Discussion of Morphological Markers of Early Neoplastic Change in the Urinary Bladder

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One of the most encouraging aspects of experimental research into the pathogenesis of bladder cancer and the search for morphological markers that accompany neoplastic transformation is the quite remarkable agreement and coincidence of information coming from 3 different research centers, in America, in England, and in Japan. Although different chemical carcinogens have been used in these various centers to induce bladder cancer in rodents, the results produced have been consistent and enable us to understand the development of early bladder cancer in a way which I believe to be unrivaled for any other organ. Rather than summarize work presented or published so far, I would like to direct attention to 2 aspects of the malignant urothelium which I find to be of particular interest.

The 1st aspect has far-reaching implications in the diagnosis and treatment of human bladder cancer. In humans, urothelial tumors are characteristically multifocal, and local extirpation of papillary tumors is frequently followed by recurrence of neoplastic disease in the bladder, ureters, or renal pelvis. This is consistent with evidence for urine-borne chemical carcinogens as the primary initiators of bladder cancer. Preneoplastic changes may therefore be present in disparate sites in the urothelium of patients with diagnosed bladder cancer. If neoplastically transformed areas in apparently “normal” urothelium can be unequivocally identified and the subsequent biological behavior of the urothelium predicted, choice of treatment for any individual patient can then be made on a more rational basis.

The malignant urothelium undergoes a remarkable change in aspect at its urinary face. The large, polyploid, polygonal cells, with their unique, asymmetrical membrane, which limits the surface of normal urothelium in both humans and animals (4, 7, 13-15), are lost, and new ones fail to differentiate. Instead, the surface of the tumor appears to be cobbled, and the small, irregular cells carry numerous microvilli, limited by a flexible membrane with a pronounced filamentous glycocalyx (1, 5, 7-11, 14). These features are of more than academic interest, since they occur not only in animals but also in humans (3, 4, 8). Furthermore, the surface cells are shed into the urine where they may be detected by their microvilli in urine sediments (12). We are now examining both urine sediments and multiple biopsies from patients with diagnosed or suspected neoplastic disease of the bladder, by scanning and transmission electron microscopy, for loss of normal differentiation and development of surface cells with microvilli and a filamentous glycocalyx (14). These techniques have already proved to be more sensitive than conventional urine cytology and histology for diagnosing unequivocal neoplastic change in noninfected urine, and their value has been confirmed subsequently after surgery.

The 2nd point I wish to emphasize is the possible role played by the blood vessels in determining the subsequent growth pattern of urothelial tumors. Very soon after treatment of an animal with a bladder carcinogen, it is sometimes possible to find areas in which blood capillaries have “invaded” and grown horizontally within a urothelium that is still flat and only slightly hyperplastic. We have evidence that this pattern of capillary invasion is followed by nodular, polyploid hyperplasia as the urothelial cells below the capillary proliferate, leading to downgrowths and the development of solid, nodular tumors in the bladder wall (6). By contrast, capillaries may project directly up into the bladder lumen, carrying with them a covering of urothelial cells which may appear to be normally differentiated, i.e., benign papillomatosis. As the capillary endothelial cells divide and multiply, thus forming branches on the main stem, a typical fronded papillary process develops, in which areas of urothelium may or may not show neoplastic change. The full range of urothelial changes from normal to neoplastic may be found in both animal and human papillary tumors.

One is tempted to ask, which comes first, neoplastic change in the urothelium or in the endothelium? In skin, the conventional view is that the neoplastically transformed epithelial cells produce a factor that stimulates mitosis in the endothelial cells (2). By contrast, it sometimes appears from morphological evidence that genesis of a papillary tumor in the bladder results from unregulated division of endothelial rather than urothelial cells. The rapidly extending blood capillaries form a matrix or surface, which the urothelium overgrows, in the same way as it will reepithelialize a serosal patch or the bladder wall after wounding. But the rate of capillary growth so far outstrips that of the urothelium that the papillary fronds are frequently covered by a urothelium that is only 1 or 2 cells thick, instead of the more normal 3- to 4-cell-thick tissue.

There is much evidence for the 2-way exchange of information between the urothelium and its supporting stroma (4, 6), and it is perhaps worth considering whether bladder carcinoma may sometimes arise as a secondary event following neoplastic change in the endothelial cells of capillaries in the supporting mesenchyme.
References


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