UROTHELIAL TISSUE REGULATION

Unraveling the Role of the Stroma

Jennifer Southgate,1 Patricia Harnden,2 Peter J. Selby,1 David F. M. Thomas,3 and Ludwik K. Trejdosiewicz1

1Imperial Cancer Research Fund Cancer Medicine Research Unit
2Department of Pathology
3Department of Paediatric Urology
St James's University Hospital
Leeds, LS9 7TF, United Kingdom

1. EPITHELIAL TISSUE ORGANIZATION AND HOMEOSTASIS

The internal and external surfaces of the body are lined by epithelial tissues. As such, epithelial tissues have a common role in forming the interface with the external environment. This commonality of function is apparent in the basic polarized structure of epithelia, with the apical cell surface abutting onto a luminal or external free space and the basolateral surface anchored to a basement membrane with an underlying mesenchymal stroma. A number of commonly-expressed epithelial gene products play a role in epithelial tissue organization and can be considered as markers of epithelial cell lineage. Such markers include the cytokeratins, E-cadherin and various junctional proteins. Different epithelial tissues also show a diverse range of highly specialized functions which are reflected in their tissue organization, cellular morphology and the expression of specific gene products.

The co-ordination of proliferation, cytodifferentiation and histioarchitecture in epithelial tissues is mediated through interactions with the associated stroma. These interactions are essential during development and tissue repair, serve to maintain tissue homeostasis in adult epithelial organs and are implicated in neoplastic disease progression. The molecular basis for regulation by the stroma is poorly understood, but is likely to be mediated at the epigenetic level through the specific ligation of cytokine/growth factor receptors and adhesion molecules involved in cell:cell and cell:matrix interactions. Cell:matrix interactions are primarily co-ordinated through the expression, localization and activation of integrins interacting with basement membrane proteins.1,2 A large number of factors have been identified which affect epithelial cell behavior. Nevertheless, it is unclear how these are co-ordinated to achieve the structural integrity and specialized...
differentiated function of normal epithelia, or to what extent these processes are involved in pathogenesis.

2. THE UROTHELIUM

The function of the urinary bladder as an impermeable, low pressure reservoir for urine is reflected in the specialized characteristics of the lining urothelium. Urothelium is a stratified transitional epithelium consisting of basal, intermediate and superficial cell zones which move relative to each other to accommodate changes in bladder volume, with no loss of permeability barrier function.\(^3,4\) The barrier function of the urothelium is dependent on the integrity of cell:cell interactions involving adhesion molecules and junctional complexes. A unique feature of the terminally-differentiated superficial “umbrella” cells is the molecular composition and structural organization of the plasma membrane. Whereas basal and intermediate cells have a normal trilaminar plasma membrane, the luminal surface of umbrella cells is composed of thickened plaques of asymmetric unit membrane (AUM), arranged in characteristic hexagonal subunits on the cell surface, bounded by “interplaque” or “hinge” regions of normal symmetrical membrane. The AUM probably functions to reduce the luminal surface area during bladder contraction by invagination, decrease the permeability of the urothelium to urine and to provide structural support. AUM plaques are formed in the vicinity of the Golgi complex by incorporation of specific proteins into the membranes of Golgi-derived fusiform vesicles which move to the surface of maturing cells where they fuse with and insert into the plasma membrane.\(^5\) Insertion of the AUM plaques into the free luminal membrane is generally considered to be the final stage of urothelial cytodifferentiation.

Urothelium represents an excellent model for the study of normal and neoplastic epithelial cell regulation. Although normally a slow turnover epithelium\(^3,6-8\), urothelium has a high proliferative potential during fetal development.\(^3,9\) This potential is maintained in the adult epithelium as seen during tissue regeneration\(^3,10\) and in a range of benign proliferative conditions.\(^11\) In addition, the AUM of the superficial cell serves as an unequivocal ultrastructural marker of terminal urothelial cytodifferentiation.\(^12\) However, the differentiation pathway of urothelial cells appears to be susceptible to re-direction, as shown by the propensity for human bladder epithelium to undergo glandular and squamous metaplasia.\(^13\) There is also evidence from experimental rodent studies that retinoid-deficiency can induce squamous metaplasia\(^14-18\) and that, under the influence of urinogenital sinus mesenchyme, urothelial cells can transdifferentiate into prostatic epithelium.\(^19,20\)

Urothelial cells also exhibit a propensity for neoplastic transformation and are the precursor for transitional cell carcinoma (TCC), the most common form of bladder carcinoma, although other types are recognized.\(^13,21\) TCC shows a spectrum of differentiation- and invasion-related stages which correlate with clinical prognosis\(^22\), although the natural succession of genetic and phenotypic changes associated with disease progression remains unclear.\(^23-25\) A panel of well-characterized bladder cancer cell lines is available, which show a range of phenotypes confirming the urothelial origin and reflecting the different grades of cancer from which they were derived.\(^26-29\)

3. MARKERS OF UROTHELIAL CELL PHENOTYPE

A prerequisite for studies of epithelial cell regulation is the availability of reliable markers of cell phenotype. In the urothelium, a number of differentiation-associated anti-