Proffered Papers

Breast cancer genetics and biology

10 ORAL

Founding BRCA1 mutations in Austrian HBOC families

T. Wagner[1], R. Möslinger[1], D. Muhr[1], K. Hirtenlehner[1], P. Underhill[3], M. Pec[1], H. Breiteneder[2], E. Kubista[1], P. Oefner[4]. [1]*Dept. of Obstet. and Gynecol.;* [2]*Dept. of Gen. and Exp. Pathology, University of Vienna, Austria; Departments of* [3]*Genetics;* [4]*Biochemistry, Stanford University, USA*

About one-tenth of annual breast cancer cases can be traced to a germline defect. Of the 10% who have an inherited susceptibility to breast and ovarian cancer, one-half are due to mutations of the BRCA1 which maps to chromosome region 17q21.1 and was sequenced in 1994. More recently, it has become clear that distinct populations (families of Ashkenazi ancestry, Icelandic population, Dutch population) may be characterized by a high frequency of certain mutations in BRCA1 and BRCA2. We screened 41 Austrian families with at least 2 BC cases <50 and/or OC or one BC < 30 by denaturing high-performance liquid chromato-graphy DHPLC, PTT of exon 11 and direct sequencing for BRCA1 mutations. Seven different BRCA1 mutations in 11 Austrian HBOC families (25%) could be detected. Two 4 bp deletions (2795del4, 3135del4), one insertion (5382insC), two nonsense mutations (Y4302X, Y5370X), one missense mutation (T300G) and one splice site mutation (331 + 1 G-A) were identified. Five out of the seven mutations reported here are novel mutations and have not been detected outside of Austria.

11 ORAL

Survival in breast cancer associated with germline mutations of BRCA1

L.C. Verhoog[1], C. Seynaeve[1], L.M.C. v.d. Bosch[1], C.T.M. Brekelmans[1], A.N. van Geel[2], A. Wagner[3], E.J. Meijers-Heijboer[3], A. v.d. Ouweland[3], P. Devilee[4], J.G.M. Klijn[1]. [4]*On behalf of the Rotterdam Committee of Medical and Genetic Counseling;* [1]*Dept. Medical;* [2]*Surgical Oncology, Rotterdam Cancer Institute;* [3]*Department of Clinical Genetics, Erasmus University, Rotterdam, The Netherlands*

Hereditary breast (ovarian) cancer (HB(O)C) associated with germline mutations of BRCA1 has been characterized by a younger age at onset, frequent bilateral disease, and pathological features suggesting a poor outcome. However, some studies on familial breast cancer suggest an identical or even better survival as compared to survival in sporadic breast cancer patients (pts.). Therefore, we investigated the features and outcome in breast cancer pts. with a BRCA1 germline mutation. Pathology reports and clinical data were retrieved from 49 breast cancer pts. belonging to 20 families with either a proven BRCA1 gene mutation (17 fam.) or linkage to the BRCA1 gene (LOD score > 1.5) (3 fam.). Control pts. were selected from the cancer registry of our institution and matched, in a 1:4 ratio, for age and year of diagnosis. Survival curves were constructed using Kaplan-Meier estimates and compared by the log-rank test.

The average number of breast cancer pts. per HB(O)C family was 2.5 (range 1–5). Breast cancer was diagnosed between 1970 and 1995 (median yr of diagnosis: 1987), median follow-up was 4.2 yrs for BRCA1 pts. and 3.1 yrs. for sporadic pts. Characteristics of hereditary cases were: median age at onset 40 yrs (range 27–76 yrs), menopausal status pre-/peri-/post-/unknown in 39/1/6/4 pts. respectively. Histologic examination showed adenocarcinoma NOS (14 pts), ductal carcinoma (21 pts), adenosquamous carcinoma (1 pt), medullary carcinoma (4 pts), and lobular carcinoma (2 pts). Stage at diagnosis was: stage I in 19 pts., stage IIA/B in 13/6 pts., stage IIIA/B in 4/1 pts., stage IV in 2 pts, unknown in 4 pts. As of January 1997, 22 pts. died of breast cancer, 23 pts. had no evidence of disease, 1 pt. was alive with disease. The DFS at 2 and 5 yrs was 74% and 56% respectively. 2- and 5-year survival for BRCA1 mutation carriers was 78% and 63% respectively, which was not significantly different from that of the matched control group (86% and 62%, p = 0.73).

In Conclusion: As compared with sporadic breast cancers, breast cancers associated with BRCA1 germline mutations do not appear to have a significantly different clinical outcome. (Supported by the Dutch Cancer Society, grant DDHK 95–953).

12 ORAL

Genetic alterations in benign and borderline malignant breast tumors

P. Dal Cin[1], M.R. Christiaens[2], J. Bullerdiek[3], H. Van den Berghe[1], Ph. Moerman[4]. [1]*Center for Human Genetics and Flanders Institute of Biothechnology;* [2]*Departments of Surgery-Senology;* [4]*Pathology, University Hospital Gasthuisberg, Leuven, Belgium;* [3]*Center for Human Genetics and Genetic Counseling University of Bremen, Germany*

Clonal chromosome abnormalities do not frequently occur in benign breast lesions. The cytogenetically most intensively investigated benign breast tumors are the fibroadenomas, and in these only about 20% of the reported cases showed karyotypic changes with, however, recurrent aberrations involving chromosome 12. Chromosome studies in other benign breast lesions i.e. phyllodes tumors, hamartomas, fibrocystic disease are still scarce, but some chromosome regions i.e. 12q15, 6p21, 6q15, 1q seem to stand out and seem to be important in the pathogenesis of these lesions.

We have cytogenetically investigated a series of benign breast lesions; we confirm the involvement of specific chromosome region(s) especially of 12q15 and 6p21, and have identified some underlying molecular lesions including rearrangements of the HMGIC gene on 12q15 and of the HMGIY gene in 6p21.

13 ORAL

Transcriptional regulation of protease-inhibitor maspin with tumorsuppressor-activity in breast cancer

N. Maass[1,2], K. Nagasaki[2], M. Zhang[2], R. Sager[2], W. Jonat[1]. [1]*Department of Obstetrics and Gynaecology, University of Kiel;* [2]*Dana Farber Cancer Institute, Harvard Medical School, Boston, Germany*

Purpose: Maspin (mammary serpin) is a novel serine protease-inhibitor with tumor-suppressor activity in human mammary epithelial cells. The maspin gene is expressed in normal mammary epithelial cells but down-regulated in a series of tumor-derived breast cell lines. Maspin's decreased expression with increased level of malignancy and its loss in metastatic cells is regulated at the transcriptional level.

Methods and Results: We have cloned and sequenced the maspin promoter region to investigate its regulation in normal and tumor cells. By Chloramphenicol-Transferase- (CAT) Assay and Deletion Analysis we have identified the PEA-3 and AP-1 sites within the maspin promoter that are active in regulating maspin expression in normal mammary epithelial cells but inactive in tumor cells. The PEA-3 site alone is sufficient to activate transcription in a heterologous promoter, while the AP-1 site cooperates with PEA-3 in activation. The enhancing function by PEA-3 and AP-1 promoter elements is decreased with malignancy (primary tumor cells 21NT) and is abolished in metastatic cells (MDA-MB231). Gel retardation experiments (EMSA) confirm the presence of PEA-3 binding proteins which differ qualitatively and quantitatively in a comparison of normal mammary epithelial cells and mammary carcinoma cells.

Conclusions: Our data demonstrate that the loss of maspin expression during tumor progression is regulated at the transcriptional level and results most likely from the absence of transactivation through the PEA-3 and AP-1 sites.