Journal of Cellular Biochemistry, Supplement 16G:159-160 (1992)

OVERVIEW

Biomarkers in Other Target Sites

This section is devoted to intermediate endpoint biomarker research in organs other than the colon. The cancer risk associated with the presence of intraepithelial neoplasia has been reasonably well established for a number of organ systems. A biomarker which appears in connection with such a lesion may be assigned a similar measure of risk. The natural history of intraepithelial neoplasia in different organs, with implications for chemoprevention strategy, has recently been reviewed [1]. A brief commentary on the presentations describing intermediate markers in various organ epithelia follows.

BREAST

Dr. David L. Page presents a comprehensive and thoroughly researched categorization of breast lesions with slightly increased cancer risk, moderately increased cancer risk, and greatly increased cancer risk. His description of the category of lesions with moderately increased risk, which he calls atypical hyperplasia of the ductal lobular unit, derives from his own well-known work. Dr. Page clearly reviews currently accepted nomenclature and, of particular importance, links anatomic terms to levels of malignancy risk, providing a framework to which other markers may be added to increase precision or to replace the anatomic markers.

Dr. Nitin Telang discusses two molecular biomarkers which he has identified in organ cultures of both mouse and human mammary tissue, the latter tissue being terminal duct lobular units. In the presence of a carcinogen, these tissues show elevated levels of *ras* p21-GPT binding and also increased C16α hydroxylation of estradiol. These results suggest that a systematic analysis of the two markers should be made in normal, precancerous, and cancerous tissue to determine their potential application as biomarkers during chemoprevention intervention in human breast cancer.

LUNG

Dr. James Mulshine discusses the lung cancer field at the histological level, giving the different epithelial cell types which generate the four basic types of lung cancer: squamous cell, large cell, small cell, and adenocarcinoma. He describes a monoclonal antibody against the gastrin releasing peptide (GRP), which is a pulmonary autocrine growth factor. Many other molecules produced by lung cancer cells may also mediate autocrine growth effects, including epidermal growth factor (EGF) and insulin growth factor 1 (IGF-1). Another important cell population of the terminal alveoli are the Clara cells, which produce a 10-kilodalton protein (CLR-10) which can be used to identify them. Clara cells are felt to be the progenitor population for a subset of adenocarcinomas called the bronchioalveolar type.

PROSTATE

Dr. Michael Brawer describes a morphological precancerous lesion of the prostate termed prostatic intraepithelial neoplasia (PIN). An antibody against cytokeratins 14, 16 and 19, as well as the lectin *Ulex*, shows expression in PIN and carcinoma but not in benign cells. Some important general statistics are given: grade 1 PIN is found in 21%, grade 2 in 53%, and grade 3 in 54% of prostates with carcinoma. On the other hand, grade 1 PIN is found in 55% and grade 3 PIN in only 17% of prostates without carcinoma. An important observation is that no cases of peripheral zone carcinoma were seen that were not associated with PIN when the entire radical prostatectomy specimen was studied. Finally, prostate specific antigen (PSA) may be elevated in patients exhibiting PIN. Thirteen of 25 patients with PIN had a serum level of PSA above the established normal range of 4.0 ng/ml. Of 21 patients who had PIN identified on biopsy because of a palpable prostatic abnormality, 12 of

the patients (57%) demonstrated carcinoma on a second biopsy.

ESOPHAGUS

Dr. Kan Yang presents the anatomical changes of precancerous lesions seen in 221 esophageal biopsies with cytological hyperplasia. Seven basic anatomical changes are described, as well as three growth patterns. The tritiated thymidine labeling index was highest in dysplasia. This comprehensive and well-documented sudy will provide baseline information for numerous future intraepithelial endpoint biomarkers of the esophagus.

REFERENCES

1. Boone CW, Kelloff GJ, Steele VE: Natural history of intraepithelial neoplasia in humans with implications for cancer chemoprevention strategy. Cancer Res 52:1651-1659, 1992.

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