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Meeting Report

UCLA Colloquium

New Insights into Breast Cancer: The Molecular Biochemical and Cellular Biology of Breast Cancer[1]

This colloquium presented an exciting array of new findings, some of which will almost certainly afford improvements in breast cancer diagnosis and therapy. The meeting began with an update of basic research into the tumorigenic mechanisms of mouse mammary tumor virus and continued with studies on growth factors, proteases, oncogenes, and antioncogenes in human breast cancer. The conference also highlighted studies on new prognostic variables and new therapeutic approaches to breast cancer treatment.

Mouse mammary tumor virus causes murine mammary cancer by host DNA integration and insertional activation of an array of mouse genes known as the *int* genes. R. Nusse (Netherlands Cancer Institute, Amsterdam, The Netherlands) presented data that *int*-1, an embryonic growth factor-like protein, was expressed in the developing mouse nervous system and in Drosophila during segmentation (where it is known as "*wingless*"). C. Dickson (Imperial Cancer Research Fund, London, United Kingdom) presented data that *int*-2, a second gene family member, was also a growth factor of the FGF[2] family. *Int*-2 has two initiations of translation sites; the product of one (starting at CUG) is routed to the cell nucleus, while the other (starting at AUG) is secreted and bound to the extracellular matrix. R. Callahan (NIH, Bethesda, MD) described a third family member, *int*-3. This gene product is also expressed in mouse embryonic development and is related to EGF.

Of these three *int* genes, Callahan presented data showing that probably only detection of amplification of *int*-2 might have prognostic value in human breast cancer. Callahan and H. Smith (Brush Cancer Research Institute, San Francisco, CA) presented data that loss of heterozygosity on multiple chromosomes (1, 3, 11, 13, 17, and 18) are common in human breast cancer. Increased breast cancer nodal status (metastases), DNA aneuploidy, and protooncogene amplifications are all correlated. The most common amplification of protooncogenes are in *int*2, c-*myc* (a nuclear oncogene), and c-*erb*B_2 (or neu, an EGF-receptor-related protein).

The next sessions dealt with control of breast differentiation and transformation *in vitro* by extracellular matrix, growth factors, steroids, and oncogenes. M. Bissell (University of California, Berkeley, CA) presented data that the extracellular matrix was essential to allow three-dimensional structure and properly polarized (luminal) casein secretion by murine mammary epithelial cells *in vitro*. B. Groner (Friedrich Miescher Institut, Basel, Switzerland, Federal Republic of Germany) further explored growth factor-oncogene controls on secretion of casein. He found that although EGF or TGFα is essential for mammary epithelial proliferation in low density culture, at high density culture they inhibited casein transcription. Transfection of cells with TGFα or v-*ras*^{H} oncogene transformed cells in association with abrogation of casein expression. However, c-*erb*B_2 protooncogene transformed cells without such dedifferentiating effects. M. Stampfer (University of California, Berkeley, CA) has examined transformation and differentiation of human mammary epithelial cells in culture. Proliferation of these cells may be arrested in the G1 phase of the cell cycle with TGFβ or with an antibody which blocks access of TGFα/EGF to its receptor. Transformation of these cells is obtained with carcinogen treatment and v-*ras*^{Ki} oncogene transfection; malignant progression is associated with loss of expression of a newly described calmodulin homologue termed NB-1.

R. B. Dickson (Lombardi Cancer Research Center, Washington, D.C.) continued discussions of normal human mammary epithelial cells by describing their production of TGFα, which acted as an autocrine growth factor when cells were at high density. Partially transformed states of the mammary epithelial cells were described in which TGFα or bFGF could induce transformed, or anchorage-independent growth. In addition, a relatively new growth factor, MDGF1 (mammary derived growth factor-1), was described for normal and some malignant mammary epithelial cells. D. Salomon (National Cancer Institute, Bethesda, MD) described a new human breast epithelial transformation model. MCF-10 (a spontaneously immortalized, but nontumorigenic line) could be transformed by transfection of v-*ras*^{H}, TGFα, or c-*erb*B_2. Similar results were obtained with the mouse NOG-8 mammary epithelial cell line. G. Todaro (Oncogenes, Seattle, WA) presented data on two new growth factor inhibitors of breast cancer, amphiregulin and oncostatin M (produced by tumor promoter treatment of a breast cancer cell line and a histiocytic lymphoma cell line, respectively). Amphiregulin is a new member of the TGFα/EGF family. Finally, R. Shiu (University of Manitoba, Winnipeg, Manitoba, Canada) examined expression of c-*myc* protooncogene in estrogen-dependent human breast cancer cell lines. He reported that estrogen-inducing effects were transcriptional in nature, and that in hormone-independent cell lines, the mRNA was constitutively expressed and had a longer half-life due to message stability.

A significant portion of the meeting was devoted to studies on c-*erb*B_2 (neu) protooncogene expression, its prognostic and pathophysiologic significance in breast cancer. D. Slamon presented data on significance for c-*erb*B_2 overexpression in poor prognosis breast and ovarian cancer. It appears that its expression contributes to chemotherapeutic drug resistance since an antibody directed to the protooncogene sensitizes an overexpressing breast cancer cell line *in vitro* to *cis*-platinum killing. M. Lippman (Lombardi Cancer Research Center, Washington, D.C.) continued the theme with evidence from patient specimens that c-*erb*B_2 overexpression was associated with resistance to 5-fluorouracil. He also presented evidence that a newly isolated M_r 30,000 form of a TGFα-like molecule from a hormone-independent breast cancer cell line induced phosphorylation and growth suppression of cell lines overexpressing c-*erb*B_2 but not EGF receptor and was a candidate for a c-*erb*B_2 ligand. W. Gullick (Hamersmith Hospital, London, United

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[1] This UCLA-sponsored colloquium was held February 3–8, 1990, in Tamarron, CO.

[2] The abbreviations used are: FGF, fibroblast growth factor; EGF, epidermal growth factor; TGF, transforming growth factor.

Kingdom) described some theoretical work proposing that the sequence Ala-X-X-Val-Gly within the transmembrane domain of c-*erb*B_2 represented a "packing" or dimerization domain, critical for receptor function. Finally, J. Pierce (National Institutes of Health, Bethesda, MD) presented evidence for a new homologue of c-*erb*B_2, called c-*erb*B_3, which is amplified in some breast cancers.

Another session dealt with molecular mechanisms of breast cell metastases. P. Steeg (National Institutes of Health, Bethesda, MD) showed data on a new gene termed *NM 23* whose expression was lost in proportion to the degree of metastatic spread of breast cancer. Reexpression of the gene in metastatic cell lines partially reversed the metastatic phenotype. The gene was related to a Drosophila development gene called *awd*. G. Goldberg (Washington University, St. Louis, MO) presented data on the structure and regulation of two types of collagenase IV (M_r 92,000 and 72,000) that probably play an important role in the initial local invasion of breast cancer. H. Rochefort (Institut National de la Sante et de la Recherche Medicale, Montpellier, France) presented structural data on cathepsin D, a protease under estrogen regulation in hormone-dependent breast cancer.

Other data were presented on antioncogenes and antiestrogens in breast cancer. E. Lee (University of California, San Diego, CA) showed that the retinoblastoma antioncogene was mutated or deleted in some breast cancer cell lines; reexpression of the gene by transfection led to decreased tumorigenic capacity. A. Wakeling (ICI, London, United Kingdom) described the properties of a new class of antiestrogens. This class lacks the partial estrogenic quality of tamoxifen and may find clinical utility as a more effective antihormonal therapy of breast cancer.

A session on prognostic variables in breast cancer was led off by W. McGuire (University of Texas, San Antonio, TX). McGuire highlighted the importance of ploidy and S-phase as prognostic markers. Also under discussion were c-*erb*B_2, cathepsin D, and a heat shock protein (HSP27) as new potential poor prognosis markers. Both McGuire and Gullick emphasized findings of a high incidence of c-*erb*B_2 in comedo and Paget's disease forms of breast cancer, and Lippman discussed poor prognostic significance of a node negative, good nuclear grade subclass which overexpressed c-*erb*B_2. G. Pasternack (Johns Hopkins, Baltimore, MD) presented data suggesting that a haptoglobin-related protein (Hpr) might be a new prognostic indicator and A. Harris (Oxford University, Oxford, United Kingdom) discussed EGF receptor as a new prognostic variable in breast cancer. Harris presented data that EGF receptor was inversely related to estrogen receptor, was associated with tamoxifen resistance and poor prognosis, and interacted with c-*erb*B_2 to the detriment of the patient.

The final session dealt with new therapeutic strategies. R. Ceriani (Johns Hopkins University Cancer and Aging Research Institute, Baltimore, MD) explored antibodies (sometimes coupled to radioisotopes) directed against milk fat globule antigen as tools for tumor imaging and treatment. J. Mendelsohn (Sloan-Kettering Cancer Center, New York, NY) described anti-EGF receptor antibodies as anti-breast cancer agents *in vitro* and in nude mouse models of breast cancer. Early clinical trials are currently employing radiolabeled anti-EGF receptor antibody as an imaging agent for human cancers. Lastly, L. Liotta (National Cancer Institute, Bethesda, MD) spoke on two new antitumor strategies. He presented structural data on a newly cloned endogenous inhibitor of Type IV collagenase, called TIMP-2. This protein has anti-invasive/metastatic properties. A second compound, a GTP homologue (carboxyamidoimidazole), which blocks breast cancer cell chemotaxis, was also described. This compound was effective in inhibiting tumor growth and metastasis in the nude mouse model with low toxicity.

In summary the meeting presented numerous new insights into breast cancer ranging from understanding basic growth control and metastasis mechanisms to using this information for new prognosis and treatment strategies.

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