UMBRELLA CELL: SURFACE SPECIALIZATIONS

The wall of the urinary passages, including the surfaces of the renal pelvis, the ureters, the urinary bladder, and proximal parts of the urethra, is covered by a unique specialized epithelium, the transitional epithelium or urothelium. The urothelium is stratified and composed of three types of cells: basal precursor cells, intermediate cells, and large superficial umbrella cells. The latter line the lumina of the organs and are responsible for the main specific urothelial functions. Results indicate that in the adult bladder after injury, intermediate cells function as progenitors for superficial cells. The urothelium enables the retention of urine and forms a barrier that makes it impermeable to water and movement of ions and metabolites. The various types of superficial cells in the distinctive parts of the urinary tract epithelium differ considerably in the expression of uroplakins, cytokeratins, and in the structure of the apical cell surface. In the bladder, the urothelium adapts to the cyclical changes of luminal contents and must maintain the permeability barrier under variations in pressure during filling and voiding. The permeability barrier ("blood-urine barrier") between tissue fluids and urine depends on the high-resistance tight junctions between the superficial cells, and on their unique apical plasma membrane visible under the electron microscope.

The survey electron micrograph of a segment of the mouse urothelium in panel A shows three cell layers containing basal cells in the lower part of the picture, neighbored by intermediate cells in the middle part of the micrograph, and an umbrella cell in superficial position. The wrinkly apical surface of the umbrella cell visible in the transmission electron micrograph in panel A is shown in scanning micrographs in panels B and C. The arrows in the rectangle in panel B label the borders between three neighboring umbrella cells. The wrinkly character of the luminal surfaces of the umbrella cells, indicated by arrowheads in the circle, is achieved by the scalloped membrane formations shown at higher magnification in panel C. A particular area marked by a rectangle is further enlarged in the inset. Multiple ridges and microplicae are visible corresponding to the "hinge" regions of the scalloped formations, which are seen as small concave areas. The scalloped membrane formations are covered almost entirely with plaques consisting of two-dimensional crystals of hexagonally packed 16 nm particles composed of uroplakins (UP), a family of at least five proteins that include the tetraspan proteins UPIa and UPIb and the type I single-span proteins UPII, UPIIIa, and UPIIIb. The formation of correct heterodimers (UPIa/UPII and UPIb/UPIII) is required for uroplakins to exit from the endoplasmic reticulum on their way to the cell surface. In the *trans* Golgi network, heterodimers interact to form heterotetramers (UPIa/UPII-UPIb/UPIII) before they leave the Golgi apparatus to form 16 nm particles. Morphologically, plaque areas are characterized by an asymmetric unit membrane (AUM), shown in the inset in panel A. Because of the particular shapes and locations of the uroplakin particles, the outer membrane leaflet seems about twice as thick as the inner leaflet. The plaques constitute a main part of the barrier system of the urothelium. In the center of the scanning micrograph in panel C, the borders between three adjacent cells are visible as thin lines. Here, the cells are connected by complexes of tight and adhering junctions.

Inactivation of the uroplakin III gene in the mouse results in vesico-ureteral reflux (VUR), and urothelial abnormalities by uroplakin defects can lead to renal failure. The bladder urothelium of patients suffering from primary VUR is heterogeneous. Panel D shows the apical surface of immature superficial cells of the urothelium of a VUR patient exhibiting abundant microvilli but only a small number of ridges and microplicae.

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Magnification: ×3,500 (**A**), ×193,000 (*inset*), ×3,700 (**B**), ×5,200 (**C**), ×10,000 (*inset*), ×1,870 (**D**)

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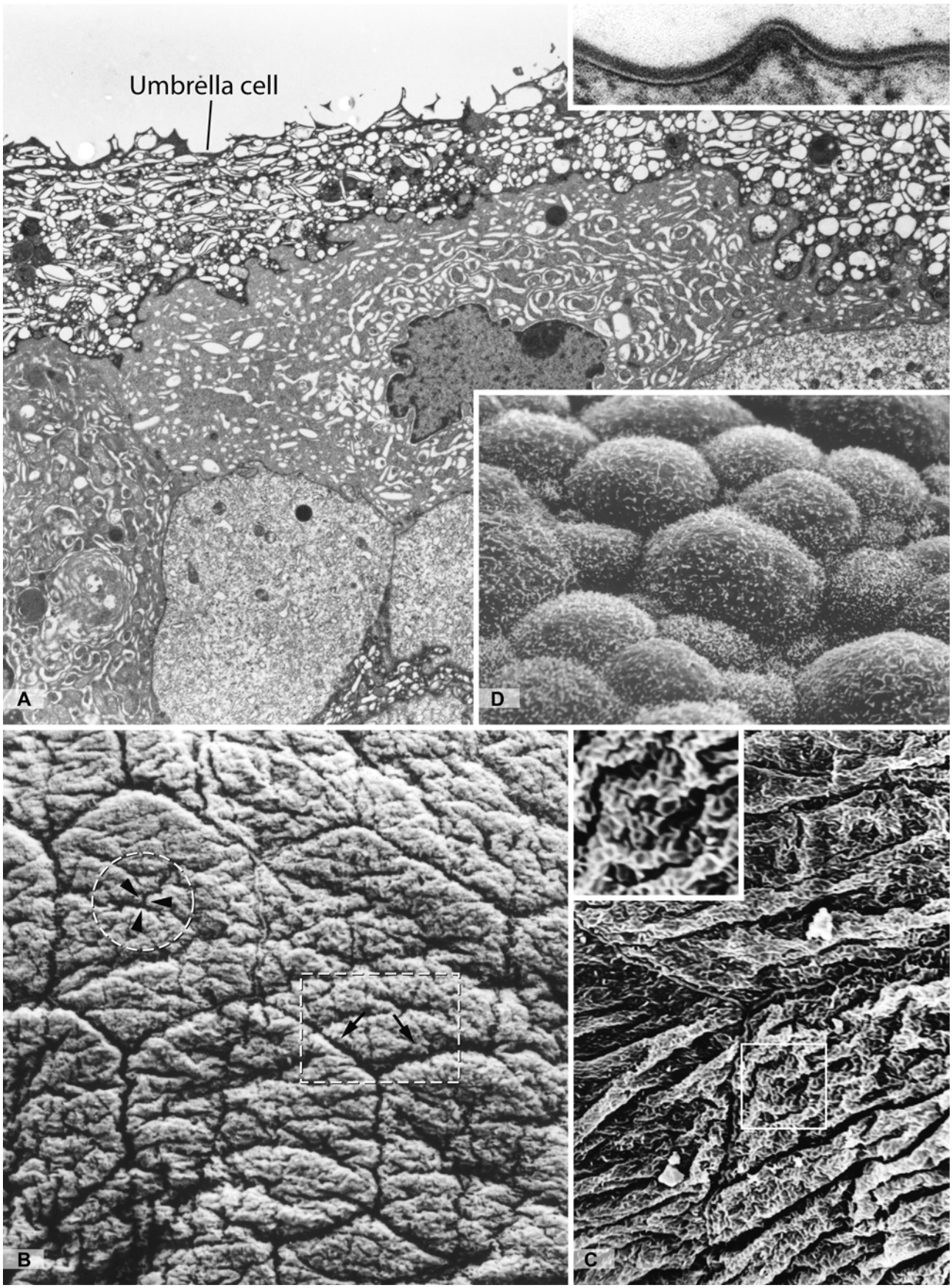
Umbrella cell
A
D
B
C

UMBRELLA CELL: FUSIFORM VESICLES

Plaques are not restricted to the apical plasma membrane of the umbrella cells (cf. Fig. 144); they are also found in special membrane vesicles, termed "fusiform vesicles," which are abundant in the cytoplasm of these cells; they are assumed to have an important role in the formation of the umbrella cells' specialized asymmetric membrane areas. Fusiform vesicles are accumulated in the apical cytoplasm of the umbrella cells. They may occur as single vesicles but are often arranged in groups or tightly packed stacks closely associated with components of the cytoskeleton, which include a trajectorial network of cytokeratins, especially of cytokeratin 20, in the subapical cytoplasm of the cells. Three-dimensional analyses of high pressure–frozen urothelium from the mouse bladder using electron tomography revealed that the vesicles actually are not "fusiform" but have the shapes of flattened discs. They measure up to 1.2 μm in diameter and in their central parts exhibit narrow lumina of 5–10 nm. Here, the opposing membranes are asymmetrically thickened and contain urothelial plaques, as revealed by freeze-fracture studies and immunolabeling. The tightly packed stacks of membrane disks are discussed as representing perfect membrane storage compartments for transport of large amounts of urothelial plaques while occupying only small amounts of the cells' cytoplasm. Results point to the role of myelin-and-lymphocyte protein (MAL) in facilitating the incorporation of uroplakin-containing vesicles into the apical plasma membrane of the umbrella cells.

Panels A and B show fusiform vesicles in umbrella cells of the mouse urothelium in an ultrathin section and in a freeze fracture replica, respectively. The asymmetric membrane (AUM) of plaques is visible in the high-magnification electron micrograph in the inset of panel B. As in the apical plasma membrane, the asymmetric membrane character is the result of the presence of uroplakin particles. In the freeze fracture replica of panel B, exoplasmic fractured surfaces of fusiform vesicle plaques are shown containing arrays of densely packed uroplakin particles (arrowheads). Fusiform vesicles presumably are preformed in the Golgi apparatus of the umbrella cells. In the highly differentiated umbrella cells, the uroplakin-positive membrane regions of the apical plasma membrane are excluded from internalization, suggesting that uroplakin plaques hinder endocytosis.

AUM particles and plaques are not rigid but change their shapes, and it is assumed that interactions of the head domains may have a crucial role in determining shapes and sizes and allowing morphological alterations.

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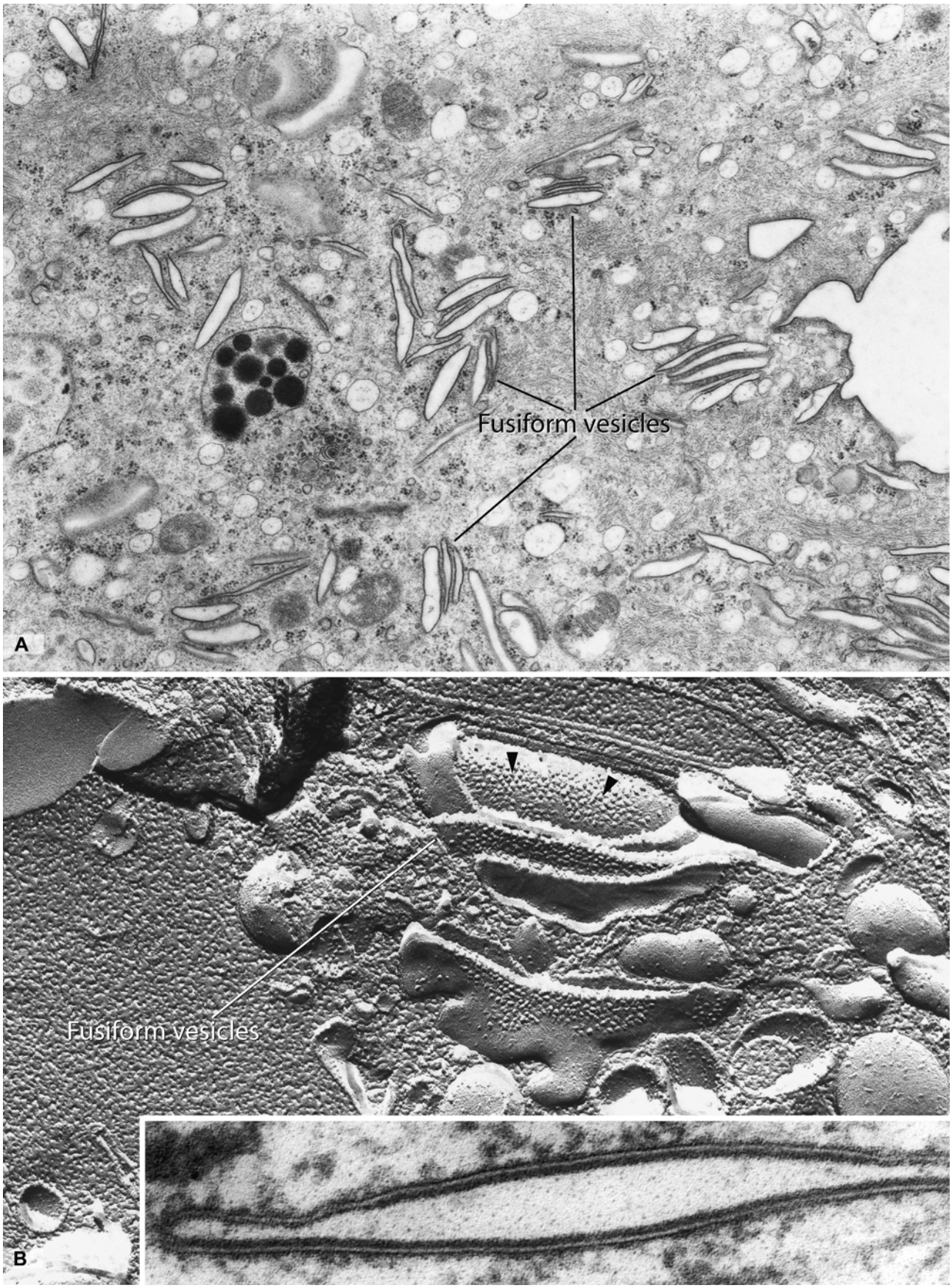
Magnification: ×4,500 (**A**), ×80,000 (**B**), ×194,000 (*inset*)


Fusiform vesicles
A
Fusiform vesicles
B