Journal of Cellular Biochemistry, Supplement 17F:165–166 (1993)

OVERVIEW

Intermediate Biomarkers

Intermediate biomarkers relevant for chemoprevention are those biochemical, molecular, and genetic alterations that occur in tissues and cells during the multi-step process of carcinogenesis. Notable changes occur in proliferation- and differentiation-associated genes in premalignant and malignant lesions. Consequently, proliferation and differentiation markers are plausible candidates for intermediate biomarkers. This session concentrated on such markers as well as on other new diagnostic markers.

Three presentations were centered on differentiation and proliferation markers. Dr. Reuben Lotan (University of Texas, M.D. Anderson Cancer Center) described the ability of retinoids to reverse the aberrant expression of keratinizing squamous differentiation markers in premalignant and malignant lesions that develop in nonkeratinizing oral cavity mucosa. He then presented recent findings demonstrating a significant decrease in the expression of retinoic acid receptor-beta (RAR-β) in dysplastic and neoplastic lesions. Further, he showed treatment of leukoplakia with 13-*cis*-retinoic acid can increase the expression of RAR-β *in vivo*. These results indicate that decreased levels of RAR-β may be involved in tumor progression and that increased expression of this receptor by retinoid treatment may serve as an intermediate marker for response.

Dr. John Crissman (Wayne State University) reviewed the expression of differentiation markers, such as keratins, proliferation markers (*e.g.*, PCNA), tumor suppressor genes (p53), and extracellular matrix constituents (*e.g.*, collagen type IV, laminin) in normal, hyperplastic, dysplastic, and neoplastic tissues of the upper aerodigestive tract and discussed their value as diagnostic markers. He demonstrated that PCNA labeling, undetectable in normal and hyperplastic lesions, increased in mild dysplasia and remained high in severe dysplasia and carcinoma. Expression of p53 was detected first in severe dysplasia and increased in carcinomas. These results point out the significant value of PCNA as a marker of early premalignant lesions.

Other markers associated with cell proliferation, epidermal growth factor receptor (EGF-R) and its ligand, transforming growth factor-alpha (TGF-α) were the focus of the presentation by Dr. Jennifer Grandis (University of Pittsburgh Medical School). She discussed her analysis of the expression of these two components of a potential autocrine loop in squamous cell carcinomas of the head and neck. Others have shown these molecules to be elevated in malignant cells. However, Dr. Grandis found that even the histologically normal tissue adjacent to carcinoma contained higher levels of TGF-α and EGF-R than normal mucosa from patients without cancer. These findings imply that elevation of these molecules is an early event in head and neck carcinogenesis.

The three other presentations were concerned with the development of new non-invasive methods for early diagnosis. Dr. James Mulshine (NCI) emphasized the need to develop non-invasive methods for the successful biomarker analysis of large numbers of patients at risk. He described the advantages of using sputum for such an analysis and evaluated the validity of immunohistochemical assays of sputum for the early detection of lung cancer. Dr. Mulshine described the plans for the analysis of two markers, gastrin releasing peptide and peptidyl aminating monooxygenase activity, by sputum analysis of patients with resected lung cancer.

Dr. David Sidransky (Johns Hopkins University) highlighted the use of molecular biological techniques for the identification of genetic changes, including mutations in tumor suppressor genes (*e.g.*, p53) and oncogenes (*e.g.*, *ras*), that may occur at early stages of tumor development and serve to diagnose premalignancy or early stages of malignancy. He described the methodology that enabled him to identify *ras* oncogene mutations in DNA isolated from the stools of patients with curable colorectal tumors. Dr. Sidransky presented preliminary results indicating that his methodology may eventually be useful for the analysis of sputum of individuals at risk for developing lung cancer.

Dr. Stimson Schantz (Memorial Sloan-Kettering Cancer Center) addressed the potential sampling errors inherent in analysis of invasive biopsies of the aerodigestive tract and described his experience with bio-optical technology to scan tissues *in vivo* by measuring intrinsic tissue autofluorescence. He found that the autofluorescence of normal, premalig-

nant, and malignant tissues was distinct and that the differences between normal and premalignant tissue can be detected at an early stage, before histological changes are obvious. Thus, the alteration of tissue fluorescence may be an intermediate endpoint.

Reuben Lotan, Phd
Professor and Deputy Chairman
University of Texas M.D. Anderson Cancer Center
Department of Tumor Biology
Box 108
1515 Holcombe Boulevard
Houston, TX 77030