Stratified Epithelia

CORNEAL EPITHELIUM

The stratified epithelium of the cornea is part of the corneoscleral coat that forms the outer tunic of the eyeball, protecting its inner structures and, together with the pressure of the intraocular fluid, maintaining the eye's shape and consistency. The anterior surface of the cornea is built up by the corneal epithelium shown in this figure.

The corneal epithelium exhibits all characteristics of a simple stratified squamous epithelium of five to seven layers of cells. In the most basal layer, high polygonal cells are aligned along the basal lamina. They are anchored to the basal lamina and to the adjacent Bowman's layer by hemidesmosomes (cf. Fig. 161). The Bowman's layer represents the anterior part of the corneal stroma and is visible in the most basal section of the figure. Basal cells are mitotically active and replace the differentiated cells of the upper layers. The corneal epithelium has a remarkable wound healing capacity. Cytokeratin intermediate filaments are associated with multiple desmosomes that attach the cells to one another. In the basal layers, cells are connected by long bridges that span the wide intercellular spaces.

The cells change shape during differentiation, migration, and transport to the upper layers, increasingly becoming flat. The squamous superficial cells in the outermost layer are particularly rich in cytokeratin filaments. They protect the cells lying beneath from the external environment. On their apical domains, short microvilli are present. They are in contact with a protective film of tear, by which the surface of the corneal epithelium is continually kept wet. Mucins in the tear film lubricate the epithelial surface during the blinking of the eyelid. They stabilize the tear film, preventing desiccation of the underlying epithelial cells, and form a barrier to penetration of pathogens.

A barrier leading to impermeability of the corneal epithelium to water-soluble substances is formed by tight junctions between the superficial cells. Tight junctions are established during differentiation from the basal to the superficial cells and may regenerate within one hour after abrasion of the superficial cells.

For maintenance of corneal transparency, a precise regulation of water content is necessary (cf. Fig. 160). Data provide evidence that the water-transporting proteins aquaporin 5 and 1, expressed in the corneal epithelium and in the corneal endothelium, respectively, provide main routes for water transport across the epithelial and endothelial barriers of the cornea.

The biophysical properties of each layer (cf. Figs. 108, 160, and 161) of the rabbit cornea from the epithelium to the endothelium in comparison to the human cornea have been determined by atomic force microscopy. The differences found between the two species are particularly interesting, inasmuch as the rabbit cornea is commonly used for evaluation of new keratoprosthetics and substrates for *in vitro* studies of corneal cellular behavior.

References

Argüeso P, Gipson IK (2001) Epithelial mucins of the ocular surface: structure, biosynthesis and function. Exp Eye Res 73:281

Daniels JT, Dart JKG, Tuft SJ, Khaw PT (2001) Corneal stem cells in review. Wound Rep Reg 9:483

Kinoshita S, Adachi W, Sotozono C, Nishida K, Yokoi N, Quantock AJ, Okubo K (2001) Characteristics of the human ocular surface epithelium. Progr Ret Eye Res 20:639

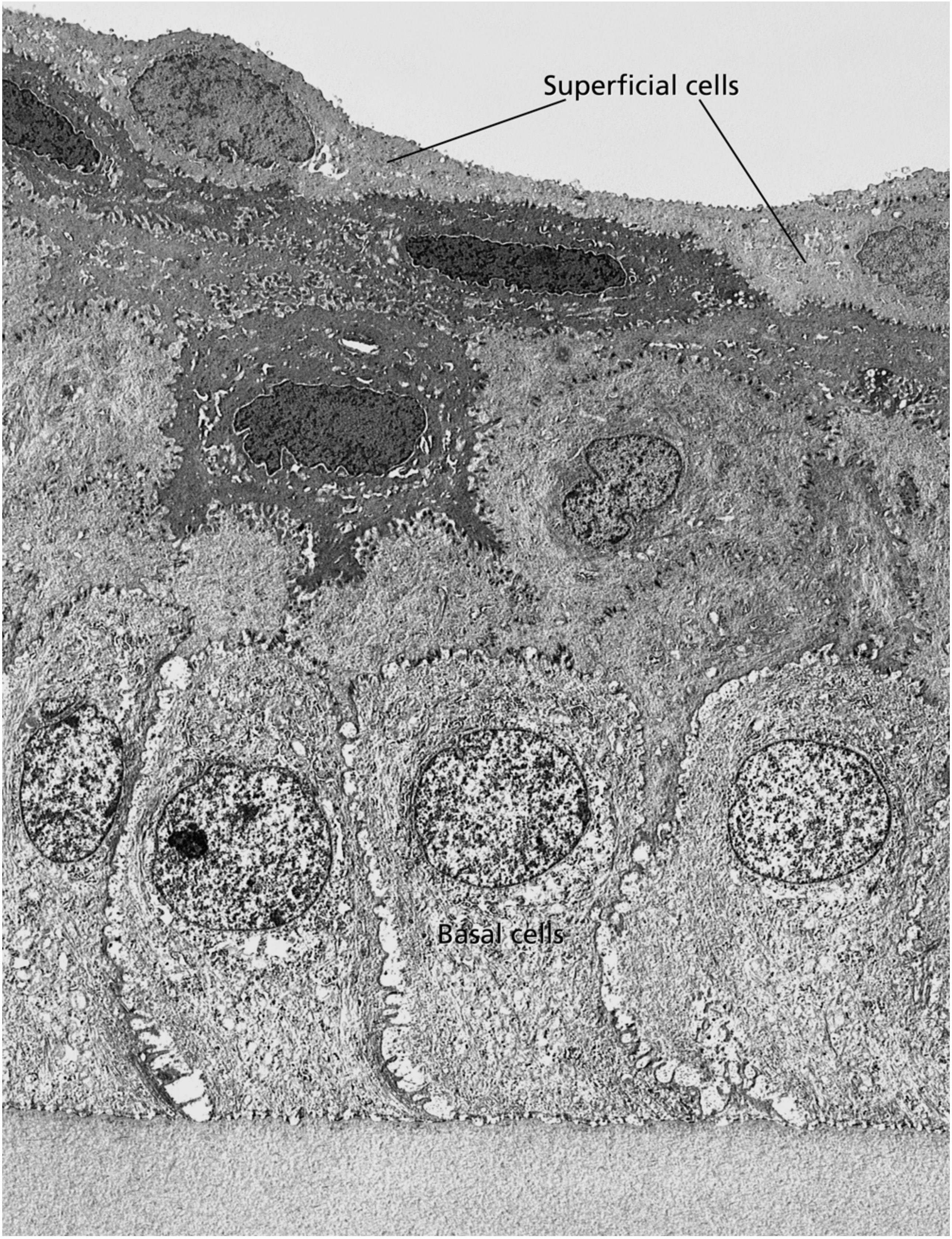
Last JA, Liliensiek SJ, Nealey PF, Murphy CJ (2009) Determining the mechanical properties of human corneal basement membranes with atomic force microscopy. J Struct Biol 167:19

Verkman AS (2003) Role of aquaporin water channels in eye function. Exp Eye Res 76:137

Thomasy SM, Raghunathan VK, Winkler M, Reilly CM, Sadeli AR, Russel P, Jester JV, Murphy CJ (2014) Elastic modulus and collagen organization of the rabbit cornea: epithelium to endothelium. Acta Biomat 10:785

Magnification: ×4,300

M. Pavelka, J. Roth, *Functional Ultrastructure: Atlas of Tissue Biology and Pathology*, Third Edition,
DOI 10.1007/978-3-7091-1830-6_17, © Springer-Verlag Vienna 2015


Superficial cells
Basal cells

EPIDERMIS

The stratified squamous keratinized epithelium of the epidermis, which forms the outermost layer of the skin, protects the body against various external influences, such as mechanical stress, radiation, microbial penetration, and exsiccation. The epidermis is self-renewing, and differentiation of the cells from the innermost germinative layer, where cells undergo mitosis, to the surface is connected with keratinization of the epithelium and the construction of a fluid barrier that is essential for terrestrial life form. The barrier consists of three main components, the terminally differentiated cells with their cell envelope, extracellular lipid and tight junctions.

Most epidermal cells belong to the class of keratinocytes, which are arranged in four layers (strata) reflecting the mechanical and barrier functions of the epithelium and the process of keratinization. All four layers of the epidermis are shown in the figure. The epidermis covers the connective tissue of the dermis, which is apparent in the lowermost part of the figure.

The polygonal cells of the basal layer (stratum basale), resting on the basal lamina, contain plenty of cytokeratin intermediate filaments of the keratin types 5 and 14, in the low-magnification micrographs appearing as dense fibrils (tonofibrils, cf. also Figs. 89 and 109). They are associated with desmosomes connecting adjacent cells and with hemidesmosomes anchoring the basal cell domains to the basement membrane, which forms the bordering layer between dermis and epidermis (cf. Fig. 109).

In the spinous layer (stratum spinosum), tonofibrils are particularly prominent. They protrude into fine cell processes bearing desmosomes. The processes connect the neighboring cells and, like bridges, span the dilated intercellular spaces. In the light microscope, these intercellular bridges appear as the "spines," hence this layer's designation.

Both cells of the basal and of the spinous layers contain multiple melanin granules appearing as particularly dense dots within the cytoplasm (arrows). Melanin is produced in melanocytes (M) by oxidation of tyrosine to 3,4-dihydroxyphenylalanin by the enzyme tyrosinase, primarily stored in premelanosomes and subsequently transformed to melanin accumulating in melanosomes. Melanocytes originate in the neural crest and migrate into the epidermis. They settle in the basal layer and develop multiple cell processes extending between the keratinocytes. Melanosomes are transported into the melanocyte cytoplasmic extensions and transferred into keratinocytes via a still enigmatic process. Mainly, four mechanisms are considered, including cytophagocytosis, formation of intercellular bridges, shedding of melanosome-containing tips of melanocytes and subsequent phagocatosis, and export of melanosomes by exocytosis followed by endocytosis. One melanocyte contacts approximately 36 keratinocytes, forming a functional unit: the epidermal melanin unit. In the micrograph, one melanocyte (M) is apparent in the central part of the basal layer. Multiple melanocyte processes are visible between the keratinocytes in Fig. 109.

The third layer is designated the granular layer (stratum granulosum) after the prominent keratohyalin granules occurring in the cytoplasm of the keratinocytes. At the transition from the spinous to the granular layer, the cells become flattened. They still are interconnected by multiple desmosomes. In addition, tight junctions are established in the granular layer. Together with the extracellular lipid layers formed by the secretions of the keratinocytes in the granular layer, tight junctions are important parts of the epidermal permeability barrier preventing exsiccation of the body.

The horny layer (stratum corneum) in its lower parts consists of transforming keratinocytes. It represents a particular stratum lucidum in the thick epidermis covering the palms of the hands and the soles of the feet. The outermost part of the horny layer is made up of terminally differentiated keratinocytes lacking cell organelles and nuclei. They form flattened squames with a highly resistant compound envelope (cf. Fig. 139).

References

Doering T, Holleran WM, Potratz A, Vielhaber A, Elias PM, Suzuki K, Sandhoff K (1999) Sphingolipid activator proteins are required for epidermal permeability barrier formation. J Biol Chem 274:11038

Furuse M, Hata M, Furuse K, Yoshida Y, Haratake A, Sugitani Y, Noda T, Kubo A, Tsukita S (2002) Claudin-based tight junctions are crucial for the mammalian epidermal barrier: a lesson from claudin-1-deficient mice. J Cell Biol 156:1099

Tsuruta D, Green KJ, Getsios S, Jones JCR (2002) The barrier function of the skin: how to keep a tight lid on water loss. Trends Cell Biol 12:355

Wu X, Hammer JA (2014) Melanosome transfer: it is best to give and receive. Curr Opin Cell Biol 29:1

Magnification: ×6,100


Horny layer
Granular layer
Spinous layer
M
Basal layer
Dermis

DIFFERENTIATION OF KERATINOCYTES AND FORMATION OF THE EPIDERMAL FLUID BARRIER

Keratinocytes undergo a specific program of differentiation on their passage through the various epithelial layers from the basal regions of the epidermis to the outer surface. Regulated biochemical events result in characteristic cell transformations that ultimately lead to the keratinocytes' death. The dead cells embedded and sealed in their lipid secretions form the insoluble and fluid impermeable superficial horny layer of the epidermis.

Panel A shows keratinocytes of the spinous layer containing thick bundles of tonofilaments (tonofibrils) that extend into the spinous-like cell bridges and attach to the plaques of the spot desmosomes (maculae adhaerentes; cf. Fig. 101) connecting the neighboring cells. The keratin types 5 and 14 present in the basal keratinocytes are replaced by keratins 1 and 10 and finally keratins 2e and 9 when the cells move from the basal over the spinous to the granular layer. Two desmosomes are shown at higher magnification in the inset. Both the dense cytoplasmic plaques containing desmoplakin and plakoglobin proteins and the intercellular dense materials composed of the glycosylated extracellular domains of the interlocking cadherins, such as desmoglein1 and desmocollin3, are well visible. Tonofilaments are anchored to the dense plaques. Some of the events leading to the characteristic cell changes during keratinization start in the spinous layer.

Panel B shows part of the uppermost granular layer and part of the horny layer. In the granular layer, the keratohyalin granules (KG) make up the most prominent structures within the keratinocytes. They contain the protein filaggrin and are associated with keratin tonofilaments (arrowheads), which are anchored to desmosomes (arrows). In a stepwise process, the keratinocytes of the granular layer differentiate into the cornified flat squames of the horny layer, apparent in the upper half of panel B. Concomitantly, cell organelles and nuclei are degraded. A cell envelope consisting of a coat underneath the plasma membrane (arrowheads in panel C), composed of keratin-filaggrin complexes, involukrin and the plakin proteins envoplakin and periplakin forms. It becomes further reinforced by insertion of additional structural proteins such as loricrin and small prolin-rich proteins. Desmosomes seem to nucleate the initial processes leading to the formation of this scaffold underneath the plasma membrane. During this process, cells become permeable, and by Ca^{2+} – influx transglutaminases are activated that irreversibly cross-link the scaffold proteins, resulting in the formation a continuous layer at the inner surface of the plasma membrane (arrowheads panel C). Numerous lamellar bodies (Odland bodies; arrows in panel C) are apparent in the cytoplasm of keratinocytes. They start to occur in the spinous layer. Their lamellar product, the glycoplipid acylglucosylceramide, is secreted into the intercellular space (asterisks in panel C) and covalently linked to involucrin. The cell envelope together with the multilamellar extracellular lipid constitutes the compound cell envelope. Under the electron microscope, the extracellular lucid and multilamellar material and the dense compact cell surface correspond to the two parts of the compound cell envelope (arrowheads and asterisks in panel B).

Changes of the keratin-filaggrin complexes continue to occur after the cells have lost their transcriptional ability. This is mirrored by the ultrastructural changes during progression from the inner to the outer horny layers, as shown in the upper part of panel B. The outermost cells are continuously shed. Cell desquamation is connected with a progressive loss of desmosomes, remnants of which can be seen in the horny layer.

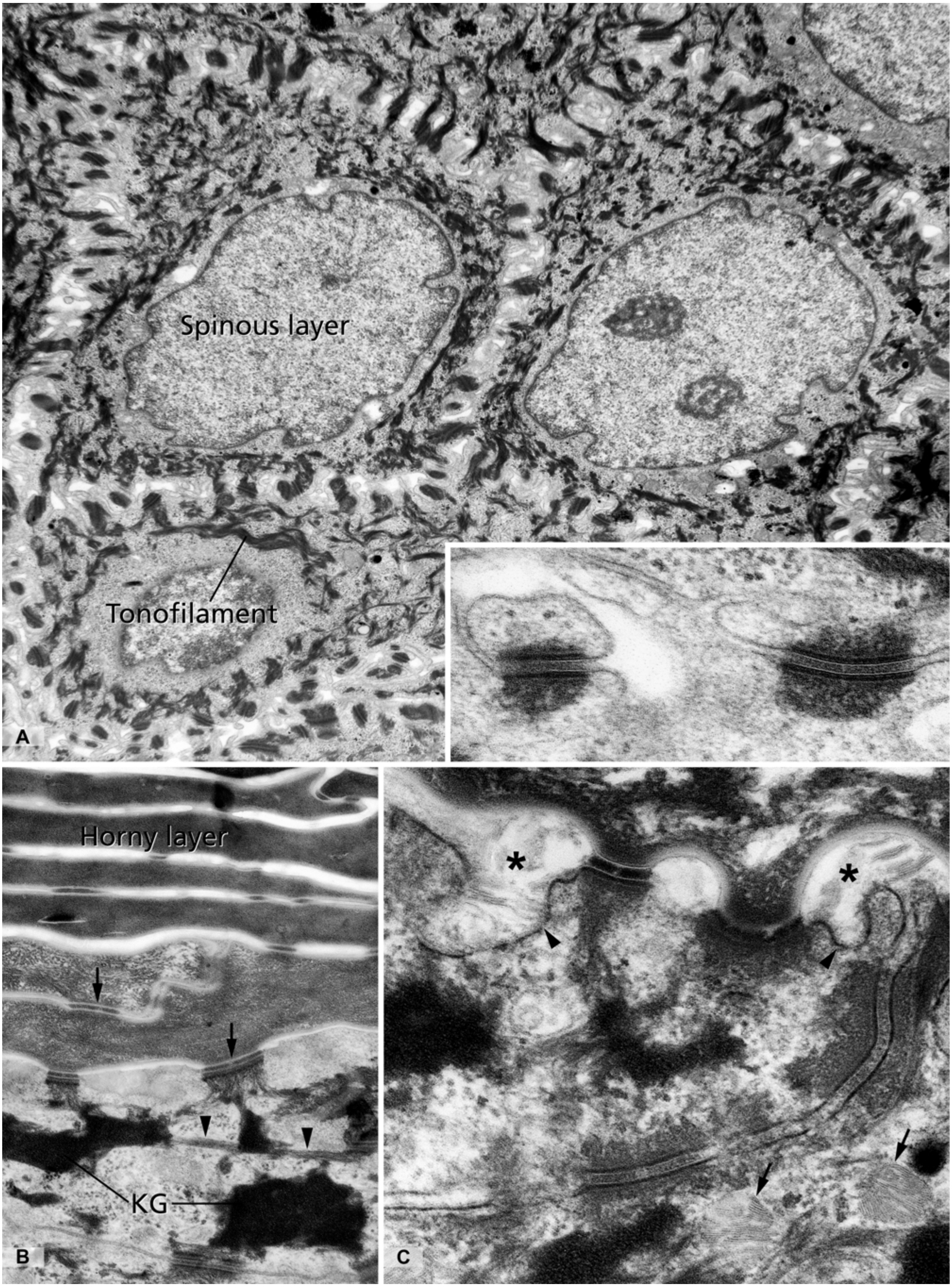
References

Doering T, Holleran WM, Potratz A, Vielhaber A, Elias PM, Suzuki K, Sandhoff K (1999) Sphingolipid activator proteins are required for epidermal permeability barrier formation. J Biol Chem 274:11038

Furuse M, Hata M, Furuse K, Yoshida Y, Haratake A, Sugitani Y, Noda T, Kubo A, Tsukita S (2002) Claudin-based tight junctions are crucial for the mammalian epidermal barrier: a lesson from claudin-1-deficient mice. J Cell Biol 156:1099

Segre J (2003) Complex redundancy to build a simple epidermal permeability barrier. Curr Opin Cell Biol 15:778

Magnification: ×10,000 (**A**); ×21,000 (**B**); ×60,000 (**C**); ×74,000 (*inset*)


Spinous layer
Tonofilament
A
Horny layer
KG
B
C