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REVIEW

The basement membrane as a structured surface – role in vascular health and disease

Claire Leclech[1,*], Carlo F. Natale[1,2] and Abdul I. Barakat[1]

ABSTRACT

The basement membrane (BM) is a thin specialized extracellular matrix that functions as a cellular anchorage site, a physical barrier and a signaling hub. While the literature on the biochemical composition and biological activity of the BM is extensive, the central importance of the physical properties of the BM, most notably its mechanical stiffness and topographical features, in regulating cellular function has only recently been recognized. In this Review, we focus on the biophysical attributes of the BM and their influence on cellular behavior. After a brief overview of the biochemical composition, assembly and function of the BM, we describe the mechanical properties and topographical structure of various BMs. We then focus specifically on the vascular BM as a nano- and micro-scale structured surface and review how its architecture can modulate endothelial cell structure and function. Finally, we discuss the pathological ramifications of the biophysical properties of the vascular BM and highlight the potential of mimicking BM topography to improve the design of implantable endovascular devices and advance the burgeoning field of vascular tissue engineering.

KEY WORDS: Basement membrane, Endothelial cells, Structured surface, Surface topography, Vascular disease, Vascular tissue engineering

Introduction

The basement membrane (BM) is a thin, sheet-like structure originally identified by electron microscopy as a dense meshwork adjacent to cellular monolayers (Stern, 1965; Susi et al., 1967; Younes et al., 1965). Subsequent research revealed that the BM is a specialized extracellular matrix (ECM) that underlies many tissues including epithelium, endothelium, muscle cells, peripheral nerve axons and fat cells (Fig. 1A–D) (Jayadev and Sherwood, 2017). Originally viewed as a passive structure that only provides mechanical support for cells, recognition of the active role of the BM emerged when defects in BM components were identified in different diseases, including skin blistering, muscular dystrophy and kidney disease, as well as eye and vascular pathologies (Edwards et al., 2010; Hudson et al., 1993; Kalluri et al., 1997; Labelle-Dumais et al., 2011). Discovery of organ-specific BM components subsequently underscored the complexity and heterogeneity of the BM (Randles et al., 2017). The BM is now recognized to be a central player in regulating cell behavior and tissue function by providing crucial biochemical signals both during development (which will not be discussed here; see Morrissey and Sherwood, 2015) and adult life.

The purely biochemical vision that used to drive the understanding of most biological processes, including BM biology, has begun to be challenged by the now well-established importance of biophysical signals, such as topography and stiffness, in many cellular functions (Janson and Putnam, 2015). In this Review, we will address this last and relatively new aspect of BM biology by focusing on the biophysical attributes of the BM and their influence on cellular processes. We will begin by only briefly describing the biochemical composition and functions of BM, which have already been the subject of many reviews (see, for example, LeBleu et al., 2007; Pozzi et al., 2017). We will then review the mechanical and topographical properties of various BMs before focusing specifically on the vascular BM as a nano- and micro-scale structured surface whose topography regulates endothelial cell (EC) homeostasis and, potentially, the etiology of various vascular diseases. The final section will be a forward-looking view of the implications of BM topography for vascular tissue engineering and the development of novel endovascular devices.

The BM across tissues – composition, organization and function

Composition and organization of the BM

The composition of the BM is highly diverse and dynamic, with tissue-specific variations in the relative amounts of its core constituents (Fig. 1A–D) (Randles et al., 2017). Typically, the BM consists of independent networks of laminin and type IV collagen linked together by several additional ECM proteins, most notably the glycoprotein nidogen and the heparan sulfate proteoglycans (HSPGs) perlecan and agrin. In addition, the BM contains ‘matricellular proteins’ or ‘minor components’ such as ‘secreted protein acidic and rich in cysteine’ (SPARC) and tenascin, which provide specific functions despite not being essential for BM assembly or architecture (for a review on minor components, see Murphy-Ullrich and Sage, 2014).

Laminin, the foundational building block of the BM, is a secreted heterotrimeric protein with α, β and γ subunits that self-assemble into a lattice structure that is tightly associated with the cell surface (Hohenester and Yurchenco, 2013). Although laminin is thought to be primarily secreted by the cells themselves and directly incorporated into the underlying BM, indirect evidence suggests that it can also be transported to a target location from distant sites via the interstitial fluid. For instance, *Caenorhabditis elegans* sublateral nerves are covered by a laminin-containing BM even though the neurons do not express the laminin subunits (Huang et al., 2003). Another example is from the mouse neural tube BM which contains laminin despite the fact that it is not expressed by all the neural tube cells (Copp et al., 2011). Following laminin assembly, a second network of covalently cross-linked type IV

[1]Hydrodynamics Laboratory, CNRS UMR7646, Ecole Polytechnique, Palaiseau, France. [2]Interdisciplinary Research Centre on Biomaterials (CRIB), University of Naples Federico II, Naples, Italy.

*Author for correspondence (claire.leclech@ladhyx.polytechnique.fr)

A.I.B., 0000-0002-7551-3631

Journal of Cell Science (2020) 133, jcs239889. doi:10.1242/jcs.239889

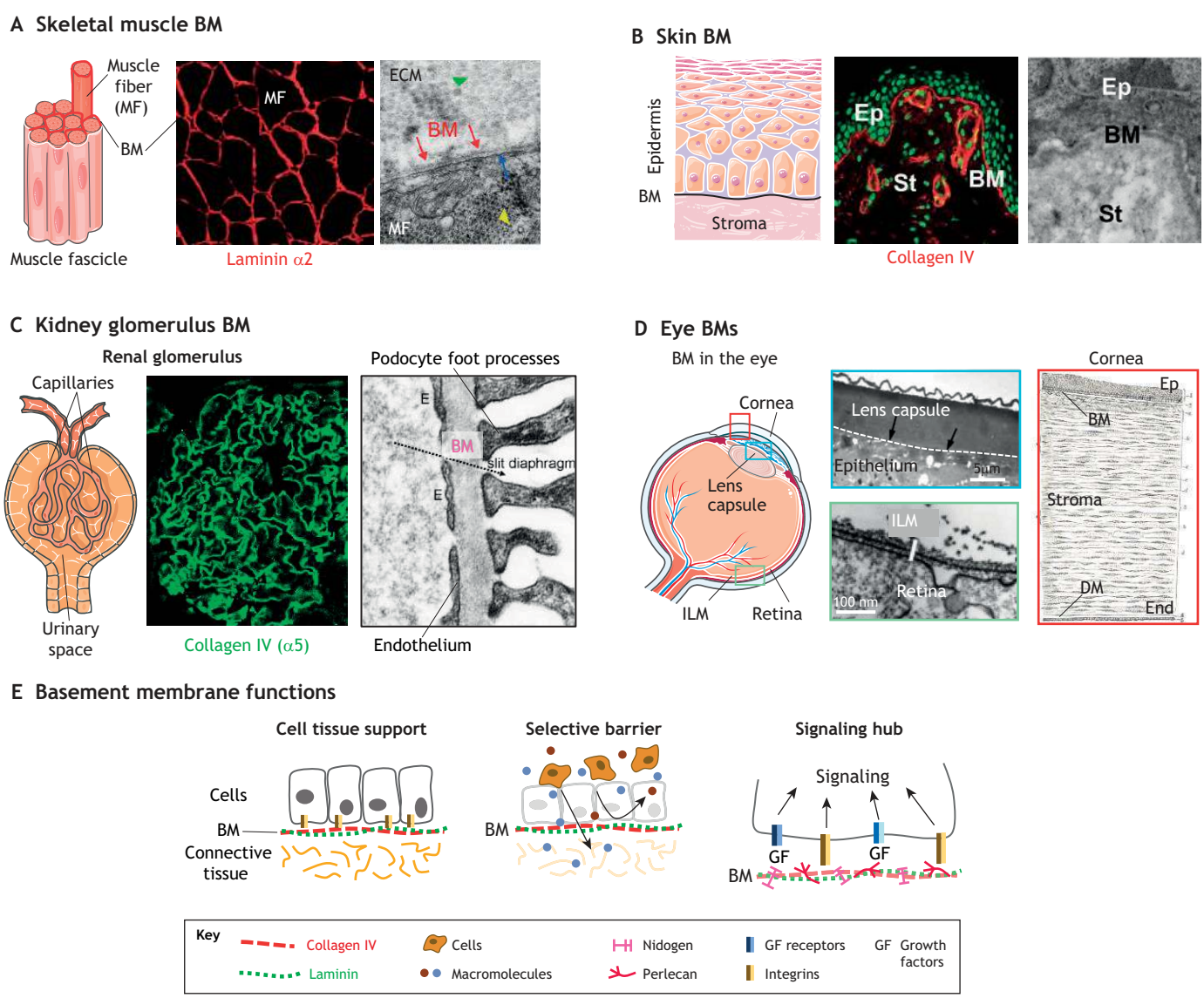


Fig. 1. Basement membrane localization and functions. Examples of various BMs in the body, as observed by immunofluorescence or electron microscopy. (A) Skeletal muscle BM separates the muscle fibers (MF) from the extracellular matrix (ECM). In the right panel, the blue arrow highlights sarcolemma, the yellow arrowhead the sarcomere, and the green arrowhead collagen fibrils in the ECM. Images from Gawlik and Durbeej (2011), where they were published under a CC-BY 2.0 license. (B) Skin BM separates the epithelial cells of the epidermis (Ep) from the stroma (St). Images from Halfter et al. (2013), where they were published under a CC-BY license. (C) The kidney BM separates the capillary endothelium from the podocytes in the urinary space. Center panel shows a large view of a renal glomerulus. Image from Clark et al. (2016), where it was published under a CC-BY 4.0 license. Right panel shows a magnified view on the glomerular BM. Image from Lee et al. (2007), where it was published under a CC-BY-NC 3.0 license. (D) Different BMs are present in the eye: in the cornea, the retina and the lens capsule. Ep, epithelium; DM, Descemet's membrane; End, endothelium; ILM, inner limiting membrane. Images reproduced from: Candiello et al. (2007) (enlarged ILM) with permission from Wiley; Gray (1918) (cornea); and Yan et al. (2002) (lens capsule). (E) Schematic representation of different functions of the BM. The BM provides mechanical support to cells (left), regulates the selective passage of cells and/or macromolecules (center), and acts as a signaling hub by concentrating various proteins (right).

collagen, also secreted by the cells, is added onto the BM. Owing to their high affinity for both laminin and collagen, nidogen, perlecan and agrin, secreted as single molecules, link the two networks together and are thus thought to provide structural stability. More details on BM composition and assembly can be found elsewhere (LeBleu et al., 2007; Yurchenco, 2011).

Interestingly, the BM appears to also participate in the assembly of adjacent ECM proteins. For instance, very recent work has shown that culturing cells on BM components (laminin and collagen IV) increases the assembly and deposition of the ECM component fibronectin and that this form of assembly is mediated by the inward sliding of focal adhesions (FAs) driven by an actomyosin contractile winch (Lu et al., 2020).

BM function

BMs first emerged in metazoans when multi-cellularity appeared, suggesting an essential role for BMs in organizing tissues (Özbek et al., 2010; Rodríguez-Pascual, 2019). In the mouse embryo, BMs appear at around embryonic day 4–4.5, subsequently playing a crucial role during the morphogenesis of the embryo (Morrissey and Sherwood, 2015;

Journal of Cell Science (2020) 133, jcs239889. doi:10.1242/jcs.239889

Sekiguchi and Yamada, 2018). In the adult, BMs fulfill a variety of essential functions (depicted in Fig. 1E), as summarized below.

Cell/tissue support and scaffolding

BMs possess laminin globular-like (LG) domains that provide binding sites for adhesion receptors (integrins and dystroglycans) or sulfated glycolipids at cell surfaces. While the laminin network is thought to constitute the principal platform for cellular binding, the collagen IV network is viewed as providing a scaffold that ensures structural stability in the face of mechanical challenges (Pöschl et al., 2004).

Barrier function

The dense structures of interconnected BM protein networks act as a barrier to the passage of both cells and large molecules. This barrier function is particularly crucial for the vascular system. In the kidney, the permeability of the glomerular BM controls the transport of plasma proteins into the urine (Miner, 2012; Suh and Miner, 2013). BMs also regulate the passage of cells under both physiological conditions, as occurs during the transendothelial migration of immune cells from the bloodstream into tissues, and pathological conditions, as in the extravasation of cancer cells in metastasis (Kelley et al., 2014; Sekiguchi and Yamada, 2018).

Signaling hub

By clustering a number of proteins, BMs act as signaling platforms that regulate critical biological processes. For instance, engagement of integrin receptors can directly activate signaling pathways involved in cell survival, differentiation, polarity and migration (Yurchenco, 2011). The BM HSPGs (perlecan and agrin) and type XVIII collagen tether growth factors that interact with receptors on cell surfaces to modulate various cellular responses (Aviezer et al., 1994; Mongiat et al., 2000; Rider, 2006). The action of ECM-modifying enzymes, such as metalloproteases, at the BM can also expose cryptic binding sites of BM proteins such as laminin with ensuing signaling events (Yurchenco, 2011; Zhu and Clark, 2014).

Biophysical properties of the BM

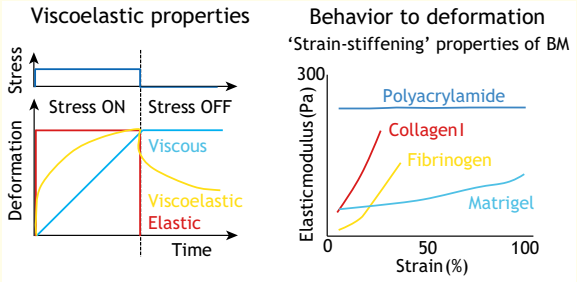
Mechanical properties of the BM

The fact that the BM endows tissues with mechanical strength along with mounting evidence that substrate stiffness regulates cellular structure, function and fate have motivated investigations of the mechanical properties of the BM. Measurement of BM stiffness *in vivo* remains experimentally extremely challenging; however, the mechanical properties of BM excised from different tissues in various species have been measured using micropipette aspiration, glass cantilever systems and atomic force microscopy (AFM). These measurements suggest that the elastic (Young's) modulus of the adult BM in many tissues is in the 1–4 MPa range, ∼1000 times greater than that of the overlying epithelial layer (1–4 kPa). As indicated in Table S1, the stiffnesses of BMs from different tissues can vary over at least four orders of magnitude (0.5 kPa to 5 MPa). It remains unclear whether or not there exists any correlation between the stiffness of a particular BM and that of the tissue that it underlies. One difficulty in establishing such a correlation is the challenge of measuring BM stiffness *in vivo* and the widely different results that different *in vitro* measurement techniques yield. It is also noteworthy that the two sides of the BM appear to have different stiffnesses, with the epithelial side being stiffer than the stromal side (Halfter et al., 2013; Henrich et al., 2012). The basis for this difference remains incompletely understood but may relate to asymmetric distributions of BM proteins.

The BM is often considered a purely (linear) elastic material (Candiello et al., 2007, 2010; Last et al., 2009) (see Box 1). However, a more recent study analyzed AFM force–relaxation data of breast gland BM and concluded that its behavior was more consistent with it being a poroelastic material, that is, a fluid-filled porous elastic solid (Fabris et al., 2018). Indeed, modeling the BM as a hyperelastic (non-linear elastic) matrix immersed in a fluid allows taking into account both BM stiffness and water diffusivity within the membrane (Fabris et al., 2018). In light of the fact that most biological materials are in fact viscoelastic, it is likely that a poro-viscoelastic framework may be an even better representation of the BM mechanical behavior.

Naturally, the mechanical properties of the BM depend on its constituents and their relative abundance. Because of its extensive crosslinks, collagen IV is often assumed to be the primary determinant of BM stiffness. In support of this hypothesis, functional abnormalities of collagen IV are associated with mechanical disruption of the BM. For instance, while collagen IV-knockout mice have normal matrix assembly in early development, they eventually exhibit prominent BM structural defects under increased mechanical loading, leading to lethality

Box 1. Mechanical properties of materials



Materials, be they solid or fluid, deform when subjected to a mechanical stress. Alternatively, a material can be subjected to a controlled deformation, which alters its state of internal stress. Thus, stress (or mechanical load) and deformation (or strain) are intricately coupled, and the nature of this coupling is determined by the mechanical properties of the material; the stiffer the material, the smaller its deformation in response to a given load. The slope of the load–deformation curve for an elastic material yields the elastic (or Young's) modulus, a measure of the stiffness of the material or its resistance to deformation. Many solids encountered in everyday life behave as elastic materials, while fluids are typically viscous. A perfectly elastic material deforms instantaneously upon the application of a load and returns immediately to its original shape upon load removal (see figure, left panel). In the case of fluids, any level of applied force causes the fluid to deform (or flow). In general, the slope of the stress–strain rate curve is a measure of the resistance of the fluid to flow, called the viscosity. Fluids whose rate of deformation is directly proportional to the applied load are termed Newtonian fluids. Many biological fluids, however, are non-Newtonian and thus exhibit a non-linear relationship between stress and deformation (or strain) rate. Virtually all biological tissues, including the BM and its constituents, are viscoelastic and thus behave as elastic solids over a certain range of applied loads and as viscous fluids outside this range (see figure). In addition, many biological materials, including components of the BM, such as collagen, exhibit strain-stiffening properties; that is, they become stiffer in response to increasing deformation (Wen and Janmey, 2013; Miller, 2017) (see figure, right panel). Strain-stiffening is often a consequence of polymer crosslinking. This type of non-linear behavior has been measured in biological gels (of collagen and fibrin), and it allows long-range cell–cell communication (Winer et al., 2009).

Journal of Cell Science (2020) 133, jcs239889. doi:10.1242/jcs.239889

(Pöschl et al., 2004). More direct evidence of the contribution of collagen IV to BM stiffness was recently provided by work demonstrating that a decrease in the density of sulfilimine-mediated collagen IV crosslinks leads to decreased BM stiffness (Bhave et al., 2017). Overall, it appears that BM stiffness is determined by a combination of factors, including protein packing and HSPGs that regulate the hydration state of BMs, thereby affecting their biomechanical properties including thickness, stiffness and elasticity (Candiello et al., 2010; Pastor-Pareja and Xu, 2011). Furthermore, the mechanical properties of the BM are dynamic and can evolve with different factors, including age. For instance, AFM measurements on 44- to 88-year-olds have revealed an increase with age of the elastic modulus of the human eye inner limiting membrane (ILM, the BM between the retina and the vitreous body; see Fig. 1D) from 1.5 to 5 MPa (Candiello et al., 2010).

Topographical properties of the BM

Another important biophysical attribute of the BM is its three-dimensional topography due to the complex micro-structural organization of its constituent proteins. The most widely studied aspect of BM topography is BM thickness. Studies based on transmission electron microscopy (TEM) reported BM thicknesses of less than 100 nm (Halfter et al., 2015). However, AFM measurements on hydrated chick, mouse and human BM reported thicknesses that are two to four times greater (Candiello et al., 2010). These larger thickness values appear more reasonable in light of the characteristic size of the collagen IV and laminin molecules (400 nm and 80 nm in length, respectively), allowing them to adopt three-dimensional orientations that are more diverse than in the schematic flat 'chicken wire' view often envisioned. The current view is that depending on anatomic location, age and pathological state, the BM thickness can range from 50 nm to as large as tens of microns (Candiello et al., 2010; Liliensiek et al., 2009; Osawa et al., 2003; Siperstein et al., 1968).

Beyond BM thickness, our understanding of the detailed structure of BM topography is still emerging. AFM maps and electron microscopy images demonstrate the presence of an intricate network of fibers and pores with characteristic dimensions on the order of 100 nm (Fig. 2B,C) on top of which lies a larger, micron-scale topography in the form of undulations (Fig. 2A) (Kawabe et al., 1985; Li et al., 2012; Liliensiek et al., 2009). Thus, BM topography can be viewed as a multi-scale structure with combined features spanning the nano- to micro-scale. How cells detect and react to these different scales of topographical cues remains incompletely understood and is a topic of active research. Interestingly, BM organization and its scale of topographical features appear relatively constant across tissues and species (Table S2). One exception is the BM of the kidney (glomerular or tubular BM), which possesses smaller features (pores and fibers) on average (<15 nm) than other BMs (Hironaka et al., 1993; Yamasaki et al., 1994). In the kidney, the BM separates the vasculature from the urinary space and lies between the ECs and the podocytes (Fig. 1C). This three-layered structure, which forms the glomerular filtration barrier, enables the flow of plasma and small solutes while restricting the flow of larger plasma proteins (Caulfield and Farquhar, 1974; Suh and Miner, 2013). This central role of the kidney BM as a filtration unit may explain the relatively small size of its constituents.

Pores are important topographical features of BM that can be created either passively by the space within the fiber networks or actively by cellular degradation mechanisms (matrix metalloproteinases). Under physiological conditions, the primary role of these pores is not only to provide a selective permeability barrier but also to regulate the passage of migrating immune cells,

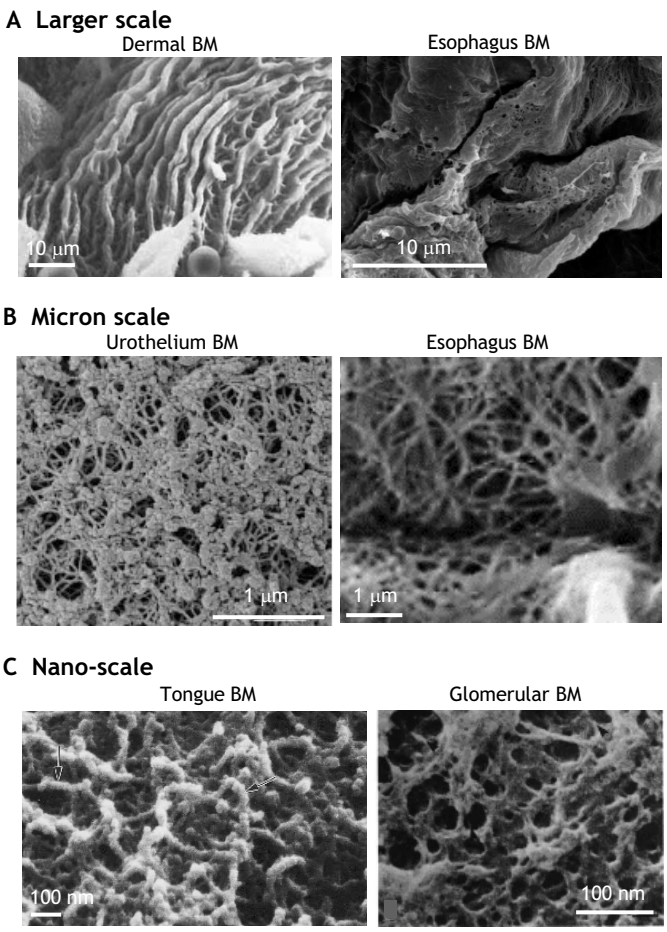


Fig. 2. Topographical organization of the basement membrane. The BM possesses topographical features at different scales. (A) At the larger scale, BM topography takes the form of undulations. Images reproduced from Kawabe et al. (1985) (left) and Li et al. (2012) (right) with permission from Wiley. (B) At the micron scale, BM topography takes the form of pores and fibers. Image of urothelium BM reprinted by permission from Nature Springer, Urological Research, Abrams et al. (2003) (left) and Li et al. (2012) with permission from Wiley (right). (C) At the nanometer scale, the topography of pores and fibers can be more clearly distinguished. Here, the fibers can correspond to individual collagen fibers. Images reprinted from Archives of Oral Biology, Abe and Osawa (1999) (left) and Kidney International, Hironaka et al. (1993) (right) with permission from Elsevier.

which may explain the significantly larger pore sizes (1.5 μm) reported in the bronchial epithelium where infiltration of immune cells is essential for protection against environmental pathogens (Howat et al., 2002). In metastatic tumors, these pores can serve as tunnels that cancer cells exploit to traverse the BM (Glentis et al., 2017). Interestingly, the mechanical properties of the BM can play a role in the remodeling of its pores. For instance, it has been shown that cancer cells in highly plastic hydrogels can use a matrix metalloproteinase-independent mechanism to pass through pores by mechanically and plastically opening up channels (Wisdom et al., 2018). A more detailed review on the breaching of the BM is given elsewhere (Kelley et al., 2014).

Bridging the gap between structure and composition, Fabris et al. recently used enhanced resolution confocal microscopy to image the organization of the collagen IV and laminin networks in BMs from spheroids derived from human breast gland epithelial cells (Fabris et al., 2018). They observed a principal collagen network with a characteristic meshwork organization, pore areas ranging from 50 nm^2 to 1 μm^2 and

Journal of Cell Science (2020) 133, jcs239889. doi:10.1242/jcs.239889

an average fiber diameter of 200 nm. In contrast, the laminin network was arranged in a denser structure of smaller characteristic size intertwined with the collagen IV network, often partially filling its pores (Fabris et al., 2018). Interestingly, no change in arterial BM topography was observed in a mouse model lacking laminin α4 or α5, suggesting that the collagen IV network is the principal structural element of the vascular BM (Di Russo et al., 2017).

The vascular BM

In the remaining sections, we will focus on the vascular BM as a specific example of a system where biophysical features have profound effects on cellular structure and function with important ramifications for health and disease. We will address principally the effects of topography since, to our knowledge, no studies have measured the mechanical properties of the vascular BM.

The vascular system consists of a branched network of vessels that transport blood throughout the body, ensuring oxygen and nutrient delivery to all tissues. The luminal surfaces of all blood vessels are lined with an endothelium, a specialized cellular monolayer that plays critical roles in vasoregulation, permeability control, mechanotransduction and vascular inflammatory responses (Mazurek et al., 2017; Pugsley and Tabrizchi, 2000). In all blood vessels, the vascular endothelium is anchored to a BM whose composition and thickness vary depending on vessel size and whether it is on the arterial or venous side (Fig. 3A). In large vessels, the wall includes both a tunica media, composed primarily of smooth muscle cells (SMCs) and matrix proteins, and a tunica externa, a layer of connective tissue with varying amounts of elastic and collagenous fibers. Some studies have documented the presence of a second BM around SMCs (George and Johnson, 2012; Hedin et al., 1999; Raines, 2001); however, this BM does not appear to be clearly separated from the rest of the ECM and will therefore not be discussed further.

Composition and architecture of the endothelial BM

Biochemical composition

As in all other tissues, the vascular endothelial BM is composed of a collagen IV and laminin network, as well as HSPGs (perlecan and agrin) and nidogens. Minor components, such as netrin-4 (Koch et al., 2000), fibulins (Chapman et al., 2010), SPARC (also known as BM-40 or osteonectin) (Brekken and Sage, 2001; Thomsen et al., 2017), collagen types VII, VIII, XV, XVIII (Sasaki et al., 2000), and thrombospondin 1 and 2 (Thomsen et al., 2017), are found in some vascular BMs, contributing to their specificity and diversity. The specificity of the biochemical composition of the vascular endothelial BM appears to relate to laminin, with the α4 and α5 chains being the two primary isoforms (Frieser et al., 1997; Sorokin et al., 1997); they typically associate with laminin β1 and γ1 to form laminin 411 and 511 (see Fig. 3A).

Topographical structure

With the exception of the glomerular BM in the kidney (Hironaka et al., 1993; Shirato et al., 1991; Yamasaki et al., 1994), the physical structure of the vascular BM has been much less investigated than its biochemical composition. To our knowledge, only two studies

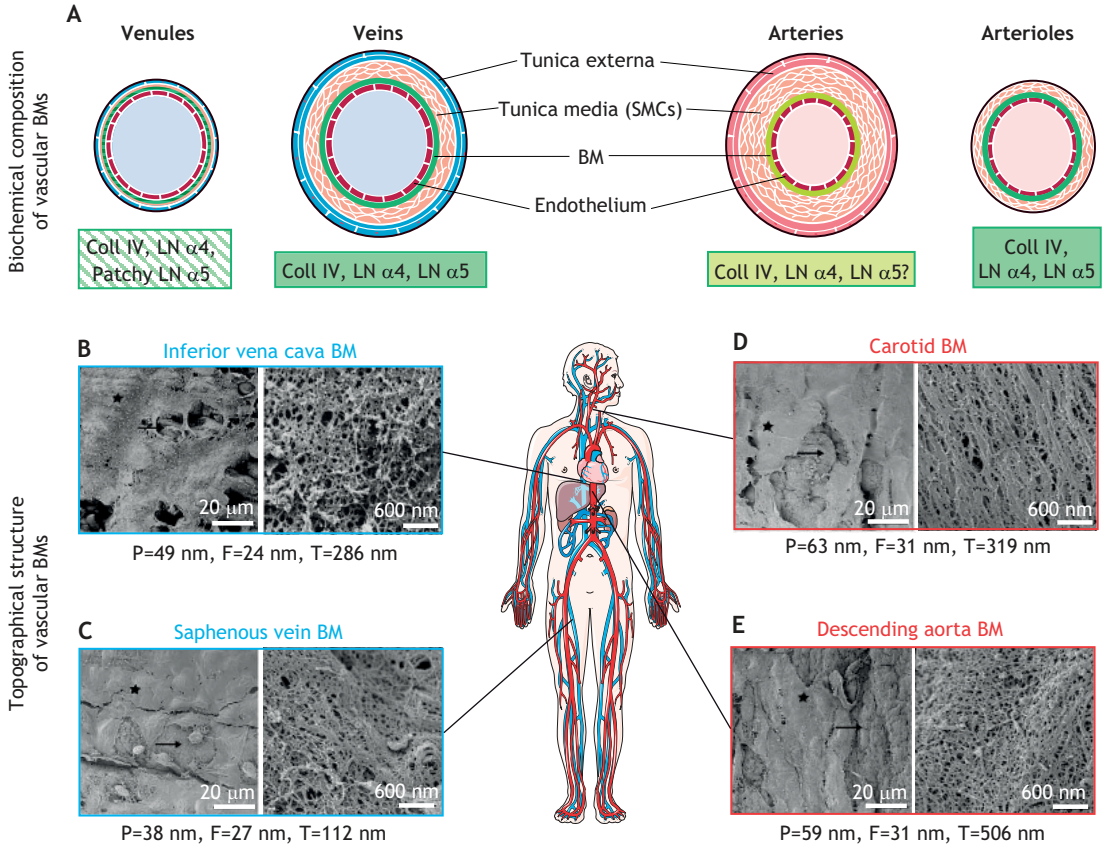


Fig. 3. The vascular basement membrane. (A) In all vessel types, the vascular BM separates the endothelium from the rest of the vessel wall. The biochemical composition of the vascular BM can vary slightly depending on the vessel type, represented by the different shades of green. Coll, collagen; LN, laminin; SMCs, smooth muscle cells. (B–E) Topographical organization of the vascular BM can vary among different vascular beds with differences in their respective values for pore (P) and fiber (F) diameters, and BM thicknesses (T). How these variations relate to the functions of the different vascular beds remains unclear. Images reproduced with permission from Liliensiek et al. (2009). The publisher for this copyrighted material is Mary Ann Liebert, Inc. publishers.

have specifically tackled this issue (Brody et al., 2006; Liliensiek et al., 2009). The vascular BM appears to share the same global topography as other BMs: a structure of intermingled fibers and pores. Based on TEM, scanning electron microscopy (SEM) and AFM images, an average pore diameter of 30 nm and fiber diameter of 29 nm were reported for porcine aortic valve BM (Brody et al., 2006). Topography heights and pore depths were also measured and found to both be in the range of 22–26 nm (Brody et al., 2006). A few years later, a second study analyzed the BMs of different blood vessels in the macaque: the descending aorta, the left common carotid artery, the left saphenous vein and the inferior vena cava (Liliensiek et al., 2009) (Fig. 3B). Measurements of the topographical features revealed that large arteries had a significantly larger pore diameter than veins, while fiber diameter was similar among all vessels. The BM thickness measured by TEM was also different among vessels, with the thickest BM found in the aorta (~500 nm), followed by the carotid artery and inferior vena cava (~300 nm), while the saphenous vein had the thinnest BM (~100 nm) (Liliensiek et al., 2009). It would be interesting to explore if the differences in BM structure among different vessels underlie differences in specific vascular functions.

Functional specificities of the vascular endothelial BM

As the interface between the bloodstream and the vascular wall, the endothelium is central to many vascular processes (Cahill and Redmond, 2016). Interestingly, many of those functions appear to be modulated by the underlying BM (Fig. 4), although this regulation remains poorly characterized. We will specifically focus on endothelial regulation of vascular permeability and responsiveness to fluid mechanical shear stress. The role of BM proteins in angiogenesis has been reviewed elsewhere (Kalluri, 2003) and will not be addressed here.

Endothelial permeability regulation

The endothelial BM serves a crucial barrier function to blood-borne molecules and transmigrating cells. Electron and intravital microscopy studies have documented migrating leukocytes traversing the endothelium in less than 5 min, but residing considerably longer (20–30 min) in the space between the endothelium and the vascular BM (Hoshi and Ushiki, 2004; Thompson et al., 2001; Wiener et al., 1966), suggesting that immune cells encounter significant resistance to migration within the BM. Interestingly, in a mouse model of autoimmune encephalomyelitis, T lymphocytes penetrate the brain endothelial BM at sites that express laminin α4 but not laminin α5 (Wu et al., 2009). Similarly, in murine cremaster venules, regions where expression of certain BM proteins, including laminin 10, collagen IV and nidogen-2, is low constitute preferred transmigration points for neutrophils and monocytes (Voisin et al., 2009; Wang et al., 2006). In fact, immune cells appear to actively seek these zones by extending ventral membrane protrusions (Voisin et al., 2009), and neutrophils appear capable of actively, but transiently, enlarging these permissive sites (Voisin et al., 2009; Wang et al., 2006). Whether these sites correspond to the pores associated with leukocytes observed by SEM (Hoshi and Ushiki, 2004; Scott et al., 1997) remains unclear. In any case, the biochemical and biophysical attributes of the BM appear to be a critical determinant of leukocyte transmigration through the vascular space.

More recently, laminin in the BM has been shown to directly affect the barrier function of the vascular endothelium. Binding of ECs to laminin 511 but not 411 is associated with decreased

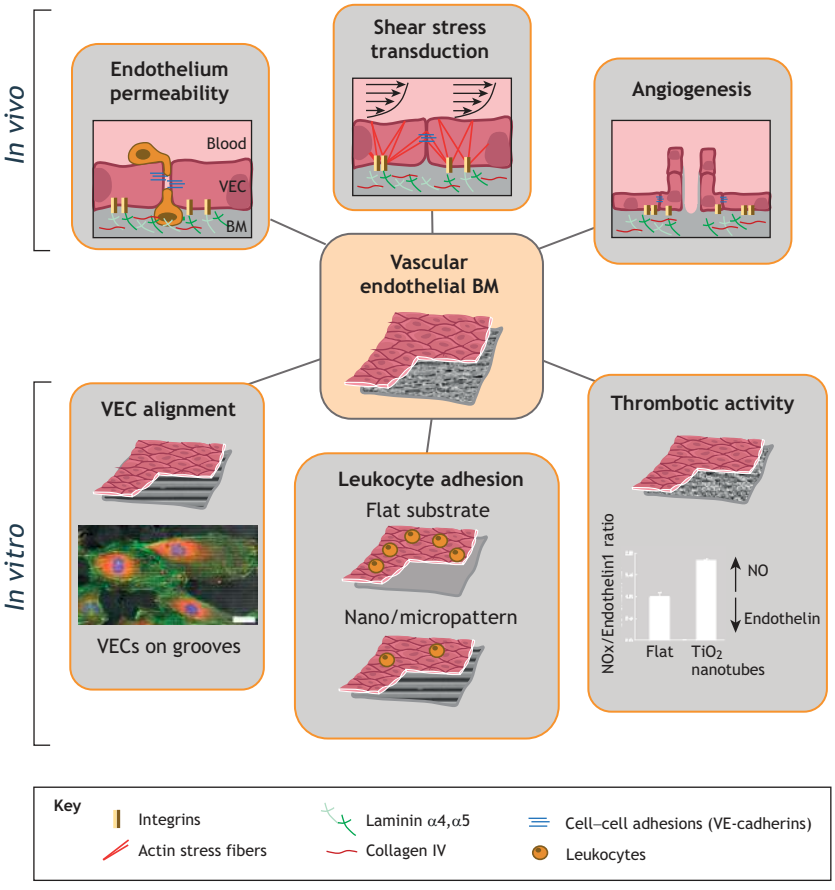


Fig. 4. Functions of the vascular basement membrane. Schematic representation of different functions of the vascular BM observed *in vivo* or *in vitro*. Top panels, *in vivo*, the vascular BM regulates endothelial barrier function and cellular transmigration (left), modulates blood flow-derived shear stress transduction (center), and contributes centrally to the process of angiogenesis (right). Bottom panels: *in vitro*, substrates that mimic aspects of the vascular BM have enhanced our understanding of BM function. Vascular endothelial cells (VECs) cultured on grooved substrates exhibit cell alignment and elongation as observed *in vivo*. Scale bar: 25 µm. Image from Sales et al., (2017) where it was published under a CC-BY 3.0 licence (left). EC monolayers on nano- or micropatterned substrates show reduced leukocyte adhesion, typical of an anti-inflammatory state (center). ECs cultured on a rough surface of TiO_2 nanotubes display an antithrombotic state as assessed by an increased NOx:endothelin-1 ratio (right). Graph adapted with permission from Brammer et al. (2008). Copyright (2008) American Chemical Society.

Journal of Cell Science (2020) 133, jcs239889. doi:10.1242/jcs.239889

permeability as a result of the elevated expression and localization of junctional proteins such as VE-cadherin at cell–cell borders (Song et al., 2017). In line with these results, using a dual pipette-pulling assay, it has been shown that ECs bound to laminin 511 exhibit stronger cell–cell adhesion (Di Russo et al., 2017).

Shear stress transduction

By virtue of their anatomic location, vascular ECs are constantly subjected to shear stress due to the flow of viscous blood. As has been reviewed elsewhere (Barakat, 2013; Chien, 2007; Davies, 1995; Fisher et al., 2001), ECs are natural mechanotransducers, converting the mechanical signals associated with shear stress into biochemical signals that regulate cell structure and function. It is important to note that EC responsiveness to shear stress involves firm anchorage of the cells to the BM, which is mediated by the binding of integrins to ECM proteins including laminin. Shear stress is known to activate a host of integrins in ECs (Jalali et al., 2001; Shyy and Chien, 2002) and to increase the mRNA and protein levels of α5 and β1 integrins (Urbich et al., 2000). Blocking integrin signaling abolishes shear stress-induced secretion of basic fibroblast growth factor and the anti-apoptotic effect of shear stress (Gloe et al., 2002; Urbich et al., 2000). Finally, recent *ex vivo* experiments on resistance arteries have shown that the response to shear stress is abolished in mice lacking laminin α5 (Di Russo et al., 2017). Taken together, these results suggest an intricate interplay between the BM and integrins that plays a key regulatory role in EC mechanotransduction.

Influence of substrate topography on the vascular endothelium

Unidirectional and multi-directional cellular contact guidance

Although studying the influence of the BM on cellular function *in vivo* remains very challenging, advances in nano- to micro-scale fabrication and surface functionalization techniques have enabled the production of topographic surfaces of controlled architecture that can serve as idealized mimics of BM topography and be used for investigations of cellular responses *in vitro* (Bettinger et al., 2009) (for more information on *in vitro* models of the BM see Box 2). The influence of topographic features on cellular behavior, a process termed contact guidance, has been shown to regulate the morphology and function of multiple cell types including vascular ECs (Kim et al., 2012). Therefore, engineered topographic surfaces provide a powerful tool for controlled investigations of relationships between cell shape and function. In the case of ECs, this is particularly interesting in light of the observation that regions where ECs are elongated and aligned in the direction of blood flow are generally spared from atherosclerotic lesions, at least in the early stages of the disease (Davies, 1995).

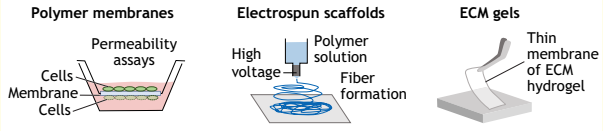
Broadly speaking, engineered topographic surfaces can be classified as either unidirectional, where cellular contact guidance is directed in one principal spatial direction, or multi-directional where the cells receive topographical cues in multiple directions. Both these types of substrates are useful and complementary for understanding the responses of ECs to the topography of the BM. Unidirectional topographies are easier to fabricate and they provide highly controlled geometries that allow more systematic studies of cellular responses. Multidirectional ‘rough’ substrates provide architectures and dimensions that better approximate the native BM; however, they lack controlled and reproducible geometries.

Unidirectional topography

Unidirectional grooved substrates consisting of parallel arrays of rectangular grooves and ridges are widely used in the literature and have the distinct advantage of directing EC elongation and alignment in the direction of the grooves even in the absence of flow, thereby producing EC morphologies that resemble those prevalent *in vivo* and providing a tool for control of EC shape and alignment independently of flow (Li et al., 2014; Zhou et al., 2009) (Fig. 4). Such substrates are particularly useful for addressing important questions with regard to relationships between cell structure and function and for elucidating the sensitivity of ECs to the dimensions and detailed architecture of substrate topography. *In vitro* studies on such patterns have revealed that ECs respond to both nano- and micro-scale cues, but the amplitude of the response is dependent on pattern dimensions. Generally speaking, in the range of dimensions that elicit a cell response, decreasing groove width and/or increasing groove depth amplify the extent of EC elongation and alignment (for more details, see the review by Anderson and Hinds, 2011); however, the effect of the topography appears significantly attenuated when the groove widths are below ∼800 nm (Morgan et al., 2012), which may relate to the size of the subcellular structures involved in topography sensing, namely cell protrusions and FAs.

Several studies have investigated not only the shape but also the function of topographically aligned ECs. One study compared gene expression in human umbilical vein ECs (HUVECs) cultured on

Box 2. Engineering a basement membrane *in vitro*



Owing to its structural and topographical complexity, the BM is difficult to reproduce *in vitro*. Nevertheless, advances in chemistry, materials science and nanotechnology have greatly improved the fabrication of surfaces with mechanical properties and nano- to micro-scale topographical patterns with features that somewhat resemble the native BM. Three main families of engineered BMs are summarized here; more detailed descriptions can be found elsewhere (Perry et al., 2018).

Polymer membranes

Early attempts to mimic the BM focused on the use of simple polycarbonate, polyester, polyethylene terephthalate (PET), or poly-tetrafluoroethylene (PTFE) membranes. These membranes are typically mounted onto inserts compatible with cell culture and can be used for various studies including permeability tests and cellular migration assays (see figure, left panel). However, they are usually thicker (1–10 µm) and much stiffer (elastic modulus in the GPa range) than physiological BMs.

Electrospun scaffolds

This technique allows the deposition of polymer (typically polycaprolactone) microfibers on a surface, thereby reproducing the fibrous character of the native BM (see figure, center panel). Different biomolecules (such as collagen) can be added to improve cell adhesion. The Young’s moduli of these substrates (tens of MPa) are close to physiological values, but they do not exhibit the strain-stiffening behavior observed *in vivo*.

Extracellular matrix gels

One of the simplest methods to mimic the BM is to coat the cell culture surface with a layer of ECM proteins (see figure, right panel). The most famous of these gels is Matrigel, which is extracted from Engelbreth–Holm–Swarm murine sarcoma and composed of the BM proteins type IV collagen, laminin, nidogens, HSPGs and a number of growth factors (Kleinman et al., 1986). The primary advantage of Matrigel is therefore its composition, which is close to the native BM. However, its constituents and their concentrations are not well-controlled, which can lead to significant experimental variability.

either nano-grooved or flat surfaces (Gasiorowski et al., 2010). Among the many families of genes differentially expressed, cell-cycle-related genes were significantly downregulated on grooved substrates, reminiscent of the homeostatic state, in which ECs are minimally proliferative (Gasiorowski et al., 2010). Other studies have suggested that ECs on topographic surfaces adopt an anti-atherogenic phenotype that is characterized by reduction in secretion of inflammatory cytokines, and in leukocyte adhesion and transmigration (Huang et al., 2013; Jeon et al., 2015; Song et al., 2012; Vartanian et al., 2010) (Fig. 4).

Although unidirectional topographic substrates do not recapitulate the complex structure of the vascular BM, they do provide the capability to separate the effects of basal topography from those of other signals, most notably blood flow. It now appears that certain anti-inflammatory characteristics of the endothelium can be generated by topographically induced cell alignment independently of flow (Jeon et al., 2015; Vartanian et al., 2010). Interestingly, there is evidence that when ECs are subjected to both substrate topography and flow simultaneously, they integrate the effects of both signals, and this integration may be either synergistic or antagonistic, depending on the dimensions and detailed architecture of the topographic substrate (Franco et al., 2012; Morgan et al., 2012).

Multi-directional topography

Different *in vitro* techniques have been used to create multi-directional topographic substrates intended to mimic more closely the structure of the vascular BM. For instance, nano-scale topography created by grafting polyethylene glycol chains on a polyurethane surface has been shown to increase EC adhesion and growth relative to smooth control surfaces (Chung et al., 2003). Surfaces structured with TiO_2 nanotubes lead to upregulation of the anti-thrombotic activity of ECs, as assessed by the increased ratio between nitric oxide, an important vasodilator synthesized by the endothelium that inhibits platelet aggregation, and endothelin-1, a vasoconstrictor that promotes platelet aggregation (Fig. 4) (Brammer et al., 2008). Electrospun recombinant elastin-like protein (ELP) matrices are fibrous matrices reminiscent of the topography of the vascular BM, with fibers similar to native ECM fibers. Increasing the fiber width from 0.8 to 2 µm is associated with disruption of the cell–cell adhesion protein VE-cadherin in HUVECs (Mascharak et al., 2017). In contrast, a less elaborate topography in the form of SiO_2 porous membranes with pore diameters in the 0.5 to 3 µm range has been reported to increase cell–cell contact and decrease fibronectin secretion compared to that seen with non-porous surfaces (Casillo et al., 2017). These results show that EC responses to multi-directional topographic surfaces are complex and emphasize the need for a better understanding of the underlying mechanisms.

Mechanisms of EC response to topography

The mechanisms underlying EC response to topography, and in particular cellular elongation and alignment on unidirectional substrates, remain incompletely understood. A natural candidate for topography sensing are FAs, which are observed on ECs *in vivo* (Di Russo et al., 2017; Van Geemen et al., 2014) and constitute the interface between the substrate and the cells. In line with this idea, our recent experiments on ECs cultured on a unidirectional microgrooved pattern have demonstrated FA clustering and maturation that subsequently drives the alignment of bundles of actin stress fibers in the direction of the pattern (Natale et al., 2019). It should be noted, however, that the contribution of the actin cytoskeleton to EC elongation and alignment on topographic surfaces remains unclear, since experiments using acto-myosin-disrupting drugs have yielded conflicting results. On the one hand, it has been reported that while not necessary for initial spreading, acto-myosin contractility is needed at later times for cell alignment with the grooves (Franco et al., 2011; Sales et al., 2017). On the other hand, other studies have observed that pharmacological disruption of actin and the acto-myosin machinery does not hinder EC elongation on topographic or patterned surfaces (Natale et al., 2019; Vartanian et al., 2008). In light of the above, the role of actin in EC contact guidance merits further study. Beyond actin, the involvement of microtubules, intermediate filaments and cytoskeleton-associated proteins in regulating EC contact guidance remains poorly characterized and would certainly warrant further investigation.

Implications for vascular diseases and potential therapies

The vascular BM in disease

Many vascular diseases, such as atherosclerosis and hypertension, are associated with abnormal remodeling of the vascular wall. These defects can include altered structure of existing matrix or dysfunction in the secretion and assembly of new ECM proteins, leading to loss of vascular homeostasis and changes in the mechanical properties of the vessels (for more details, see Xu and Shi, 2014). The major alteration specific to the BM identified in vascular diseases is BM thickening. In diabetes, an ∼2-fold capillary BM thickening was first reported in 1968 (Siperstein et al., 1968) and subsequently confirmed during the ensuing decades (Feingold et al., 1989; Klein et al., 1987; Merimee et al., 1970). The same appears to occur in atherosclerosis as evidenced by the increased BM thickness of intramyocardial capillaries in acute myocardial infarction patients (Begieneman et al., 2009). Further evidence of a link between BM abnormalities and atherosclerosis is provided by the observation that markers of BM degradation and remodeling correlate with higher mortality in atherosclerotic patients (Nielsen et al., 2018).

The mechanisms governing vascular BM thickening remain unclear but may involve an imbalance in the production and/or degradation of BM components, or a change in the relative abundance of these components. Indeed, quantitative electron microscopy images show that retinal and renal glomerular BM thickening in a rat model of diabetic retinopathy is associated with an increase in type IV collagen and laminin, while the levels of HSPGs remain unchanged (Das et al., 1990). Although it has not been directly demonstrated, we can hypothesize that changes in BM thickness may influence the biochemical and mechanical properties of the BM, which may in turn directly or indirectly impact the progression of the disease. For example, some patients with diabetes develop diabetic nephropathy, characterized by a thicker glomerular BM that can lead to microalbuminiria (Tsilibary, 2003). But overall, whether BM thickening is a cause or a consequence of the disease remains unclear.

Therapeutic applications

A particularly exciting direction in vascular BM research is the idea of using the topography of the BM as an inspiration for designing improved implantable devices (Tan et al., 2017). Cardiovascular implants, such as endovascular stents, artificial vascular grafts and prosthetic heart valves, are the ‘frontline soldiers’ in the current treatment of cardiovascular pathologies. Despite significant advances in the past two decades, challenges related to biocompatibility as well as the possible occurrence of complications, such as thrombosis and restenosis (the recurrent

narrowing of an artery), continue to pose significant risk to patients. A key requirement for the success of implantable endovascular devices is sufficiently rapid endothelialization. In light of the influence of grooved surfaces on EC adhesion, morphology and migration as discussed above, the idea of incorporating these types of topographies into stents or grafts in order to improve endothelialization has begun to be explored. In a porcine model of coronary injury, endothelialization was significantly improved in stents with luminal grooves compared to what was seen with control stents without the grooves (Sprague et al., 2012). This effect was subsequently confirmed in human patients where microgrooved stents were found to be associated with significantly lower levels of neointimal hyperplasia (abnormal proliferation and migration of SMCs leading to restenosis) and appeared to promote a more homogeneous surface healing of the stent compared to standard bare metal stents (Vesga et al., 2017). More recently, a freeze-cast technique has been used to develop a small-diameter vascular graft with luminal nano-grooves; this surface was able to induce EC alignment and reduce the number of adherent platelets (Wang et al., 2019). In addition, numerical simulations revealed that this lamellar topography reduced blood flow disturbance compared to a random topography. Finally, implantation of this graft in a rabbit carotid artery showed a persistent anti-thrombotic effect and vessel patency after 3 months, whereas occlusions were observed in the control grafts after only 1 month (Wang et al., 2019). Overall, topographical modification of stents or grafts appears to be a promising strategy for improving cardiovascular device efficacy and performance.

Concluding remarks and open questions

The BM, a structure first identified in skeletal muscle 180 years ago (Bowman, 1840) and initially thought to simply be a passive support for cells and tissues, is now recognized as a dynamic entity that regulates cell structure and function. Beyond its role as a cell and/or tissue anchor and a signaling hub that concentrates and sequesters molecules that regulate essential cellular functions, the BM is physically a structured surface with topographic features over the nano- to micro-scale. Although recent research has begun to unravel the impact of this topography on cellular processes, many open questions remain. For instance, how does the three-dimensional organization of the BM develop, how dynamic is this organization, and how does it end up determining the mechanical properties of the BM? While addressing these questions in excised BMs using a combination of microscopic imaging and AFM appears feasible, extending such studies to an *in vivo* setting is much more challenging and will necessitate significant advances in techniques that combine high-resolution imaging with the assessment of mechanical properties (such as elastography). Another question, more biological in nature, is what are the mechanisms underlying cellular responses to BM topography? An integrated picture of the signaling pathways governing contact guidance on structured surfaces remains a work in progress and is under intense investigation by several groups. A third question is how do cells integrate the biophysical cues emanating from the BM with other biophysical and/or biochemical stimuli to which they may be simultaneously subjected? *In vivo*, there is a need to decipher the effective environmental landscape that a cell can detect and to which it can respond. *In vitro*, the challenge is to design new and controlled environments that combine different relevant physiological features while retaining the capability for real-time monitoring of cellular responses. Finally, how closely can engineered surfaces be made to mimic not only the true multi-directional and multi-scale topography of the BM but also its complex mechanical and biochemical properties? Addressing this issue will require significant advances in materials science, nanofabrication techniques and surface functionalization approaches. These questions and others will undoubtedly be the focus of BM research in the coming years, and addressing them will enhance our understanding of the BM in both health and disease, and will guide strategies aimed at the development of novel biomedical devices.

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Competing interests

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Supplementary information

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