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OVERVIEW

Markers of Early Lesions

Over 49,000 new cases of bladder cancer are diagnosed every year in the United States [1]. Superficial transitional cell carcinomas (TCCs) account for approximately 75–80% of these tumors, while the remaining 20–25% are clinically muscle invasive or metastatic lesions at the time of initial presentation. Approximately 70% of superficial bladder tumors will have one or more recurrences [2,3], with 25% of these expressing a higher histologic grade and 10–15% subsequently developing invasive disease [2].

It is clear that following complete transurethral resection (TUR) of superficial exophytic tumors, the likelihood of subsequent recurrence and/or progression is determined by the status of the remaining mucosa. Mucosal instability manifested as atypia or carcinoma *in situ* (CIS) provides the soil for new tumors. The natural history and biologic potential of an individual urothelial diathesis is unpredictable and currently based on histopathologic criteria. Certain pathologic features such as grade, size, multifocality, presence of CIS and distant mucosal abnormalities have been identified as a means to predict the clinical course of patients with superficial bladder cancer. Furthermore, mapping studies of cystectomy specimens indicate significant rates of dysplasia and CIS in areas remote from visible tumors. The heterogeneity of preneoplastic lesions and superficial bladder tumors is clinically manifest in varying patterns of tumor recurrence and progression. Such heterogeneity cannot be reliably and consistently related to conventional morphologic features. Clearly, additional means of characterizing tumors and preneoplastic lesions are needed. The hope is to identify more sensitive and specific markers of tumor heterogeneity that may serve as reliable predictors in the individual patient.

The reports included in the session of "Markers of Early Lesions" focused on blood group antigens, epidermal growth factor (EGF) receptors (EGF-R), integrins, the retinoblastoma (RB) gene and p53 as potential markers of bladder tumor heterogeneity, disease behavior, and patterns of recurrence and/or progression.

Blood group antigens have been extensively evaluated as potential markers in superficial bladder cancer. Dr. Sheinfeld discussed how improved immunohistochemical techniques and highly specific monoclonal antibodies coupled with a detailed description of the genetic and biosynthetic pathways have contributed to a better understanding of this antigenic system as it pertains to benign and malignant urothelium. In particular, the influence of an individual's secretor status is emphasized; nonsecretors do not express A, B, H, Le^b or Le^y antigens in benign urothelium and thus antigenic deletion of A, B, or H cannot be ascertained in this group of patients. Secretor individuals do express A, B, H, Le^b and Le^y in normal urothelium and delete A, B or H antigens during malignant transformation. Furthermore, the Le^x determinant appears to be a very promising tumor-associated antigen in urothelium. It is not detected in normal urothelium except for occasional umbrella cells, while papillomas, CIS and TCC express the Le^x antigen in approximately 85% of cases. Detection of this antigen on exfoliated bladder epithelial cells from over 300 cases resulted in a sensitivity rate of 87% and appeared to predict tumor recurrence in high risk, disease-free patients.

Dr. Reznikoff gave a very thorough review of the current status of EGF and EGF-R and their potential role as markers and targets for bladder cancer chemoprevention. The distribution of EGF-R is strictly confined to the basal layer in normal urothelium, but in premalignant and malignant urothelium, EGF-R is expressed on cells of all epithelial layers. This altered expression could provide premalignant or malignant urothelium access to EGF. Importantly, EGF, normally excreted in very high concentrations in urine, has recently been found to be reduced in TCC patients. The potential clinical relevance of this observation was discussed. Interestingly, Messing [4] demonstrated the influence of pH on EGF affinity to human TCC cells, with acidification greatly reducing EGF binding to the EGF ligand.

Integrins are dimeric cell surface glycoproteins that play important roles in cellular adhesion and differentiation. Dr. Grossman described in detail the integrin $\alpha 6\beta 4$ which in normal urothelium appears to have a pattern of expression restricted to the basal cell layer. Altered expression of this antigen occurs in bladder cancer, even in early stage lesions. Its potential role as an early tumor marker was discussed. The preliminary data presented on DD23, an IgG1 monoclonal antibody, appear encouraging but will require further characterization and evaluation.

Tumor suppressor genes have been the focus of significant investigative efforts over the past several years. In particular, the human RB gene and the gene encoding the cellular protein p53 are thought to regulate and limit normal proliferation of cells; their loss has been reported in human bladder cancer cell lines and primary bladder tumors. Transfection of the RB gene into RB-negative bladder cell lines resulted in significant tumor suppression. Dr. Benedict gave an overview of the biology of the RB gene and its potential role as a marker of bladder tumor progression. Altered RB expression occurs with higher frequency in advanced stage tumors compared to low stage tumors. Furthermore, altered RB expression was shown to be an independent adverse prognostic marker in predicting response to therapy in locally advanced bladder cancer.

It has been shown that mutations or deletions of p53, located on the short arm of chromosome 17, are common genetic events associated with tumorigenesis. Dr. von Eschenbach and Dr. Reuter reviewed very exciting data from independent laboratories regarding p53 alterations in bladder cancer and the very promising role they may have in identifying patients at increased risk for disease progression. In an immunohistochemical study using antibody PAB-1801, Reuter *et al.* showed that detection of abnormal p53 expression in ≥20% of tumor cells was the only significant marker of tumor progression in 43 patients with T1 bladder carcinoma.

In summary, a number of very promising markers were discussed during this session; however, prospective validation is imperative if they are to serve as surrogate endpoints in future chemoprevention trials.

REFERENCES

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