were highest in a patient who progressed early and lowest in patients who showed a response. In an independent study, a striking, though infrequent, feature was the marked infiltration of $CD1a^+$ monocyte derived cells in p53 overexpressing tumors, a phenotype which was most pronounced in both tumours with a mutation in codon $175^{ang\text{-}his}$. CD1a is an MHC class I-like protein, expressed mostly on immature or mature human dendritic cells (DC). These cells are derived from monocytes and thought to be involved in the presentation of lipids and peptides to T cells. The presence of $CD1a^+$ inflammatory cell infiltrates correlated significantly with p53 overexpression ($3–4^+$) ($p = 0.035$) and with the expression of HLA class II (DP, DQ, DR) by tumour cells ($p = 0.025$). Furthermore, these tumour cells had low immunsotaining for M-CSF ($p = 0.04$) and patients with p53 overexpressing tumours also had low circulating M-CSF plasma levels ($p = 0.05$).

Conclusions: M-CSF production by tumour cells impairs dendritic cell differentiation suggesting that cancer patients with high circulating levels are unlikely to respond to immune manipulations as a consequence of functional incapacity to produce effective antigen presentating cells. Patients with low levels may be able to develop a spontaneous cellular immune response.

150 INVITED

Inactivation of E-cadherin in breast cancer

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The E-cadherin protein is located in the cell membrane of many epithelial cells and is involved in cell-cell interactions and probably also in signal transduction.

The E-cadherin gene is located on chromosome 16q in a region exhibiting frequent loss of heterozygosity (LOH) in breast cancer. In recent years, it was shown that a subset of breast carcinomas containing LOH in this region contain inactivating E-cadherin gene mutations. A more detailed analysis of these tumors revealed that most invasive lobular carcinomas exhibit inactivation of the E-cadherin gene, whereas inactivation of E-cadherin is never found in invasive ductal carcinoma.

The E-cadherin protein is located in the cell membrane and its cytoplasmic tail interacts with alpha-, beta- and gamma catenin. In all tumors with loss of E-cadherin expression alpha- and beta-catenin expression is also lost and gamma-catenin expression is lost in 50% of these cases. Loss of expression of alpha-, beta- or gamma-catenin in the absence of E-cadherin inactivation is very rare.

In lobular carcinoma in situ (LCIS) of the breast, expression of E-cadherin is also absent and in a limited number of cases inactivating mutations in the E-cadherin gene have been identified in LCIS. This indicates that inactivation of E-cadherin takes place before the tumor cells become invasive and is an early step in breast cancer development.

It appears that there is a distinct genetic pathway leading to the development of invasive lobular carcinoma of the breast and that inactivation of E-cadherin is a crucial step in this pathway.

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SYMPOSIUM

The final answer? Breast conserving therapy versus radical mastectomy: long term follow up on randomized trials

151 INVITED

Long-term follow-up of the first breast conservation trial (Guy's Wide Excision Study)

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Breast conservation therapy is now accepted as a proven approach for selected patients with operable breast cancer. It important to appreciate