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Book Review

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Cancer Surveys - Volume 18: Breast Cancer
Edited by J. Taylor-Papadimitriou and I.S. Fentiman. New York, Cold Spring Harbour Laboratory Press

RECENT YEARS have seen a remarkable convergence of experimental laboratory results and clinical research in breast cancer. At last, there is a new understanding of the biological basis of the disease, and this has led to exciting ideas for innovative therapies. This volume brings together work from both basic and clinical scientists that is likely to have a major impact on the outlook for women with breast cancer.

Cultured cells provide an important experimental system for analysing differences between normal and malignant cells. The well-characterised system described by Stampfer and Yaswen for culturing normal human mammary epithelial cells has allowed the authors to investigate the responses of these cells to growth factors and how these responses can change when the cells are immortalised or transformed. They show that the signals generated by activated epidermal growth factor receptor (EGFR) are necessary for the growth of both the cell strains and immortalised cells. However, the inhibition of growth seen in these cells when they are treated with transforming growth factor-β is not seen in transformed cells. Studies with breast cancer cell lines, reported by Callahan and Salomon, suggest that EGRF, as well as the p185 c-*erb*B2 receptor, may be a suitable target for breast cancer therapy. These authors discuss in detail the various growth factors (including oestrogen) involved in the stimulation or inhibition of growth of breast cancer cells and give an idea of the complex interactions between the factors that may be occurring *in vivo*.

Recent years have also seen an increase in the efforts of many investigators to identify and understand the genetic alterations associated with the malignant change in breast cancer, and these efforts are beginning to yield exciting results. The importance of this area of activity is reflected in the fact that four of the chapters in this volume deal with aspects of genetic change in breast cancer.

Callahan and Salomon summarise the changes that have been recorded, particularly those causing loss of heterozygosity. The most frequent genetic change seen in breast cancers in TP53 gene, the "guardian of the genome" [1], and a full account of what is known about the function of the molecule and the various types of mutations seen in breast cancers is given by Eeles and colleagues. Since patients can show immune responses to TP53, the suggestion that an immunotherapy based on TP53 may be a viable proposition, made by Callahan and Salomon, should be taken seriously. In those Li-Fraumeni families that have germline mutations in TP53, some form of gene therapy may also be possible.

The amplification of a group of genes on chromosome 11, discussed by Fantl and colleagues, was originally identified via the FGF3/*int2* gene, the mouse homologue of which is expressed in a fraction of mammary tumours induced by mouse mammary tumour virus. Although this gene appears not to be expressed in breast cancers, its chromosomal location has identified an amplicon encompassing other oncogenes that are expressed, and that might have a role in tumorigenesis. The association of amplification of this region of chromosome 11 with oestrogen receptor positivity is intriguing.

In addition to TP53, two other genes are associated with an inherited susceptibility to breast cancer in women, namely the BRCA1 gene on chromosome 17 (17q21) and the ataxia telangiectasia (AT) gene on chromosome 11 (11q21-22). The relative risks and proportions of breast cancers attributable to these genes are outlined by Easton and colleagues. The cloning of the BRCA1 gene, which appears imminent, will allow the identification of young women at risk who can then be kept under close surveillance and given counselling and possibly preventative therapy. An understanding of the functioning of the gene product should also give insights into the mechanisms underlying the malignant change in sporadic breast cancers.

Histopathology has always provided a bridge between clinical and laboratory research, and this is even more obvious now that so many molecular markers for nucleic acids and proteins are becoming available. Holt and colleagues discuss how these may be used in diagnosis and to define prognosis, in particular in relation to non-invasive ductal carcinoma *in situ*. The use of differential screening of cDNA libraries to identify genes expressed at different levels in normal breast tissue and tumours could lead to the identification of other markers and may further our understanding of the phenotype of the malignant or potentially malignant cells.

In the past 10 years or so, great advances have been made in understanding some of the mechanisms involved in antigen presentation to and recognition by cells of the immune system. These advances, together with the identification of specific tumour-associated antigens, give new hope for using the host defence mechanisms to reject tumours. The possibility of applying immunotherapy to breast cancer is discussed by Burchell and colleagues, with particular reference to the use of antigens

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based on the products of the MUC1 gene. The product of this gene, polymorphic epithelial mucin (PEM), is expressed by normal epithelial cells but is overexpressed and aberrantly glycosylated in tumours. Cellular and humoral responses to PEM have been detected in both breast and ovarian cancer patients, and the cytoxic T cells recognising this antigen are not dependent on presentation by HLA class 1 molecules. Clearly, antigen presentation is of crucial importance, since tumours have not been rejected in cancer patients even though the cancer cells express not only PEM, but also mutated oncogenes, such as TP53, or proto-oncogenes, such as c-*erb* B2. This emphasises the importance of preclinical studies with mouse model for evaluation of vaccine formulations, including the possible use of co-stimulatory molecules, such as B7, and DNA-based vaccines.

Optimisation of existing therapies is still perhaps the most important consideration for clinicians and for patients presenting now with breast cancer. Recent research from Guy's Hospital on the timing of surgery in premenopausal women and its effect on prognosis is described by Fentiman and Gregory. Of patients who underwent tumour excision at the time of unopposed oestrogen (days 3–12), the 10-year survival was 54% compared with 84% for those undergoing surgery at other times of the menstrual cycle. This effect was mostly confined to patients with axillary node involvement, and the data are consistent with tumours being less cohesive under conditions of unopposed oestrogen. There has been controversy concerning this finding, and an overview has been conducted which showed that overall no significant effect was demonstrated, but that the heterogeneity of the results suggest that the positive findings are not the chance result of a normal distribution.

Being able to predict response to therapy is clearly desirable to avoid the considerable side-effects of some drugs if they are likely to be ineffective. Klijn and colleagues comprehensively review the data on prognostic factors and response to both endocrine and cytotoxic therapy. They emphasise that in fact valuable prognostic factors may be worthless in determining response to therapy, and poor prognostic factors may predict response. For example, those tumours expressing c-*erb*B2 are more likely to respond to chemotherapy, unlike those displaying multidrug resistance. In premenopausal women, the primary tumour and metastatic disease may differ in response as a result of the endocrine effects of adjuvant chemotherapy. These biological markers may eventually serve as targets for new biological therapies.

Advanced breast cancer is not curable, and yet the long natural history of the disease means that it is a very common problem, which is discussed by Rubens. Optimal management takes into account not only duration, but also quality of survival. As more patients receive systemic adjuvant therapy, so the response of recurrent disease may be reduced. Bone metastases are a common problem and these can be successfully palliated with both bisphosphonates and beta-emitting radioisotopes, with response being monitored biochemically as well as by imaging.

With breast cancer, our aim is not just to diagnose the disease at an earlier stage and treat optimally with a multidisciplinary approach, but also to identify women at risk so that preventative strategies may be used. Morrow and Jordan review this timely topic, focusing on the use of tamoxifen, in the context of the National Surgical Adjuvant Breast Project trial, which is now running in the U.S.A. They conclude that although tamoxifen is likely to prove safe and effective, there are some unanswered questions with regard to long-term toxicity, and this must be determined by a prospective randomised trial.

In considering the body of breast cancer-related work produced by scientists and clinicians, a survey of which is presented here, it becomes very clear that interaction between the laboratory and the clinic continues to be vital to progress in the development of diagnostic procedures and therapies. Although the clinical relevance of some laboratory research is still a distant prospect, much of this research has reached the stage where its "potential" needs to be tested in clinical practice. The science has advanced tremendously; the challenge remains to make the exciting results coming from the laboratory into a practical benefit for the large number of women who are going to be confronted with the disease. It is our hope that this volume of *Cancer Surveys* takes a small step in the direction of achieving that aim.

1. Lane DP. p53, guardian of the genome. *Nature* 1992, 358, 15–16.

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Letters

Combination Chemotherapy With Carboplatin and Etoposide of Brain Metastases From Cancer

A. Santini, P. Malacarne, M. Indelli and A. Maestri

ETOPOSIDE HAS proved useful in the case of small cell lung cancer (SCLC) [1, 2], while carboplatin has been successfully used in head and neck cancer and in ovarian cancer [3]. Platinum derivatives and etoposide have been employed even in the treatment of brain tumours [4]. The association of etoposide and cisplatin, useful in the treatment of many solid tumours, has proven to be highly effective in the management of brain metastases from breast carcinoma [5].

The present study was designed to assess the efficacy of carboplatin and etoposide in brain metastases from solid tumours.

22 consecutive patients (15 males and 7 females, median age 55.7 years, range 40–71) have been studied; 13 patients [10 lung cancers, 3SCLC, 7 non-small cell lung cancer (NSCLC), 3 occult tumours] who had not received any previous chemotherapy, and 9 (4 breast cancers, 4 lung tumours, 2 SCLC, 2 NSCLC, 1 uterus

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