Parallel Symposia

SY-1. Genetic Aspects and Molecular Pathology (September 11)

SY-1-1 Quality Control in Molecular Pathology

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Somatic alterations to key regulatory genes — oncogenes & anti-oncogenes — act additively in the genesis of tumors and can be measured in tumor biopsies. Research on the molecular genetics of cancer has invaluable cognitive importance and shows some major impacts for cancer treatment: first, some oncogenes or anti-oncogenes endow cancer cells with a special phenotype, hence alteration to certain oncogenes display prognostic and predictive value, as in the case of *erb*B2 in breast cancer. Second, inheritance of mutated alleles of certain genes predispose to the development of specific types of cancer, so that detection of those alleles may select out people to special preventive strategies. Lastly, the characterization of the leading molecular change in a tumor is the necessary step to devise a specific gene therapy. Molecular biology has introduced spectacular methodologies, which allow evaluation of gene deletion, amplification, rearrangement, single-base mutations and expression, even when few tumor cells are available. However, it is common to observe in the literature large discrepancy between different studies, especially when considering statistical aspects, e.g. the frequency of a specific mutation in a given type of cancer or the frequency of cases overexpressing a given oncogene. This is mainly due to differences in the methods and reagents employed, which are usually drawn directly from the basic research lab and display large individual-based variation. More and more frequently, molecular pathology is being involved in large-scale clinical applications. In breast cancer, this is well illustrated by the cases of *erb*B2, *p53, myc*, BRCA 1 & 2. A review on the myriad of reports on *erb*B2, for example, reveals impressive variation in frequencies and correlations, as measured by distinct methodological approaches. Clinical use of molecular pathology requires that multicentric comparative methodological trials be run and that adequate qualitative & quantitative reference standards be implemented.

SY-1-2 Genes Predisposing to Breast Cancer

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Much progress has been made over the past few years in identifying breast cancer predisposing genes. Three genes have been identified that confer high risks, i.e. *TP53, BRCA1,* and *BRCA2.* Germline mutations in *TP53* are associated with the Li-Fraumeni syndrome, and are presumably very rare. Female mutation carriers of *BRCA1* have been estimated to have an 87% risk to develop breast cancer before the age of 70, and 63% risk to develop ovarian cancer before that age. Similar breast cancer risks are predicted for *BRCA2,* while this gene is also particularly associated with breast cancer in males. The existence of at least two moderate risk genes is now also clear. Recessive heterozygous mutations in the gene for Ataxia telangiectasia *(ATM)* are expected to be present in 2–7% of all breast cancer cases, but have been estimated to confer only moderately increased risks for the disease. *CDS,* for Cowden's Syndrome, is rare in the population and its associated lifetime risk of breast cancer is approximately 30%. *BRCA1* and *BRCA2* are thus peculiar in that they are predicted to be relatively frequent in the general population and to confer high breast cancer risks. Finally, it is becoming increasingly evident that other genetic factors may modify the expressivity or penetrance of these genetic factors. One of them appears to be the variable number of tandem repeat (VNTR) locus of *HRAS1. BRCA1* carriers with a history of ovarian cancer were found to carry one or two rare alleles at this locus more frequently than carriers without ovarian cancer (odds ratio 2.85: P = 0.002).

SY-1-3 Loss of Heterozygosity and Prognosis

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The etiology of breast cancer involves a complex interplay of various factors, including genetic alterations. Many studies have been devoted to the identification and characterization of mutations that occur frequently during breast tumorigenesis. The major types of genetic abnormalities frequently observed in breast tumor DNAs are amplification of proto-oncogenes (*MYC, ERBB2*) and chromosome band 11q13, mutation of *TP53,* and loss of heterozygosity (chromosomes and chromosome arms 1, 3p, 6q, 7q, 8p, 11, 13q, 16q, 17, 18q and 22q). The latter may correspond to losses or inactivations of tumor suppressor genes.

Certain of these genetic anomalies appear to be of prognostic value in clinical oncology. The principal alterations of potential prognostic value are amplification and overexpression of the *MYC* and *ERBB2* proto-oncogenes and of the amplification unit 11q13, as well as alterations in the *NME1* and *TP53* suppressor genes (see review by Gasparini et al., 1993). However, this first list of alterations is provisional, since the identification of deletions associated with a poor prognosis, such as those in 7q31, 16q and 17p13.3, suggests that other tumor-suppressor genes may be of prognostic value.

Identification of these putative suppressor genes and their confirmation as novel factors of great prognostic value will require further studies.

SY-1-4 P53 Mutations and Other Genetic Changes in Invasive and Intraductal Breast Cancer

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Knowing the genetic alterations present in breast cancer (and the alterations in protein expression resulting from these alterations) may help in predicting clinical behaviour and guiding therapy. Using immunohistochemistry, we have investigated paraffin embedded tumour specimens from 441 node-negative premenopausal patients who were randomized in a trial comparing perioperative chemotherapy with no adjuvant therapy for the expression of p53, c-erbB-2/neu, estrogen- and progesterone receptor and Ki-67. Patients with p53 negative staining tumours showed a benefit from adjuvant chemotherapy ($P < 0.01$), whereas patients with p53 positive staining tumours did not.

Ductal carcinoma in situ (DCIS) is heterogenous with respect to histologic type, clinical presentation and clinical behavior. In 120 cases of DCIS, p53 was overexpressed in 26% of cases, c-erbB-2/neu overexpression (as a result of gene amplification) in 46% of cases and for both was associated with the poorly differentiated type of DCIS, which is more likely to progress to invasive carcinoma. Loss of heterozygosity for loci on chromosome 16 was associated with well differentiated DCIS, whereas LOH on chromosome 17 was associated with poorly differentiated DCIS.

SY-2. Ductal Carcinoma In Situ (DCIS) (September 11)

SY-2-1 The Classification of Ductal Carcinoma in Situ of the Breast

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Ductal carcinoma in situ (DCIS) is a heterogeneous lesion being diagnosed with increasing frequency as it is often detected by mammography. Treatment by conservation therapy is still controversial. Success may depend on several factors, including lesion size, adequacy of excision and histological type. Traditional histological classification is unsatisfactory. There is considerable interest in establishing alternative criteria based on nuclear features,