Cell and Tissue Research (2018) 374:439–453
https://doi.org/10.1007/s00441-018-2934-7

REVIEW

Basement membranes in the cornea and other organs that commonly develop fibrosis

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Received: 23 June 2018 / Accepted: 20 September 2018 / Published online: 3 October 2018

Abstract

Basement membranes are thin connective tissue structures composed of organ-specific assemblages of collagens, laminins, proteoglycan-like perlecan, nidogens, and other components. Traditionally, basement membranes are thought of as structures which primarily function to anchor epithelial, endothelial, or parenchymal cells to underlying connective tissues. While this role is important, other functions such as the modulation of growth factors and cytokines that regulate cell proliferation, migration, differentiation, and fibrosis are equally important. An example of this is the critical role of both the epithelial basement membrane and Descemet's basement membrane in the cornea in modulating myofibroblast development and fibrosis, as well as myofibroblast apoptosis and the resolution of fibrosis. This article compares the ultrastructure and functions of key basement membranes in several organs to illustrate the variability and importance of these structures in organs that commonly develop fibrosis.

Keywords Basement membrane · Cornea · Skin · Lung · Fibrosis

Introduction

Basement membranes (BM) are specialized extracellular matrix protein complexes found in every organ of the human body. They have specific structures that provide adhesion for epithelium, endothelium, or parenchymal cells and separate them from connective tissues, nerves, and muscles. BMs delineate boundaries and compartmentalize tissues in organs while providing scaffolds that guide morphogenesis and tissue repair. BM-mediated cell signaling events and cellular behavior are altered by tissue-specific BM composition and structure. BMs are best detected with transmission electron microscopy (TEM) or immunohistochemical staining. The four major components most BMs have in common are nidogens, perlecan, laminins, and collagen type IV (Fig. 1). However, even though there is great heterogeneity of the primary components, other components also are commonly present and provide specificity of function. Basement membrane components are key players in specialized extracellular matrices and changes in BM composition play significant roles in facilitating the development of various diseases in different organs (Kruegel and Miosge 2012).

BM proteins were first discovered in mouse yolk sac tumors which produce typical extracellular matrix (ECM) proteins (Chung et al. 1977; Kleinman and Martin 2005; Orkin et al. 1977). Further analysis showed that laminins (Chung et al. 1979; Timpl et al. 1979), nidogens (Carlin et al. 1981; Timpl 1989), perlecan (Carlin et al. 1981), and collagen type IV (Kleinman et al. 1982) are large multi-domain proteins that self-polymerize, bind to other proteins to augment function and promote stability of the tissue (Timpl and Brown 1996).

Laminins are alpha1, beta1, and gamma1 heterotrimeric glycoproteins with more than 15 trimer combinations identified that contribute to tissue specificity of BMs (Miner and Yurchenco 2004). The laminin nomenclature has been simplified to refer to the alpha, beta, and gamma chains that comprise a specific laminin—such as laminin 332 (Aumailley et al. 2005). Laminins initiate the BM self-polymerization process during development, repair, and regeneration following injury, and other BM components bind to and assemble the mature BM (Miner and Yurchenco 2004; Smyth et al. 1999). Collagen type IV has six

Supported in part by US Public Health Service grants RO1EY10056 (SEW) and P30-EY025585 from the National Eye Institute, National Institutes of Health, Bethesda, MD.

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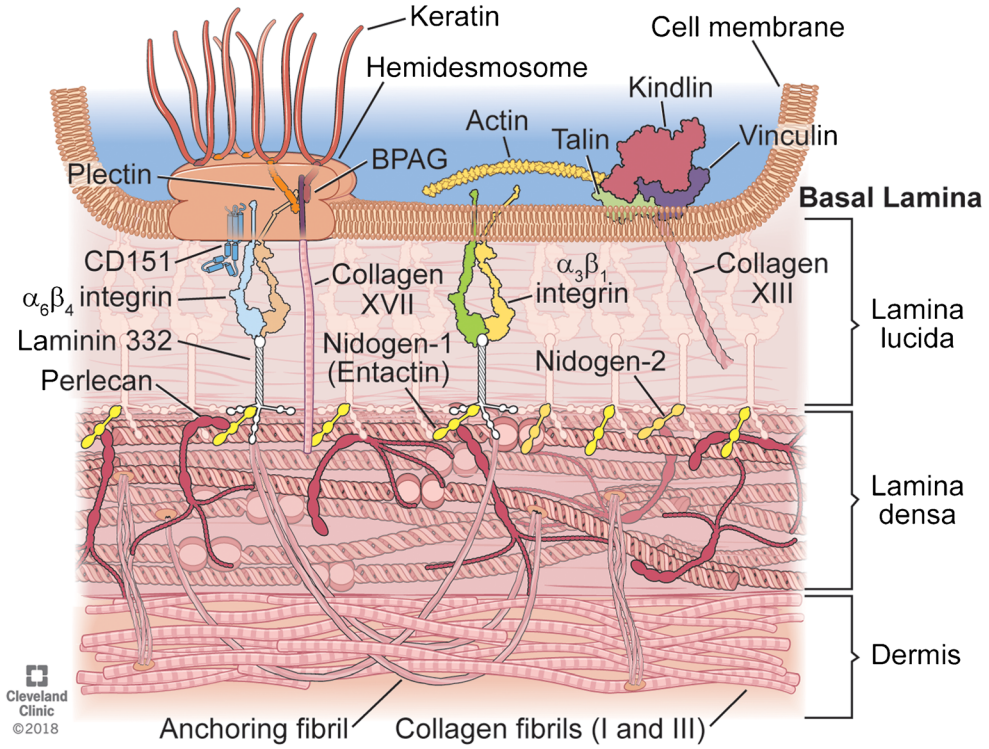

Fig. 1 Schematic diagram of typical components found in basement membranes, using skin as an example. A basal keratinocyte adheres to the underlying basement membrane and dermis via the focal adhesions that transmit mechanical force and regulatory signals that consist of numerous interacting components such as the hemidesmosome with bullous pemphigoid antigen (BPAG), integrin a6b4, laminin 332, perlecan, anchoring fibrils, and dozens of other components that vary depending on the organ and the status (homeostasis, post-injury, etc.) of the tissues. Many of these components extend into, and are part of, the lamina lucida of the basement membrane. The underling lamina densa of the basement membrane is composed of collagen type IV, nidogens, perlecan, laminin 332, that directly interact with each other, and other components. Lamina lucida is not as wide naturally as it is drawn here for clarity reasons. Illustration by David Schumick, BS, CMI. Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography© 2018. All Rights Reserved

genetically different α-chains that assemble into three linear collagen type IV heterotrimers (Khoshnoodi et al. 2008). The stability of the BM structure is attributable primarily to the network formed by laminins and collagen type IV along with other linker components (Halfter et al. 2015; Timpl 1989; Yurchenco et al. 1986).

Nidogen-1 and nidogen-2 are sulfated monomeric glycoproteins (Ho et al. 2008) with the molecular mass of ~ 150 kDa that specifically interact with other BM components such as laminins and collagens to organize and stabilize the BM. Perlecan, also known as basement membrane-specific heparan sulfate proteoglycan core protein (HSPG) or heparan sulfate proteoglycan 2 (HSPG2), is a large multi-domain HSPG that also interacts with other BM components (Hassell et al. 1980). Unlike laminin and collagen type IV, nidogen and perlecan form irregular polymers using their multiple binding sites. They bridge these scaffolds for laminin and collagen type IV, as well as for each other, and hence they are called as bridging molecules (Aumailley et al. 1993; Ettner et al. 1998; Fox et al. 1991). Complete perlecan deficiency is lethal for mouse embryos at the mid-gestational stage (Arikawa-Hirasawa et al. 1999; Costell et al. 1999) and the deletion of both nidogens is prenatally lethal (Bader et al. 2005). Although nidogen-1 and nidogen-2 are present in all tissues, nidogen-2 alone show more restricted expression patterns and tissue specificity (Kimura et al. 1998). In vitro, both proteins interact with laminins and collagen type IV and play a critical role in assembly of the mature BM (Fox et al. 1991; Salmivirta et al. 2002). Perlecan establishes a high negative charge in the BM because of its three heparan sulfate side chains. Therefore, perlecan plays a major role in regulatory processes of BMs by providing a barrier for some regulatory molecules in addition to serving as an anchoring port and connecting bridges in BMs (Behrens et al. 2012; Yurchenco et al. 1986).

In general, BMs have at least one component from the four major proteins and the tissue specificity depends on the differential expression of the respective isoforms and inclusion of other tissue-specific BM components. Thus, the main structural elements, collagen type IV and laminin form a highly-organized network which is non-covalently interconnected by nidogen and perlecan (Paulsson 1988; Timpl 1989; Yurchenco et al. 1986). Laminin gamma 3 chain binds specifically to nidogen (Gersdorff et al. 2005). In vivo, laminin is necessary for the initial steps involved in the BM assembly (Miner and Yurchenco 2004; Smyth et al. 1999) but the stability of the

entire BM is determined by the collagen type IV network (Poschl et al. 2004) forming structured polymers (Fig. 1). Gene deletion analysis of the several mutant phenotypes demonstrate the numerous tissue-specific roles of the four major BM components (LeBleu et al. 2007). Additional components such as fibrillin (Tiedemann et al. 2005), collagen type V (Bonod-Bidaud et al. 2012) and BM-associated collagen type XV and type XVIII may also be involved in these complexes depending on the specific tissue (Breitkreutz et al. 2013; Miosge et al. 2003). Agrin is a major proteoglycan component in some BMs, such as the glomerular basement membrane (Denzer et al. 1995; Tsen et al. 1995). Collagen type XVIII has also been found to be BM heparan sulfate proteoglycan that is important in retinal BM (Halfter et al. 1998; Saarela et al. 1998).

Epithelial, endothelial, and parenchymal cells adhere to the BM via a large family of transmembrane cell adhesion proteins called integrins, which are commonly tissue-specific in distribution, and are receptors that tie the matrix to the cell's cytoskelatin (Boudreau and Jones 1999). There are also other cell-associated receptors that bind BM besides integrins (Boudreau and Jones 1999). The binding of cell surface receptors to BM proteins initiates' intracellular signaling pathway that influence cellular functions such as migration, proliferation, differentiation, and maintenance of the BM.

BMs have many biological functions ranging from tissue organization to functions as depositors for very active molecule such as growth or differentiation factors, including TGFβ and PDGF that can alter the cellularity and composition of underlying tissue such as the stroma in the cornea (Schubert and Kimura 1991; Torricelli et al. 2013b). The binding of such growth factors to BM is a very efficient way to regulate the signaling of these growth factors and differentiation factors that can, for example, trigger fibrotic wound healing changes in tissues underlying BMs. The following sections will highlight some of the organ-specific structures and functions of a few BMs.

BM in cornea

In the cornea, the epithelial BM is present between the basal epithelial cells and the underlying stroma composed primarily of extracellular matrix and fibroblastic keratocytes (Fig. 2). The functions of the epithelial BM include anchoring of the epithelium to the stroma, bi-directional regulation of the passage, and therefore functions, of growth factors and cytokines that modulate functions such as cell proliferation, migration, and differentiation in the epithelium and stroma, as well as the production of chemokines, metalloproteinases, and collagenases (Torricelli et al. 2013b). The composition of corneal BM is different from other organ BMs due to their heterogeneity. Corneal epithelial BM components include laminins,

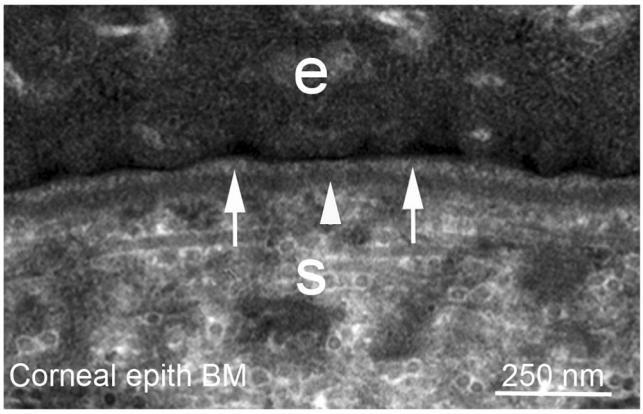

Fig. 2 Transmission electron micrograph from central rabbit cornea of the epithelial basement membrane (EBM) at ×36,000 magnification. In the cornea, the EBM functions to adhere basal epithelial cells (e) to the underlying stroma and to modulate growth factor-mediated communications between the epithelium and the keratocytes within the stroma (S). As artifacts of fixation, the lamina lucida (arrows) and lamina densa (arrowhead) can be seen. Although this morphology is an artifact of fixation, it signifies the presence of a mature BM. The regular packing of the collagen fibrils, visible as uniform diameter circles, in the stroma contributes to corneal transparency

collagen type IV and other collagens, heparan sulfate proteoglycans, and nidogens (Tuori et al. 1996). Descemet's membrane (DM) is the basement membrane of the posterior cornea that lies between the corneal endothelium and posterior stroma. It has functions similar to the epithelial BM but contributes to the "leaky" barrier function of the endothelial-Descemet's membrane complex important to corneal function (Murphy et al. 1984). Descemet's membrane, in contrast to the epithelial BM in the cornea, increases in thickness during both prenatal development (striated BM) and post-natal during the life of the animal by addition of non-striated, non-lamellar extracellular matrix (Murphy et al. 1984). The structure and function of Descemet's layer is altered in corneal diseases such as Fuchs' endothelial dystrophy and bullous keratopathy (Johnson et al. 1982; Zhang and Patel 2015).

Initially, it was reported that laminin-111 and laminin-332 were the major laminins in the epithelial BM of the human cornea (Ljubimov et al. 1995; Tuori et al. 1996). Later, however, Filenius et al. found that the BM of human cornea contain only laminin-332 and laminin-511 but not laminin-111. Laminin-332 is produced by the epithelial cells (Filenius et al. 2001) and laminin-511 is produced by the keratocytes (Hassell et al. 1992) and epithelial cells (Saikai and Wilson, unpublished data, 2018). Corneal epithelial cells adhere to the laminins in the epithelial BM through integrins. Human corneal epithelial cells have been shown to express integrins α6β4, α3β1, and α2β1 involved in these interactions (Tervo et al. 1991; Virtanen et al. 1992). Epithelial BM contains collagen type IV, as well as collagen types VII, XVII, and XVIII (Michelacci 2003). Several investigators identified collagen type IV in the epithelial BM, but some were not able to

identify this molecule in the BM of the central cornea in some species (Cameron et al. 1991). Collagen type IV is known to be present in the human corneal BM as early as 8 weeks of gestation and throughout life (Ben-Zvi et al. 1986). After injury, collagen type IV is present in the re-synthesized BM and it is involved in the binding of the basal surface of the epithelial cells to the BM. In vitro, collagen type IV has been shown to promote migration and adhesion of corneal epithelial cells (Cameron et al. 1991). Thus, collagen type IV is one of the native components in BM involved in the development, maintenance, and wound healing process in the cornea. Collagen type XVII and α6β4 integrin are present in the hemi-desmosomes, the stud-like structures present in basal corneal epithelial cells that adhere the epithelium to the underlying stroma via anchoring fibrils (Gipson et al. 1988). In vitro, it has been shown that collagen type XVII interacts with the β3 chain of the laminin-332 to support cell binding (Torricelli et al. 2013a).

Collagen type XVIII is the only known BM component with heparan sulfate glycosaminoglycan side chains (Dong et al. 2003). In cornea, collagen type XVIII is localized in the epithelial BM and Descemet membrane (Lin et al. 2001). Knockout of collagen type XVIII does not result in a known corneal phenotype but is known to cause other eye abnormalities (Fukai et al. 2002; Maatta et al. 2007), including pigment granule release, massive disorganization of retinal pigment epithelium, and photoreceptor and iris abnormalities (Marneros et al. 2004; Marneros and Olsen 2003). In humans with Knobloch syndrome, a rare disorder with retinal degeneration and high myopia, have mutations in the gene encoding the α1 chain or deficiency of collagen type XVIII (Menzel et al. 2004; Nystrom et al. 2017; Suzuki et al. 2002).

Perlecan is a key component of the corneal epithelial BM which interacts with other basement membrane components to establish the epithelial barrier function and epithelial morphology. A thinner corneal epithelium and microphthalmos were observed in perlecan-deficient mice (Inomata et al. 2012). *Pseudomonas aeruginosa* is a bacterium that can produce corneal ulcers and perlecan is known to serve as a binding site for these bacteria. Chen and Hazlett (2001) showed that anti-perlecan antibody can decrease binding of *P. aeruginosa* to corneal epithelial cells in the human cornea. After epithelial scrape injury in humans that damages the corneal epithelial basement membrane, stromal keratocytes were shown to produce high levels of perlecan and nidogen-2 and, therefore, contribute to epithelial BM regeneration (Torricelli et al. 2015).

Nidogens are present in the epithelial BM, stroma, and Descemet's membrane of the cornea. Nidogen-1 and nidogen-2 bind to various BM-associated proteins and they are known to be a connecting element between laminin and the collagen network in BM (Kabosova et al. 2007). Keratocytes and myofibroblasts have been shown to produce nidogen-1 and nidogen-2 in vitro (Santhanam et al. 2015). In nidogen-1 knockout mice, minimal pathological changes were observed in the anterior segment of the eye, including the epithelial BM (May 2012). These changes were not seen in the nidogen-2 knockout mice (May 2012).

In addition to epithelial BM, cornea possesses another basement membrane called Descemet's membrane (DM) that lies between the corneal endothelium and posterior stroma (Fig. 3) that participates in the "leaky barrier function" of the corneal endothelium (Zhang and Patel 2015; Kapoor et al. 1986). For example, the endothelial-DM complex allows critical nutrients to pass into the stroma but restricts the passage of transforming growth factor beta from the aqueous humor into the stroma in the absence of endothelial-DM injury (Marino et al. 2017a). The thickness of DM increases with age, with it having approximately 3 μm of thickness in children and 10 um in adults (Chi et al. 1958; Johnson et al. 1982). DM is composed of two layers: an anterior banded layer which is composed of collagen lamellae and proteoglycans and a posterior non-banded layer which is continually

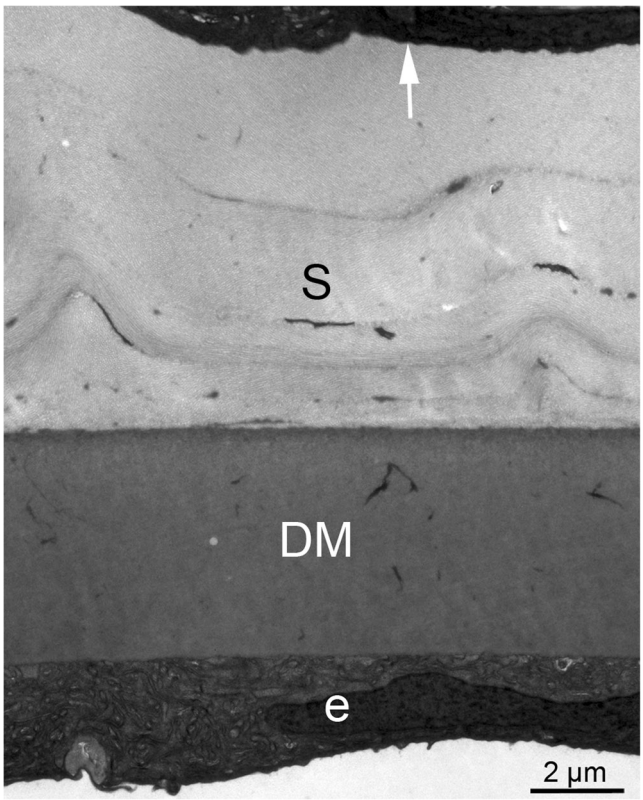

Fig. 3 Rabbit cornea Descemet's basement membrane at ×12,600 magnification. Notice the impressive thickness (greater than 6 μm) of Descemet's basement membrane (DM) in a rabbit only 14 weeks old. Descemet's basement membrane continues to increase in thickness throughout life. Descemet's basement membrane provides adhesion for the monolayered corneal endothelial cells (e) that modulate corneal hydration critical to corneal transparency, allows passage of nutrients from the aqueous humor into the stroma, and modulates the passage of TGFβ from the aqueous humor into the corneal stroma that would drive keratocyte differentiation into myofibroblasts and trigger fibrosis. S is the stroma that makes up greater than 90% of the corneal thickness. A stromal fibroblastic cell referred to as a "keratocyte" is indicated by the arrow

synthesized and thickens over decades (Kefalides et al. 1976). Freeze-fracture, deep-etch replica method has clearly showed that the lattice of the DM is constructed of mainly four components (Sawada 1982): (1) round densities forming the nodes of the lattice, (2) rod-like structures connecting the nodes, (3) fine filaments two-dimensionally distributed in the interstices, and (4) amorphous materials. Biochemical studies of DM revealed similarities with other BM in major molecular components, including collagen type IV, fibronectin, laminins, and heparan sulfate proteoglycan (Carlson et al. 1981; Kefalides and Denduchis 1969) and nidogens (Medeiros et al. 2018). In contrast to other BMs, collagen type VIII is a major constituent in DM, which forms ladder-like structure visible with electron microscopy (Labermeier and Kenney 1983). The finding that corneal endothelial cells in vitro synthesized collagen type VIII supports the presence of type VIII collagen in DM (Benya and Padilla 1986; Sage et al. 1981). Collagen type VIII is a heterotrimer composed of two distinct alpha chains, α1 and α2, each with molecular weight of about 60,000 Da (Benya and Padilla 1986; Shuttleworth 1997). The hexagonal lattice structure creates a matrix that can resist compression and maintains the open porous structure that allows nutrients to pass in to stroma (Shuttleworth 1997), an important function of the Descemet's membrane-endothelial complex. Fuchs' endothelial corneal dystrophy (FECD) has typical pathological changes that include progressive loss of endothelial cells, thickening of the DM, and deposition of anomalous extracellular matrix in the form of guttae (Chi et al. 1958). FECD is likely a group of genetic disorders affecting the corneal endothelium and DM.

BM in skin

Skin consists of two compartments, epidermis and dermis (Fig. 4). Epidermis serves as the first line of defense between the external environment and the animal's internal organs, and it is connected to the dermis compartment by the BM (Breitkreutz et al. 2013). Apart from structural properties, the BM controls keratinocyte adhesion, traffic of cells, and diffusion of molecules such as growth factors and cytokines, including keratinocyte and platelet-derived growth factor, that regulate both keratinocyte and dermal fibroblast functions through regulation of activation and release (Breitkreutz et al. 2013). In addition, BM plays an important role during the remodeling process after injury and damage to BM by cancer leads to cell activation in the stroma (Mueller and Fusenig 2004).

Skin BM components, such as perlecan, collagen types IV and VII, are produced by dermal fibroblasts and epidermal keratinocytes. Other components, like laminin-511 and laminin-332, are primarily synthesized by keratinocytes, although the main source of nidogens is thought to be dermal fibroblasts (Bechtel et al. 2012; Fleischmajer et al. 1995). Additionally, dermal fibroblasts transiently synthesize laminin-211 during wound healing in adult skin (Sugawara et al. 2008).

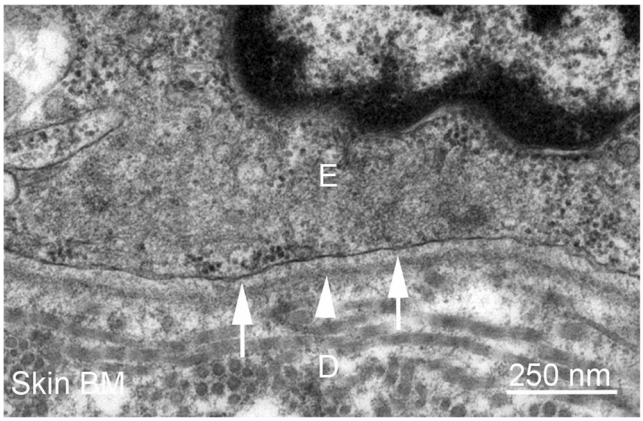

Fig. 4 Transmission electron micrograph of rabbit inner thigh skin basement membrane (BM) at ×40,000 magnification. The overlying basal keratinocyte adheres to the dermis (D) via the basement membrane (BM) composed of lamina lucida (arrows) and lamina densa (arrowhead). The BM in skin also regulates growth factor-mediated interactions between the epithelium and skin fibroblasts in the dermis. Note that the basal epithelial cell membrane in skin is much more prominent than in the cornea

The upper layer epidermis is connected to the BM by hemidesmosomes containing plectin and bullous pemphigoid antigen 1 (BPAG1) proteins (Sterk et al. 2000). These proteins are linked to alpha 6/beta 4 (Sonnenberg et al. 1991), CD151 (Sterk et al. 2002), and collagen type XVII (Qiao et al. 2009). Integrin alpha6/beta 4 also binds to laminin-332, the only integrin associated with keratins (Aumailley et al. 2005). The BM is connected to the dermis beneath by loop structures of collagen type VII and anchoring fibrils. Also, anchoring fibril-collagen type VII tightly binds to collagen types I and III fibrils in the dermis (Villone et al. 2008). Together, these bridges are essential to maintenance of the structural and functional integrity of skin. Defects in the skin BM or BM-associated molecules is often associated with severe or lethal disease (Sterk et al. 2002; Aumailley et al. 2005).

Mice lacking nidogen-1 and nidogen-2 live to birth and have skin that appear grossly normal (Bader et al. 2005). But the ultrastructure of the skin reveals abnormal basal cells with micro-blistering, microvascular aberrations, BM duplications, and leakiness of small vessels (Mirancea et al. 2007). These mice die from lung and heart abnormalities that are directly related to BM defects, but kidney BMs appear normal (Bader et al. 2005).

Co-cultures of epidermal keratinocytes and dermal fibroblasts have been investigated extensively to study on skin physiology and repair. However, these approaches have major drawbacks that limit communications between two cell types that occur in vivo. Therefore, organotypic co-cultures have been used to provide a better understanding of cellular interactions and BM generation in skin (Fleischmajer et al. 1995;

Smola et al. 1998). Thus, in these models, normal epidermal phenotype and BM structure is generated with cells from different sources and with several combinations of epithelial and fibroblastic cells. For example, normal BM structure and epidermal phenotype, including hair follicles, can be generated in organotypic co-culture (Limat et al. 1996; Stark et al. 1999). These systems serve as alternative approaches to study the functions of mutated BM components (Di Nunzio et al. 2008; Fritsch et al. 2009; Murauer et al. 2011).

Transplantation models offer other strategies to study the regeneration of skin and BM in mice. Cultured mouse keratinocytes regain full differentiated function, including the production of BM, when transplanted on the backs of C_3H mice (Breitkreutz et al. 1984). Similarly, HaCat cells or keratinocytes from human skin transplanted on nude mice generate normal epidermal tissue and BMs when examined with immunohistochemistry for BM components and ultrastructure examined with TEM. In these studies, the first BM component to appear is laminin-332, followed by nidogens, laminin-511, and collagen type IV (Breitkreutz et al. 1997, 1998).

Skin BMs from histological specimens, transplantation models, and organotypic co-cultures appear structurally and functionally the closest in morphology to corneal epithelial BM (compared to other imaged organs), although at high magnification after identical fixation and processing, a difference in morphology appears obvious and could relate to transparency in the cornea (compare Figs. 2, 3, 4).

There are a number of skin disorders associated with skin blistering, including epidermolysis bullosa affecting at least 18 genes associated with the epithelial basement membrane (EBM) and adhesion to the EBM (Uitto et al. 2017), pemphigus, and bullous pemphigoid (Hammers and Stanley 2016). Pemphigus and bullous pemphigoid are auto-antibody-mediated blistering diseases of the skin. In pemphigus, keratinocytes in epidermis and mucous membranes lose cell-cell adhesion, and in pemphigoid, the basal keratinocytes lose adhesion to their basement membrane. Detailed discussion of these disorders is beyond the scope of this review, but they have been instrumental in understanding the specific functions of many BM components.

BM in kidney

The glomerular basement membrane (GBM) lies between the glomerular endothelial cells and the podocytes (Fig. 5) and functions in the removal of waste and other molecules from blood plasma into the urine without the release of other plasma components such as albumin. The podocytes, which adhere to the GBM, play an active role in preventing plasma proteins from entering the urinary ultrafiltrate by providing a barrier comprising filtration slits between the podocyte foot processes (Fig. 5) (Reiser and Altintas 2016). Unlike other BMs, the GBM is unusually thick and composed primarily of collagen type IV and laminins (Timpl 1989). Mutations in these components cause filtration defects and result in severe renal disease (Miner 2012). Agrin is the major heparan sulfate proteoglycan in GBM (Timpl 1989). This structure allows the passage of plasma water and small waste solutes but limits the flow of large plasma proteins such as albumin. Defects in one of these layers will result in high levels of albumin in the urine.

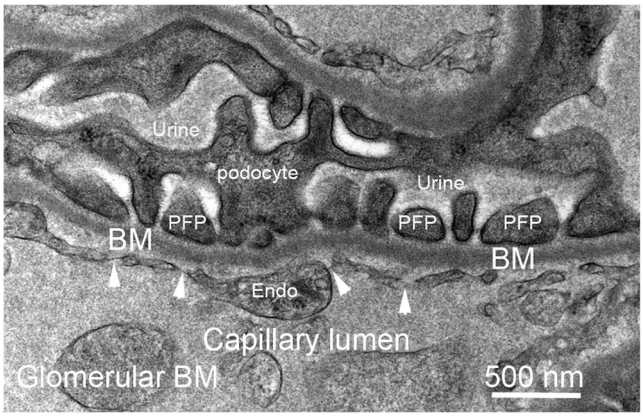

Fig. 5 Transmission electron micrograph of glomerular basement membrane (BM) in rabbit kidney at ×45,000 magnification. The BM that functions in the excretion of waste molecules from capillaries into the urine is a "double" BM that provides adhesion of capillary endothelial cells (endo) with fenestrations (arrowheads) on one side and podocyte foot plates (PFP) of podocytes on the other

In adult GBM, laminin-521 is the major laminin. During GBM formation and maturation, however, laminins go through a transition from laminin-111 to laminin-511 and then to laminin-521 (Miner et al. 1997; Miner and Sanes 1994) and genetic defects in this transition results in GBM breakdown. For example, in mice, a mutation in laminin α5 inhibits the laminin-111 to laminin-511 transition and results in the failure of glomerular vascularization (Miner and Li 2000). Mutation in laminin β2 in humans or in mice results in a congenital nephrotic syndrome with neurological manifestations and it is known as Pierson syndrome (in humans) (Matejas et al. 2010).

Collagen type IV plays a critical role in BM stability (Poschl et al. 2004). Collagen also undergo developmental transitions in GBM during glomerulogenesis. Initially, GBM contains an α1/α2 network but when the glomerular capillaries begin to function, the podocytes secrete α3α4α5 trimers. Then, these components polymerize to form a collagen type IV network characteristic of the fully mature GBM (Abrahamson 2009). Mutations in genes encoding any one of the collagen chains can cause defects in the GBM resulting in mild to severe disease. For example, "thin basement membrane disease" has been found

in 40 to 50% of patients having mutations in COL4A3 or COL4A4, which encode the α3 and α4 chains of collagen type IV, respectively (Voskarides et al. 2007). Alport syndrome is a severe basement membrane disease, which eventually leads to kidney failure along with deafness and ocular abnormalities. The X-linked form is the most common version of Alport syndrome and it is caused by mutations in COL4A5 encoding the α5 chain of collagen type IV (Heidet et al. 2000).

In mice, deletion of both nidogen-1 and nidogen-2 genes results in perinatal lethality. Nidogen-1 binds to both laminins and collagen type IV and, therefore, is an important component for BM formation. However, BM can form in the absence of both nidogens and the GBM can appear ultrastructurally normal. However, renal dysgenesis or hydronephrosis can be noted in the fully developed kidney (Bechtel et al. 2012; Miosge et al. 2002). The absence of one or both nidogens does not alter basement membrane composition in adult murine kidney (Gersdorff et al. 2007).

Agrin is the major heparan sulfate proteoglycan of the GBM (Groffen et al. 1998; Timpl 1989). As a heparan sulfate proteoglycan, and also due to the presence of sulfated glycosaminoglycan side chains, agrin has a high net negative charge. All BM, and particularly the GBM, have a net negative charge. Perlecan and agrin are thought to be the most important contributors to this negative charge (Kanwar et al. 2007). It is thought that the net negative charge of the GBM is crucial for function, including the filtration of molecules by the glomerulus. Thus, studies show that molecules that are positively charged cross the filtration barrier more easily than the neutral molecules, which in turn cross more easily than the negatively charged molecules. For example, plasma albumin, which is negatively charged, is repelled by the GBM. Defects in GBM allow albumin to pass the filtration barrier and results in high albumin content in urine. However, selective knockout of agrin had no effect on the glomerular filtration barrier in one study (Harvey et al. 2007).

There are a number of diseases that affect the glomerular BM. In mature GBM, the major collagen type IV molecule is the alpha-3 alpha-4 alpha-5 isoform, associated with laminin-521 (alpha-5 beta-2 gamma-1), nidogen and agrin heparan sulfate proteoglycans. Several hereditary glomerular diseases are linked to structural anomalies of GBM tissue-specific components; for example, the alpha-3 alpha-4 alpha-5 isoform of collagen type IV in Alport syndrome and thin basement membrane nephropathy (benign familial hematuria), and laminin in Pierson syndrome (Gubler 2008). Tumor necrosis factor-α has been shown to drive Alport glomerulosclerosis in mice by promoting podocyte apoptosis (Ryu et al. 2012). Another example is the Goodpasture's antigen associated with Goodpasture's syndrome that is the NC1 domain of the alpha-3 chain of collagen type IV found in the glomerular BM (Derry and Pusey 1994).

BM in lung

The BMs of the alveolus functions in cell adhesion for alveolar epithelial and endothelial cells, to facilitate gas exchange between the alveolar space and the alveolar capillaries (West and Mathieu-Costello 1999), to regulate cytokine and growth factor functions, and other alveolar cellular processes in the lung (Sannes and Wang 1997). The polarity of the lung is maintained by the BMs and they act as physical barriers between epithelium, endothelium and mesenchymal tissues.

Pulmonary alveoli have been shown to have a thinner side and a thicker side (Vaccaro and Brody 1981; Weibel 1973). The thinner side consists of alveolar epithelium and capillary endothelium separated only by a common fused BM that is thought to facilitate gas exchange. The thicker side consists of alveolar epithelium and capillary endothelium, each with their respective BMs (alveolar BM (Fig. 6) and capillary BM, respectively) separated by connective tissues within the interstitial space (Vaccaro and Brody 1981; Weibel 1973). These two lung BMs appear to have similar ultrastructure when examined with standard TEM techniques. However, staining with ruthenium red demonstrated that the two lung BMs have different ultrastructural characteristics and that the type and distribution of proteoglycans differs between alveolar BM and capillary BM (Vaccaro and Brody 1981). Otherwise, the component differences between these BMs have not been fully characterized. The integrity of the BMs maintains the normal lung architecture and the alveolar BM is crucial for restoration

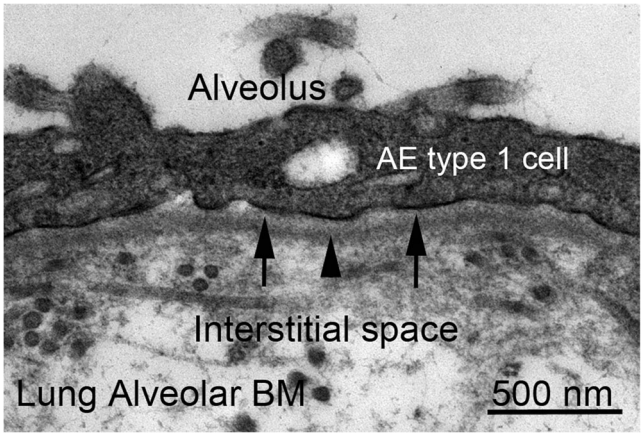

Fig. 6 Transmission electron micrograph of alveolar basement membrane (BM) of rabbit lung at ×46,000. Shown is the "thicker side" of the alveolus where the alveolar BM and capillary BM are separated by an interstitial space containing collagen fibrils and other extracellular matrix materials. The alveolar epithelial (AE) type 1 cell rests on the BM with lamina lucida (arrows) and lamina densa (arrowhead). On the "thinner side" of the alveolus (not shown) the alveolar BM and capillary BM fuse, at least focally, to form a single BM separating alveolar epithelial type 1 cells and capillary endothelial cells—a BM morphological variation that is thought to facilitate gas exchange between the alveolar space and the alveolar capillaries (Vaccaro and Brody 1981)

of alveolar epithelial homoeostasis following lung injury (Strieter and Mehrad 2009).

Loss of alveolar BM/capillary BM integrity has been observed in idiopathic pulmonary fibrosis (IPF) (Chen et al. 2016). Mechanisms underlying this disruption have not been well defined. Specific alveolar BM components have been described, including the Goodpasture's antigen associated with Goodpasture's syndrome that is the NC1 domain of the alpha-3 chain of collagen type IV, which is also found in the glomerular BM (Derry and Pusey 1994). The absence of the basement membrane component nidogen-2, but not of nidogen-1, has been shown to result in increased lung metastases in mice (Mokkapati et al. 2012).

BM in the liver

BMs are found in blood and lymphatic vessels and around the bile ducts in human liver (Hahn et al. 1980; Mak and Mei 2017). Their presence in the tubular regions, particularly between sinusoids lining cells and hepatocytes, is still controversial (Schaffner and Poper 1963). Lack of a typical BM in the perisinusoidal space in normal liver (Fig. 7) is thought to allow the intimate contact between blood and parenchymal cells necessary for normal hepatocyte function. However, the appearance of a continuous perisinusoidal BM in experimental liver injury and in human liver fibrosis has been reported (Bucher 1963; Mak and Mei 2017). These disease-related changes may severely restrict the normal functions of the liver.

Thus, liver hepatocytes lack the typical electron-dense structure of BM in other organs and contains non-BM constituents such as collagen type I and fibronectin, in addition to some typical BM constituents (Martinez-Hernandez and Amenta 1995; Matsumoto et al. 1999). Sinusoidal endothelial cells in liver can secrete collagen type IV, laminin, nidogen, and perlecan (Wells 2008). Collagen type IV, laminin, and perlecan are also produced by perisinusoidal hepatic stellate cells (HSCs) (Wells 2008). In the portal tracts, biliary epithelial cells are the principal cells producing collagen type IV, laminin, and perlecan, while portal fibroblasts and myofibroblasts, when generated, also contribute to their production. Expression of collagen type IV along with increased deposition of laminin in the space of Disse results in the formation of a perisinusoidal BM in liver fibrosis (Mak et al. 2013). Laminin expression is not detected in the parenchyma of normal human liver, only in liver fibrogenesis, where β2 laminin chain may be deposited in the space Disse, along with collagen type IV and perlecan, forming a continuous basement membrane beneath the endothelium of liver sinusoids (Mak and Mei 2017).

BM in other organs

Most other organs in a human or animal, including brain, heart, gut (with variation in the different segments of the small

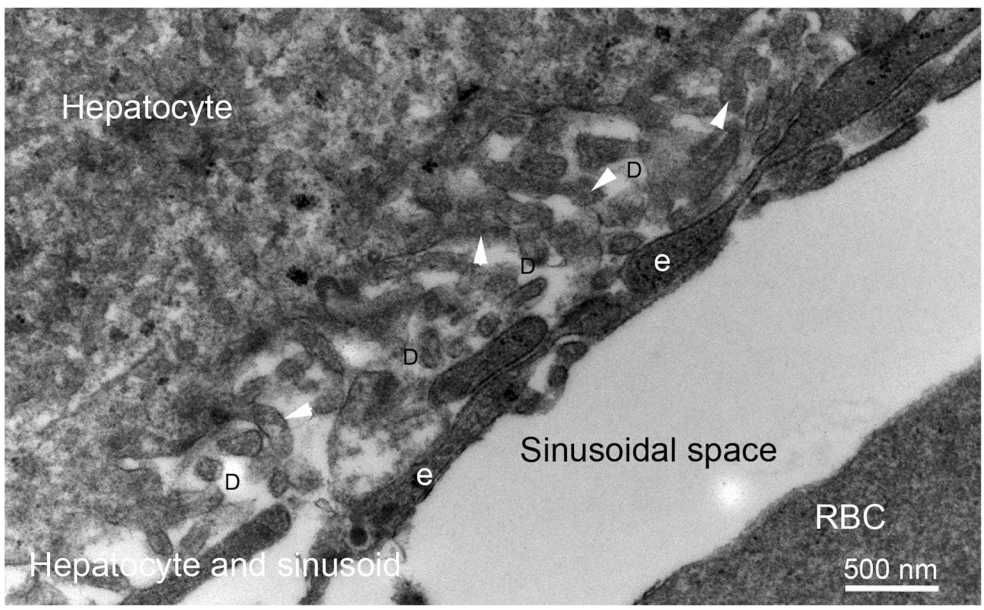

Fig. 7 Transmission electron micrograph of rabbit liver hepatocyte, sinusoids and spaces of Disse at ×30,000 magnification. Hepatocytes are organized into plates separated by the space of Disse (D) from vascular channels termed sinusoids. Hepatocyte processes (arrowheads) extend into the space of Disse. Sinusoids have a discontinuous, fenestrated endothelial cell lining. Of note, there is no basement membrane between either hepatocytes or endothelial cells and the space of Disse—allowing direct cellular contact that is thought to facilitate hepatocyte functions such as detoxification, modification, and excretion of exogenous and endogenous substances

intestine and the large intestine), pancreas, gall bladder, and testis, have BMs that are similar in overall composition to those that have been described for cornea, skin, lung, and kidney, but with tissue-specific alterations in BM components that facilitate the specific functions of these organs. A specific description of the differences in BM composition between these many different organs is beyond the scope of this review.

EBM injury, regeneration and fibrosis in different organs

Corneal EBM injury and regeneration, and its relationship to organ fibrosis, is one of the best-characterized systems. Whether the injured cornea heals with transparency or with fibrosis and transparency depends on the type and level of injury (Torricelli et al. 2013b). Corneal stromal keratocytes are fibroblastic cells that are normally relatively quiescent and function to maintain the precise structure of the stromal extracellular matrix associated with transparency (Chaurasia et al. 2009; Hassell and Birk 2010; Ishizaki et al. 1993; Jester et al. 1995, 1999; Kaur et al. 2009). Corneal injuries "activate" keratocytes at the site of injury and in the proximate stroma to "corneal fibroblasts" that participate in the healing response and can differentiate into myofibroblasts when exposed to sustained transforming growth factor β1 or β2 (Jester et al. 1987; Kaur et al. 2009; Wilson 2012). In vitro cell culture experiments have identified several key growth factors such as TGFβ1, TGFβ2, and PDGF that play critical roles in mediating keratocyte differentiation to wound healing corneal fibroblast and myofibroblast phenotypes (Jester et al. 1987, 2002; Tuli et al. 2006; Wilson 2012). In addition, after corneal injury, bone marrow-derived fibrocytes penetrate the corneal stroma and differentiate into myofibroblasts when TGFβ and PDGF are present in the stroma at sufficient and sustained levels (Barbosa et al. 2010). It has been well documented that these key growth factors are produced in high levels by corneal epithelial cells but their penetration into the stroma is negligible when the EBM is intact (Fini 1999; Torricelli et al. 2013b; Wilson 2012). The corneal epithelium, like other epithelial layers in animals, is continuously subjected to physical, chemical, and biological insults. If an insult is sufficiently severe, the EBM is also injured, allowing the penetration of pro-fibrotic TGFβ, PDGF, and possibly other growth factors and cytokines, into the corneal stroma to *initiate* the development of corneal fibroblasts and myofibroblasts from local (keratocyte) and bone marrow-derived (fibrocyte) precursors (Torricelli et al. 2013b; Wilson 2012). If the EBM is promptly repaired, for example, after most simple corneal abrasions, the penetration of TGFβ and PDGF into the stroma is consequently cut off and the developing myofibroblast precursors undergo IL-1-mediated apoptosis (Kaur et al. 2009) before they become mature vimentin+ alpha-smooth muscle actin+ desmin+ myofibroblasts (that secrete large amounts disordered extracellular matrix) (Chaurasia et al. 2009), keratocytes repopulate the anterior stroma and transparency of the corneal stroma is maintained (Fig. 8a–c). If, however, repair of the EBM is sufficiently delayed, then TGFβ and PDGF continue to penetrate the stroma at high levels, resulting in the development of large numbers of stromal myofibroblasts, and the prodigious amounts disordered extracellular matrix they produce, results in fibrosis and loss of transparency that is crucial for corneal function (Fig. 8d–f) (Torricelli et al. 2013b; Wilson 2012). Delayed regeneration of EBM can result from mechanical factors such as corneal stromal surface irregularity produced by injury, surgery, infection, or disease (Netto et al. 2006). Another mechanism for delayed EBM regeneration, however, is likely insufficient stromal keratocyte contributions of basement membrane components needed for full restoration of EBM structure and function (Santhanam et al. 2015, 2017; Torricelli et al. 2015). Thus, keratocytes produce laminins, nidogen-1, nidogen-2, perlecan, and possibly other EBM components. The working hypothesis is that after corneal injury, the healed corneal epithelium lays down a self-polymerizing laminin nascent EBM and that this layer produces a barrier to the penetration of more posterior EBM components that must be provided, at least in part, by keratocytes (Santhanam et al. 2017; Wilson et al. 2017). If the original injury is sufficiently severe, resulting in substantial loss of adjacent keratocytes by apoptosis and/or necrosis (Marino et al. 2017a; Mohan et al. 2003; Wilson et al. 1996) and, therefore, there are diminished keratocyte contributions of components to EBM repair, then defective regeneration of the EBM promotes the development and persistence of myofibroblasts via ongoing penetration of TGFβ and PDGF into the stroma. These persistent myofibroblasts produce the fibrosis in the anterior subepithelial stroma. After a period of time, importantly without recurrent injury and typically measured for the cornea in many months to years, the normal mature EBM may be regenerated—likely via keratocyte penetration of the layer of myofibroblasts and their disordered extracellular matrix—where the keratocytes coordinate with the overlying epithelium to facilitate EBM regeneration. Once the EBM is fully repaired, myofibroblasts, deprived of their ongoing source of TGFβ, undergo apoptosis (Wilson et al. 2007). Subsequently, the anterior stroma is repopulated by keratocytes, which remove and reorganize the disordered extracellular matrix and restore corneal stromal transparency (Marino et al. 2017b; Wilson et al. 2017).

The importance of the coordination and interplay between the epithelial cells, stromal cells, bone marrow-derived cells, and the EBM in modulating transparency and fibrosis in the cornea at every stage of the corneal

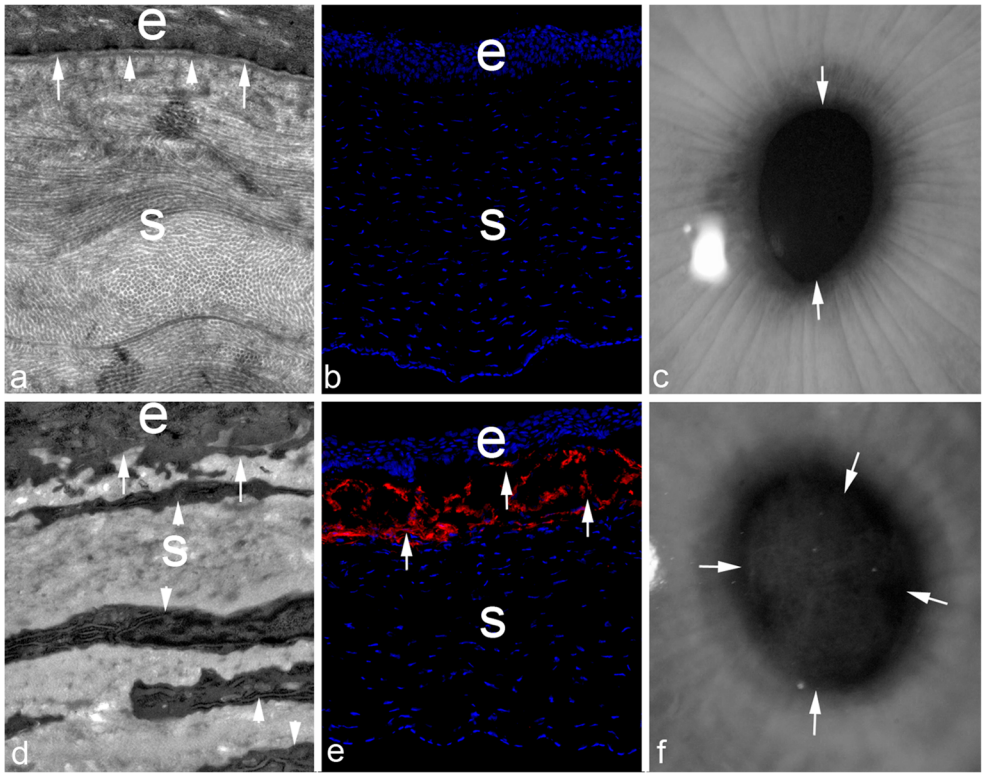

Fig. 8 Regenerative vs. fibrotic repair of the rabbit cornea after injury. At 1 month after minor injuries to the rabbit cornea, such as epithelial abrasion or − 4.5 diopter photorefractive keratectomy (PRK) that is shown (**a**–**c**), in which the EBM and a small amount of the anterior stroma is ablated with the excimer laser and relatively few stromal keratocytes die by apoptosis or necrosis, transmission electron microscopy (TEM) shows that the EBM regenerates normally (**a** ×22,000 mag., arrows are lamina lucida and arrowheads are lamina densa), keratocytes repopulate the anterior stroma (**b** ×400 mag., arrows) and few, and in this case no, myofibroblasts are detected by staining for the alpha-smooth muscle actin (SMA) myofibroblast marker (**b** ×400 mag. showing DAPI stained keratocytes in the stroma (s). The cornea overlying the pupil (arrows) is transparent and iris details are clear when photographed with a slit lamp at 1 month after − 4.5D PRK (**c** ×20 mag.). After a more severe injury (such as high correction − 9 diopter PRK) (**d**–**f**), the EBM is not regenerated at 1 month after surgery and no lamina lucida or lamina densa is detected (**d** ×22,000 mag., arrows note no EBM beneath the epithelium) and myofibroblasts (arrowheads) with large amounts of rough endoplasmic reticulum fill the anterior stroma of the cornea. **d** The disorganization of the collagen in the stroma surrounding the myofibroblasts compared to **a**, where the collagen fibrils are uniform diameter and regularly packed—an important contributor to the transparency of the normal corneal stroma. After this level of injury (**e** ×400 mag.) the anterior stroma beneath the epithelium (the ongoing source of TGFβ that penetrates the stroma to maintain the viability of the myofibroblasts in the absence of normal EBM) has a layer of SMA+ myofibroblasts (arrows). A slit lamp photograph of the cornea at 1 month after surgery shows fibrosis (**f** ×20 mag., arrows delineate area of fibrosis that is also called haze) in the area of the previous PRK surgery. e = epithelium and s = stroma (**a**–**e**)

wound healing process, as well as in homeostasis in the normal uninjured cornea is remarkable and likely relevant to the interactions between epithelial cells, parenchymal cells, fibroblasts, endothelial cells, bone marrow-derived cells, and basement membranes that occur in other organs during homeostasis in normal tissues, and after injuries in which fibrosis may occur. Fibroblasts and other non-epithelial and non-parenchymal cells have been shown to produce basement membrane components in many other organs (El Ghalbzouri et al. 2005; El Ghalbzouri and Ponec 2004; Fleischmajer et al. 1995; Fox et al. 1991; Furuyama et al. 1997; Marinkovich et al. 1993; Simon-Assmann et al. 1998; Smola et al. 1998). Thus, keratinocyte-fibroblast interactions have been shown to be important in basement membrane generation in organotypic skin cultures (Smola et al. 1998). Similarly, assembly of the alveolar basement membrane after lung injury is likely orchestrated by cooperation between alveolar epithelial cells and pulmonary fibroblasts (Furuyama et al. 1997). In addition, fibrosis has been shown to resolve in other organs after removal of sources of chronic injury. For example, bleomycin-induced lung fibrosis in mice can reverse spontaneously after removal of the inciting agent (Cabrera et al. 2013; Lawson et al. 2005; Li et al. 2011). In humans, skin fibrosis associated with systemic sclerosis can at least partially resolve following neutralization of the antifibrinolytic function of plasminogen activator inhibitor 1 (Lemaire et al. 2016). Further research should be directed at fully understanding these critical cellular and extracellular matrix interactions that likely lie at the core of the development and resolution of fibrotic diseases that occur in many organs.

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