sis of these data also identified a subset of genes that distinguish tumor specimens from each other as well as from normal prostate tissue. Random permutation of the sample labels clearly indicates that the subset of genes separating tumor subgroups far exceeds that expected by chance alone (P=0.002). This work indicates that investigation of prostate cancer based on gene expression can identify genes that may help distinguish more aggressive forms of this disease.

Dunn, Sandra, E. [52]

Gene expression profiling of normal breast epithelial cells following treatment with insulin-like growth factor I

Jennifer S. Oh[1], Pierre Buchel[2], Karla Martin[2], Jill E. Kucab[3], Tomo Oshimura[2], Lee Bennett[2], Kelli Reynolds[2], David M. Cykert[1], J. Carl Barrett[4], Richard P. DiAugustine[1], Cynthia Afshari[2] & Sandra E. Dunn[3]

[1]*Laboratory of Molecular Carcinogenesis, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA*
[2]*Micorarray Group, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA*
[3]*Functional Genomics Program, North Carolina State University, Raleigh, North Carolina, USA*
[4]*Laboratory of Biosystems and Cancer, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA*

Clinical and experimental data support a role for insulin-like growth factor I (IGF-I) in breast cancers. Our laboratory previously showed that IGF-I is a stimulus for mammary gland branching morphogenesis as well as breast tumor growth and metastasis. Recent epidemiological studies indicate that elevated serum IGF-I levels in premenopausal women are linked with increased mammographic density, ductal carcinoma *in situ* and breast cancer risk. The IGF-I receptor is reportedly overexpressed in 30–40% of early-stage breast cancers. It is unclear why activation of IGF-I receptor signaling is associated with the development of cancer. We are using complementary DNA microarrays to profile gene expression in normal breast epithelial cells and to investigate the mechanism behind cancer risk related to IGF-I. We profiled the gene expression of normal breast epithelial cells in the absence or presence of IGF-I at 0, 0.5, 1, 2, 4, 6, 8 and 24 h on 2K cDNA microarray chips and observed inhibition of pro-apoptotic genes, including *fas* ligand. We also found increased expression of invasion and neovascularization genes. For example, the potent vascular mitogen VEGF was induced by IGF-I at the 2-h time point. To confirm differential gene expression, messenger RNA was validated by a real-time quantitative polymerase chain reaction, and the protein products were confirmed by enzyme-linked immunosorbent assay. Cellular trafficking was studied to illustrate that the cells were responding to IGF-I through a PI3K/AKT pathway. We demonstrate that the activated forms of AKT, GSK, CREB and HIF-1a translocated into the nucleus in response to IGF-I treatment. The differential gene profiling of normal breast epithelial cells to growth factors has not been reported to date, and this investigation provides insight into the expression of gene products that may have fundamental importance to the development and progression of breast cancer.

Eckart, Meese [53]

Genes overexpressed in the transition zone from normal to tumor tissue in larynx and pharynx carcinoma

Eckart Meese, Jörg Bohlender, Helmut Steinhart & Ulrike Fischer

Department of Human Genetics, University of Saarland, 66421 Homburg/Saar, Germany

To identify genes relevant in the development and progression of larynx and pharynx carcinoma, we investigated samples derived from the transition zone between normal tissue and tumor. For larynx and pharynx carcinoma this transition zone offers an ideal starting point to identify genes involved in early tumor development. Using microarray expression analysis we found overexpression of a group of genes, including the gene for PA-FABP. Overexpression of PA-FABP in the transition zone was confirmed by northern blot hybridization using RNA from normal tissue as control. Northern blot expression analysis also revealed overexpression of PA-FABP in the corresponding tumor samples. A second group of genes was predominantly overexpressed in the transition zone from larynx carcinoma to normal tissue, whereas no overexpression was detectable in the transition zone from pharynx carcinoma to normal tissue and in all corresponding tumor samples. These genes may be relevant in the early development of larynx carcinoma and may serve as a valuable diagnostic marker.

Einspahr, Janine [54]

Mutation and overexpression of p53 as intermediate biomarkers in the chemoprevention of skin cancer

Janine Einspahr, David Alberts, Nancy Hart, Nelson Mark & Bowden Timothy

University of Arizona Cancer Center, Tucson, Arizona, USA

The incidence of skin cancer is increasing in the United States, and effective primary prevention and chemoprevention strategies are needed to reduce its incidence, morbidity and mortality. Squamous cell carcinoma, in contrast to most internal cancers, is characterized by a high rate of p53 mutations and p53 overexpression in premalignant actinic keratosis (AK). Similarly, p53 mutations are frequently found in normal-appearing, chronically sun-exposed skin. We have been using p53 mutations and p53 overexpression as a potential biomarker of response to chemoprevention agents. Difluoromethylornitine (DFMO), an irreversible inhibitor of ornithine decarboxylase, inhibits the synthesis of polyamines, which have an important role in the process of skin carcinogenesis. In a randomized, placebo-controlled study of topical DFMO for six months in 48 subjects with AK, topical DFMO was effective in significantly reducing AK number (23.5%; P=0.001), spermidine levels (26%; P=0.04) and p53 protein expression (22%; P=0.04), but not cell proliferation. There were no significant differences in the frequency of p53 mutations (exons 5–8) (23.8% at baseline, 28.6% after placebo and 26.2% after DFMO). DFMO seemed to be more effective in reducing AK, spermidine and potentially p53 mutations on right arms (33%=one p53 mutation) as compared with left arms (67%=one p53 mutation), suggesting that left arms are more resistant to the effects of topical DFMO. The addition of biomarkers, developed on the basis of the molecular biology of the disease, to chemoprevention studies is essential.