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Basement membranes in development and disease

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Abstract

The basement membrane is a thin but dense, sheet-like specialized type of extracellular matrix that has remarkably diverse functions tailored to individual tissues and organs. Tightly controlled spatial and temporal changes in its composition and structure contribute to the diversity of basement membrane functions. These different basement membranes undergo dynamic transformations throughout animal life, most notably during development. Numerous developmental mechanisms are regulated or mediated by basement membranes, often by a combination of molecular and mechanical processes. A particularly important process involves cell transmigration through a basement membrane because of its link to cell invasion in disease. While developmental and disease processes share some similarities, what clearly distinguishes the two is dysregulation of cells and extracellular matrices in disease. With its relevance to many developmental and disease processes, the basement membrane is a vitally important area of research that may provide novel insights into biological mechanisms and development of innovative therapeutic approaches. Here we present a review of developmental and disease dynamics of basement membranes in *Caenorhabditis elegans*, *Drosophila melanogaster*, and vertebrates.

Keywords

basement membrane; development; morphogenesis; extracellular matrix; cell migration; invasion; proliferation; cancer; basement membrane pores

Introduction

The extracellular matrix (ECM) is a non-cellular component of multicellular organisms that plays essential roles in animal development and throughout life (Naba et al., 2016). Constantly undergoing remodeling, the ECM provides highly dynamic microenvironments. Two types of ECM—interstitial connective tissue and basement membrane—have both overlapping and distinct biological functions through their bidirectional interactions with cells and tissues. Both interstitial connective tissue and basement membrane ECMs can modulate cell proliferation, differentiation, angiogenesis, branching morphogenesis, tissue repair, and homeostasis (Bonnans et al., 2014; Rozario and DeSimone, 2010). Through binding and sequestering of soluble growth factors in the presence of appropriate cell-

mediated forces or proteolytic degradation, both types of ECM can also enable spatial-temporal regulation of receptor-ligand interactions. ECMs provide adhesive scaffolds and sometimes even concentration gradients for migratory cells. Furthermore, ECMs can generate and transduce mechanical signals. Through their interactions with cell-surface receptors, ECMs modulate a remarkably wide range of signaling processes (DeSimone and Mecham, 2013; Hynes and Yamada, 2012).

On the other hand, interstitial connective tissue and basement membrane ECMs have many unique characteristics. Interstitial connective tissue ECMs can range from a gel-like scaffold comprised of collagen I, fibronectin, and/or cartilage proteoglycans to tough, dense sheets or tendons (DeSimone and Mecham, 2013; Jayadev and Sherwood, 2017). Other components can include a wide variety of glycoproteins, proteoglycans, other types of collagen except type IV, and integrins (transmembrane heterodimeric receptors). The interstitial connective tissue ECM provides structure to spaces between cells and modulates intercellular and inter-tissue interactions via integrins and other cell surface ECM receptors.

In contrast, the basement membrane is an ultrathin, dense, sheet-like ECM that is associated with virtually all organized cells (Yurchenco and Patton, 2009). The basement membrane underlies epithelial and endothelial cells and surrounds muscle, fat, and Schwann cells. Its primary structural elements consist of two polymeric networks comprised of laminin and type IV collagen, which are interconnected with nidogen, perlecan, and other molecules (Yurchenco, 2011).

The basement membrane is essential for animal development. It provides tissue integrity, elasticity, and biochemical and mechanical signaling, while facilitating intracellular and intercellular interactions. Mutations in basement membrane components lead to a variety of detrimental conditions affecting multiple organs and structures across embryonic and postnatal stages. During development, the basement membrane displays the opposing but complementary traits of rigidity and plasticity—it defines tissue boundaries and protects tissues from mechanical damage while exhibiting a high degree of plasticity that permits growth, development, and cellular and tissue interactions (McClatchey et al., 2016). The basement membrane achieves these seemingly contradictory tasks through its physical pliability and versatility in tissue- and time-specific structures and functions. The focus of this review will be on basement membranes in development: their functions, spatial and temporal variations in biochemical and biophysical properties, mechanisms by which they coordinate tissue morphogenesis, and the relevance of such developmental mechanisms to pathological conditions, including cancer invasion and congenital or acquired disorders.

Functions

The basement membrane provides tissues with a wide array of functions that include tissue separation, barrier, provision of an adhesive substrate and signaling platform for migration, polarization, differentiation, tissue shaping, and growth.

Tissue Separation and Barrier

While the basement membrane comprises a mere fraction of total ECM mass, the stable interlocking lattice of cross-linked type IV collagen and laminin forms a major structural barrier to transmigration of most cells (except leukocytes) in normal physiology and pathological conditions (Kalluri, 2003).

Basement membrane permeability varies greatly throughout the body. In the developing kidney, two basement membranes—one associated with the vascular endothelium and another with the podocyte epithelium—merge to form the glomerular basement membrane (Figure 1F) (Deen, 2004). The glomerular basement membrane serves as the kidney's filtration barrier with selective molecular permeability. With its controlled porosity based on size and charge, the glomerular basement membrane is impermeable to plasma proteins while permitting low-molecular weight substances to pass readily. Lung alveolar development also involves a merger of alveolar and capillary basement membranes, which establishes a gas-exchange surface (Figure 1C) (Rodeck and Whittle, 2009).

In brain development, the blood-brain barrier is formed at the interface between the vascular system and the brain by merging capillary endothelial and parenchymal basement membranes (Figure 1A). The blood-brain barrier has particularly restrictive permeability and strictly controls the exchange and transport of molecules between the two tissues (Engelhardt et al., 2017). Integrity of the embryonic and neonatal blood-brain barrier is largely regulated by laminin $\alpha 4$ in the endothelial basement membrane, and genetic deletion of laminin $\alpha 4$ leads to hemorrhage (Thyboll et al., 2002). Cellular sources of laminin for regulating the blood-brain barrier vary across time. Barrier integrity is mainly regulated by pericyte-derived laminin during development, but by astrocytic laminin in adulthood (Yao et al., 2014). Mice defective in pericytic laminin occasionally manifest hydrocephalus and blood-brain barrier breakdown accompanied by reductions in pericytes, AQP4, and tight junction proteins (Gautam et al., 2016). In adulthood, pathological conditions such as stroke and Alzheimer's disease can cause disruption of blood-brain barrier integrity. Basement membrane proteins are reduced in stroke whereas in Alzheimer's disease, basement membrane thickening is accompanied by increased collagen IV deposition and amyloid- β accumulation (Thomsen et al., 2017).

The basement membrane separates tissues through adhesions mediated by hemidesmosomes at the epithelial-mesenchymal interface. Laminin, a key component of hemidesmosomes, contributes to cell-matrix adhesion by interacting with cell-surface integrins and anchoring fibrils predominantly comprised of collagen VII (Hohenester and Yurchenco, 2013). The formation of a stable adhesion complex between the two tissue layers protects tissues from destabilizing shear forces. The epidermal basement membrane and associated molecules collectively build a protective skin barrier (Figure 1E). For example, collagen VII anchoring fibrils connect the epidermal basement membrane to the dermis (Rousselle et al., 1997). Collagen VII originates within the basement membrane where it binds to laminin, projecting into the papillary dermis where anchoring plaques interweave with collagen I and III fibrils (Breitkreutz et al., 2013). Collagen VII mutations result in recessive dystrophic epidermolysis bullosa characterized by blistering and infection owing to a perturbed basement membrane barrier and impaired wound healing (Guerra et al., 2017). Sadly, the

majority of those affected by the severe generalized subtype also develop lethal cutaneous squamous cell carcinoma (Fine et al., 2014).

Basement membranes serve as an important anatomical landmark for the clinical diagnostic classification of tumors. Conditions associated with more favorable prognoses, i.e., dysplasia and carcinoma in situ, represent confinement of the primary neoplasm by an intact basement membrane. Once neoplastic cells breach the basement membrane, however, they are considered to be invasive and have the capacity to metastasize (Moasser, 2013). Therefore, basement membranes have important barrier functions in both development and disease.

Cell Adhesion and Migration

Basement membranes provide an adhesive substrate for cells, and they are linked functionally to the actin cytoskeleton via integrins or other ECM receptors to mediate cell attachment and migration, as well as modulating intracellular signaling pathways. Adhesion to basement membranes via cell surface receptors allows cells to mechano-sense local stiffness, stiffness gradients, and other physical cues, which ultimately affect cellular behavior (Hynes, 1992). During *Drosophila* development, the receptor-ligand interplay between integrins and laminins in the basement membrane regulates follicle cell migration. Whereas integrin levels in follicle cells remain relatively stable, laminin expression in the basement membrane increases over time. The onset and speed of follicle cell migration are determined by this balance between integrin and laminin levels. Laminin-mutant eggs display altered cell migration and disrupted tissue shaping of developing follicles (Díaz de la Loza et al., 2017). Similarly, peripheral nerve establishment in mice requires laminin $\alpha 5$ -dependent migration of neural crest cells, which differentiate into the peripheral nervous system and glial cells as they complete migration (Coles et al., 2006).

An *in vitro* model of cell migration demonstrates the profound effects of ECM dimensionality (2D vs. 3D) on cellular behavior (Hakkinen et al., 2011). Human foreskin fibroblasts in a 3D basement membrane extract (Matrigel) lose directionality and fail to migrate, yet the same substrate in a 2D configuration analogous to a basement membrane sheet allows highly efficient migration. These changes in cell migration patterns can be attributed to differences in ECM dimensionality. Even though useful for cell culture of epithelial cells, immersion of cells in a 3D basement membrane extract does not accurately simulate the basement membrane *in vivo*. A better representation of an *in vivo* environment is the 2D basement membrane extract model, which allows efficient cell migration. Indeed, cells *in vivo* migrate efficiently adjacent to the basement membrane. In the mouse submandibular gland, outer bud epithelial cells adjacent to the basement membrane show the highest rates of motility (Daley et al., 2017; Hsu et al., 2013). Motility of the outer bud cells is myosin II- and integrin $\alpha 6 \beta 1$ -dependent, which suggests cell-ECM interaction. These findings highlight the importance of interactions between basement membranes, cell surface receptors, and cellular processes in regulating cell migratory behavior.

Polarity

During early morphogenesis, the basement membrane coordinates epithelial tissue organization by modulating apical polarity. Epithelial polarity is established through

organizing polarity proteins and lipids at the plasma membrane as well as utilizing adhesion molecules as positional cues in interactions with other epithelial cells and the adjacent basement membrane (Tanos and Rodriguez-Boulan, 2008). Loss of epithelial polarity is observed in pathological conditions such as cancer, and the extent of loss often correlates with tumor aggressiveness. Evidence exists for a potential role of myoepithelial cell-derived laminin α chains in regulation of neoplastic mammary gland epithelial polarity (Slade et al., 1999).

Laminin is a key molecule for establishing apical polarity during tooth development (Fukumoto et al., 2006). Laminin $\alpha 5$ is a subunit of the major laminins in the tooth germ basement membrane, LM-511 and LM-521. Laminin $\alpha 5$ -null mice display altered localization patterns of integrin $\alpha 6\beta 4$ (the laminin $\alpha 5$ receptor) and hypoplastic tooth germs with reduced proliferation of the dental epithelium and loss of basal cell polarity. Importantly, the enamel knot (the signaling center for tooth morphogenesis) is defective in these mutant mice, with reduced sonic hedgehog (SHH) and fibroblast growth factor 4 (FGF4) (Fukumoto et al., 2006). Disruption in polarity formation is also evident in mammary epithelial cells when basement membrane stability is perturbed by loss of collagen IV or cell-basement membrane adhesions (Plachot et al., 2009).

Polarity formation is mediated through bidirectional interactions between the basement membrane and epithelial cells. Basal epithelial cells interact reciprocally with the basement membrane, providing positional cues for establishing spatially-restricted organization of the basement membrane (Gervais et al., 2016). The basal epithelial cells synthesize basement membrane proteins and organize their basal deposition, which requires expression of the polarity protein, PAR-1b. In the embryonic mouse submandibular salivary gland, establishment of basement membrane organization relies on basal expression of PAR-1b in the epithelium (Daley et al., 2012). Through reciprocal interactions with the epithelium, the basement membrane contributes to the establishment of apical polarity, cellular organization, and coherent tissue architecture.

Tissue Shaping

The basement membrane mediates tissue remodeling through molecular and mechanical processes. Unlike localized biochemical intercellular signaling, mechanical stress can exert global tissue-shaping forces due to the transmission of tension through interconnected cells (Legoff et al., 2013). Involvement of the basement membrane in tissue shaping is best exemplified in *Drosophila* wing and egg chamber development. Collagen IV knockdown attenuates Dpp signaling (the *Drosophila* homolog of BMP) and reduces *Drosophila* wing size (Ma et al., 2017). During egg chamber development, the initially spherical egg chamber elongates in response to constrictive forces applied by the surrounding basement membrane. This constricting collagen IV, along with laminin and perlecan, is organized in a robust circumferential fibril-like orientation (Haigo and Bilder, 2011; Isabella and Horne-Badovinac, 2016). Secreted in site-specific fashion by Rab10 into the pericellular space between egg follicle cells, this fibril-like “molecular corset” of basement membrane proteins has been thought to arise from the collective rotation of follicle cells in a direction that coincides with the orientation of deposited collagen IV protein (Haigo and Bilder, 2011;

Isabella and Horne-Badovinac, 2016). However, more recent findings suggest the involvement of an additional tissue-shaping mechanism independent of collective tissue rotation. Mutation of the atypical cadherin *Fat2* results in egg chambers that fail to rotate; nonetheless, mutant eggs still display aligned collagen IV and proper egg chamber elongation (Aurich and Dahmann, 2016).

Though these findings demonstrate the role of basement membranes in tissue shaping, some important questions remain to be answered: what is the biological significance of collective epithelial migration; what establishes and regulates the fibril-like circumferential collagen IV alignment; how does fibril-like collagen IV biophysically compare to collagen I fibrils; and how do these findings in *Drosophila* translate to mammalian systems?

Signaling

Although many developmental mechanisms are known to be regulated by molecular signals, a combination of mechanical and regulatory gene processes can often provide a more complete mechanistic blueprint. For instance, pattern formation of avian feather follicles is initiated by mechanical compression of the epidermis by the contracting dermis, followed by β -catenin translocation to the nucleus in the compressed epithelial cells. New follicles emerge as the primordium basement membrane buckles increasingly (Shyer et al., 2017). Downstream genes associated with follicle formation are activated upon creation of cell aggregates by such dermal contraction. Since tissue morphogenesis is influenced by the level of tension in cells and the basement membrane (Moore et al., 2005), basement membrane buckling itself may also be involved in this mechanical crosstalk that regulates pattern formation of skin follicles.

During development and throughout animal life, basement membranes can function as signaling platforms by sequestering growth factors and other ligands. Perlecan, agrin, and collagen XVIII bind to many growth factors via heparan sulfate glycosaminoglycan chains. By signaling through cell surface receptors, growth factors such as FGFs, bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), and transforming growth factor- β (TGF- β) regulate stem cell maintenance, cell migration, proliferation, and survival (Jayadev and Sherwood, 2017). Further, stem cell maintenance can be achieved directly by laminin; a combination of laminin and E-cadherin is capable of maintaining clonal survival and self-renewal of human embryonic stem cells (Rodin et al., 2014).

In addition to growth factors, a large number of ECM-modifying enzymes that mediate proteolysis, sulfation, and glycosylation act at basement membranes to modulate signaling (Yoshizaki and Yamada, 2013). Protease-mediated degradation of basement membranes can activate signaling pathways, not only by releasing bound growth factors, but also by releasing or exposing cryptic fragments of basement membrane proteins with signaling functions. Mouse submandibular salivary gland branching morphogenesis is enhanced by membrane-type 2 matrix metalloprotease (MT2-MMP) which releases bioactive collagen IV noncollagenous 1 (NC1) domains (Rebustini et al., 2009). MMP-9 also cleaves collagen IV, releasing a collagen IV fragment that regulates angiogenesis (Hamano et al., 2003). MMP-2

cleaves LM-111 (laminin-1), exposing a laminin fragment that mediates the epithelial-to-mesenchymal transition (EMT) in embryonic stem cells (Horejs et al., 2014).

Moreover, intact laminin and collagen IV can directly activate signaling pathways. Collagen IV modulates avian lung development through regulation of lung epithelial differentiation, myofibroblast proliferation, differentiation, and migration (Loscertales et al., 2016). By interacting with dystroglycan and integrin family receptors, laminin regulates cell survival, migration, differentiation, and proliferation (Bonnans et al., 2014). Laminin-integrin interactions create dynamic cell-ECM links that involve signaling pathway induction and intracellular cytoskeleton organization (Berrier and Yamada, 2007; DeSimone and Mecham, 2013; Hynes, 1999; Kim et al., 2011; Yurchenco, 2011). The signaling activated by laminin-cell membrane receptor binding can control gene transcription and chromatin remodeling of gene promoters (Domogatskaya et al., 2012). In mammary epithelia, functional differentiation leading to milk production is determined by growth hormones and interaction with neighboring cells as well as the basement membrane. Induction of β -casein expression in single cells depends on the types of substrate in which they are embedded (Streuli et al., 1991). Single cells in a collagen I substrate are unable to express β -casein unless they are permitted cell-cell contact. In contrast, single cells in a laminin-rich basement membrane substrate are capable of expressing β -casein. The binding of LM-111 to dystroglycan leads to growth hormone-induced activation of STAT5 and increases in β -casein and insulin growth factor-1 (IGF-1) expression (Leonoudakis et al., 2010). These findings show that the basement membrane-cell surface receptor interaction modulates growth hormone induction and functional differentiation of mammary epithelia.

Basement membrane receptors are spatially and temporally regulated throughout development. For example, isoforms of syndecan, a non-integrin ECM receptor, switch their binding specificity to growth factors. Through its heparan- and chondroitin-sulfate glycosaminoglycan side chains, syndecan binds to a variety of growth factors that include FGF, VEGF, epidermal growth factor, hepatocyte growth factor, and platelet-derived growth factor (PDGF), (Carey, 1997). In the embryonic mouse neuroepithelium, syndecan-1 switches its binding ligand from bFGF to aFGF in a stage-dependent manner (Nurcombe et al., 1993).

Basement membrane-mediated signaling can modulate tissue morphogenesis by sensitization of cells to growth factors. During *Drosophila* renal tubule development, targeted deposition of the basement membrane that ensheaths renal tubules is achieved by hemocytes (Bunt et al., 2010). Deposited collagen IV enhances sensitivity of the tubule cells to localized Dpp guidance signals, thereby guiding directional morphogenesis of renal tubules. Collagen IV mediates activation of this Dpp signaling pathway in a subset of tubule cells, which enables stereotypic positioning and outgrowth of *Drosophila* renal tubules (Bunt et al., 2010). More recently, migrating macrophages have been identified as major contributors to de novo basement membrane formation in the *Drosophila* embryo (Matsubayashi et al., 2017). The basement membrane of the *Drosophila* embryo exhibits a hierarchical pattern of deposition of laminin, followed by collagen IV, and finally perlecan. Absence of laminin severely impairs subsequent collagen IV and perlecan incorporation

(Matsubayashi et al., 2017), which suggests that environmental cues from initial laminin deposition are likely necessary for matrix formation.

The basement membrane also contributes to neuronal extensions in *Drosophila* by enhancing the response of extending axons to environmental signals that guide their growth (Isabella and Horne-Badovinac, 2015). For example, perturbation of laminin results in axon guidance defects (Garcia-Alonso et al., 1996). Syndecan, as a coreceptor for Slit (Johnson et al., 2004), also provides guidance cues for developing axons. Slit is an extracellular protein that serves as a repulsive signal for axons that express the Robo receptor (Brose et al., 1999). Syndecan binding to Slit stabilizes the Slit-Robo interaction (Hussain et al., 2006). Taken together, basement membranes have diverse signaling functions through interactions with cell receptors, release of cryptic fragments upon proteolytic breakdown, and mechanical processes combined with molecular signaling.

Composition

Present in nearly all human tissues, basement membranes are spatially and temporally customized, with associated proteins that display time- and tissue-specific expression patterns. Databases of ECM molecules are provided by the Matrixome Project (Manabe et al., 2008), the Matrisome Project (Hynes and Naba, 2012), and the Human Protein Atlas (Uhlen et al., 2015). The Matrixome Project offers a high-resolution atlas that focuses on spatial and temporal localization of mouse basement membrane proteins. Based on immunohistochemical analyses of proteins following large-scale *in silico* and *in vitro* screening, this project has compiled a comprehensive atlas of more than 40 basement membrane proteins at <http://www.matrixome.com/bm> (Manabe et al., 2008). The Matrisome Project lists databases that contain the ECM compositions of 14 types of tissue and tumor at <http://matrisomeproject.mit.edu> (Hynes and Naba, 2012; Naba et al., 2016). The Human Protein Atlas provides a map of the human tissue proteome based on transcriptomics combined with immunohistochemistry (Uhlen et al., 2015).

Basement membranes emerged in the evolution of animal multicellularity. Basement membrane proteins are highly conserved among mammals (Ozbek et al., 2010). Particularly ancient molecules are the core basement membrane proteins collagen IV, laminin, nidogen, and perlecan (Yoshizaki and Yamada, 2013). These ECM proteins are commonly comprised of repeated domains and evolved by exon shuffling (Engel, 1996; Pathy, 1999). The small number of core basement membrane molecules is disproportionate to the diversity of their functions. This complexity of functional diversity stems from the addition of other proteins, post-translational modifications, protein-protein interactions, RNA splicing variants, alternative promoters, and spatiotemporal expression of, or functional changes in, basement membrane components and membrane receptors (Jayadev and Sherwood, 2017; Yoshizaki and Yamada, 2013). The combination of these mechanisms generates biochemically and biophysically unique basement membrane structures. This allows specialized biological functions tailored to individual tissues and organs.

Collagen IV

Collagen IV builds a network of triple-helical molecules, which most commonly consists of one $\alpha 2$ and two $\alpha 1$ subunits (Yurchenco, 2011). This network binds integrins, provides surrounding tissues with tensile strength, and tethers laminins, proteoglycans, and growth factors (Fidler et al., 2017). Collagen IV and laminin generate two independent but interconnected polymeric networks that serve as the foundation for basement membranes (Figure 2C). The collagen IV network is assembled in response to an extracellular Cl^- ion signal, which triggers a conformational switch in NC1 domains (Cummings et al., 2016). The network assembly process of collagen IV trimers involves three modes of interactions: NC1 dimerization, N-terminal (7S) tetramerization, and lateral associations (Figure 2A) (Timpl et al., 1981; Yurchenco and Ruben, 1987). Found primarily in basement membranes, collagen IV has unique characteristics that distinguish it from other types of collagen. Due to the absence of a glycine at every third residue, collagen IV is unable to form a tight collagen helical structure (Abreu-Velez and Howard, 2012). Furthermore, its NC1 domain remains attached at the C-terminus. This restricts NC1 domain interactions, permitting only head-to-head fiber connections with the flat NC1 surfaces facing each other. As a result, collagen IV networks are structurally flatter and more pliable (Abreu-Velez and Howard, 2012). Mutations in collagen IV $\alpha 3$, $\alpha 4$, and $\alpha 5$ give rise to the kidney disease Alport's syndrome and, in some cases, hemorrhagic stroke (Hudson et al., 2003).

Laminin

Laminins are a family of large heterotrimeric multidomain proteins that consist of three chains, α , β , and γ (Aumailley et al., 2005; Miner and Yurchenco, 2004). At least 16 different isoforms are present in vertebrates (Yurchenco, 2011). The first ECM proteins identified in the mammalian preimplantation embryo are the laminins subunits $\alpha 1$, $\alpha 5$, $\beta 1$, and $\gamma 1$ (Miner et al., 2004). While laminin $\beta 1$ and $\gamma 1$ subunits are nearly ubiquitous and shared by many laminin isoforms, laminin α subunits have more specific spatiotemporal distribution patterns (Pickering et al., 2017). Laminins generate honeycomb-like networks connected in a spot-welding-like manner by adhesive aggregates containing perlecan (Behrens et al., 2012).

Laminins assume a cross or Y shape. The short arms are comprised of α , β , or γ chains, with LN domains located at the end of each arm. LN domains provide a site for laminin polymerization (Figure 2B). LG domains at the end of the long arm (coiled-coil) bind to a cell surface through sulfated glycolipids, integrins, and α -dystroglycan (Yurchenco, 2011). The LG domain-cell surface receptor binding promotes laminin polymerization and therefore enhances network assembly. The LG1-3 cluster provides the principal binding sites for a variety of integrins such as $\alpha 6\beta 1$, $\alpha 6\beta 4$, $\alpha 7\beta 1$, and $\alpha 3\beta 1$ (Nishiuchi et al., 2006a). Laminin-integrin interactions create dynamic cell-ECM links that involve signaling pathway induction and intracellular cytoskeleton organization (Berrier and Yamada, 2007; DeSimone and Mecham, 2013; Hynes, 1999; Kim et al., 2011; Yurchenco, 2011).

Laminins have various cell type-specific expression patterns, and laminin mutations can cause embryonic lethality or severe diseases affecting multiple organs (Domogatskaya et al., 2012). LM-211 (laminin-2) is prominent in pancreas, muscle, and the nervous system,

whereas LM-311 (laminin-6) and -321 (laminin-7) are found in lung and skin (Mecham, 2011). LM-332 (laminin-5) is the most abundant laminin expressed by keratinocytes (Botta et al., 2012). LM-332 binds tightly to the noncollagenous domain of collagen VII of anchoring fibrils (Rousselle et al., 1997) and the laminin-specific integrin $\alpha 6\beta 4$ (Nishiuchi et al., 2006b). Integrin $\alpha 6\beta 4$ binds to intracellular plectin, another important component of hemidesmosomes (Litjens et al., 2006). Disruption of this cell-matrix adhesion complex comprised of laminin, integrin, and anchoring fibrils causes epidermolysis bullosa (Pulkkinen and Uitto, 1999). LM-221 (laminin-4), -421 (laminin-9), and -521 (laminin-11) are found in the neuromuscular junction, where lack of laminin $\alpha 4$ leads to failure of innervation due to mismatched nerve-muscle connections of the active zones at the axon terminus and the junctional folds of the muscle endplate (Patton et al., 2001). LM-511 (laminin-10) is widely expressed in skin, intestine, lung, kidney, and salivary gland (Mecham, 2011). Laminin $\alpha 5$ regulates transformation of the neural tube into the emerging central nervous system during early embryonic mouse neurulation (Miner et al., 1998).

Nidogen

Nidogens are monomeric glycoproteins that contribute to a linkage of polymeric networks with stable affinity to the laminin and collagen IV (Figure 2C) (Fox et al., 1991; Mayer et al., 1993; Yurchenco, 2011). Expressed mainly by mesenchymal cells, nidogen 1 and nidogen 2 are ubiquitous basement membrane proteins (Nischt et al., 2007). Both nidogen 1 and nidogen 2 promote basement membrane stability by contributing, at least in part, to the connection of laminin and collagen IV networks (Has and Nyström, 2015). Nidogens consist of three globular domains termed G1-G3 (4-5 nm in diameter). The domains are interconnected by a flexible segment between G1 and G2 and a stiff rod between G2 and G3. G2 (collagen and proteoglycan-binding domain) and G3 (laminin-binding domain) are separated by 15 nm, which permits various orientations and interactions with other basement membrane proteins (Fox et al., 1991).

Nidogen-deficient mice generally manifest mild phenotypes in skin without effects on formation of the basement membrane. In contrast, a loss of endothelial basement membrane integrity results from substantial reductions in collagen IV, laminin-411 (laminin-8), and perlecan (Mokkapatil et al., 2008). Mice lacking both nidogen-1 and -2 can have cardiac and pulmonary abnormalities associated with basement membrane assembly defects (Bader et al., 2005) and in some cases, altered FGF distribution, syndactyly (digit fusion), and failure to form the limb bud ectodermal basement membrane (Bose et al., 2006). Strikingly, a severe phenotype results from specific ablation of the nidogen-binding site in laminin $\gamma 1$ (Willem et al., 2002). These mice exhibit renal agenesis, impaired lung development, and neonatal lethality, suggesting the importance of laminin-nidogen interaction in development and the potential role of the nidogen-binding site of laminin $\gamma 1$ in other developmental mechanisms. Laminin $\gamma 1$ -nidogen interaction is also known to regulate pial development (Halfter et al., 2002). In addition to the nidogens, other binding molecules such as perlecan likely have compensatory and redundant functions that are independent of each other, since the basement membrane has many essential life functions.

Heparan Sulfate Proteoglycans

Heparan sulfate proteoglycans are glycoproteins with one or more heparan sulfate chains, which are a type of glycosaminoglycan (GAG) chain (Domogatskaya et al., 2012). The heparan sulfate proteoglycans present in the basement membrane are perlecan, agrin, and collagen XVIII. These glycosaminoglycans define basement membrane structure in collaboration with other matrix proteins. Due to the hygroscopic properties of glycosaminoglycans, perlecan and agrin increase the volume of matrix (Domogatskaya et al., 2012). Collagen XVIII is a hybrid collagen-proteoglycan expressed at the initiation of lung and kidney organogenesis (Patel et al., 2017). Inhibition of collagen XVIII disrupts lung and kidney branching morphogenesis (Karihaloo et al., 2001; Lin et al., 2001).

Heparan sulfate binds to many growth factors including FGF with high affinity. Association and dissociation of heparan sulfate-ligand interactions can create a gradient of FGF ligand through mass action involving adjacent binding sites. In addition, heparan sulfate can approximate two adjacent proteins, facilitating growth factor-receptor tyrosine kinase interaction, such as for FGF and FGFR (Sarrazin et al., 2011). FGF10-FGFR2b signaling is essential for early embryonic development of multiple organs, including the lung, trachea (Min et al., 1998), mammary gland (Mailleux et al., 2002), lacrimal gland (Entesarian et al., 2005), and salivary gland (De Moerloose et al., 2000; Ohuchi et al., 2000). Heparan sulfate alters the level of FGF10-FGFR2b affinity: when present in a ternary complex with heparan sulfate, the affinity between the receptor and the ligand increases (Kan et al., 1999). Proteolysis by heparanase (an endoglucuronidase that cleaves heparan sulfate) releases the growth factor, which in turn promotes neural differentiation of murine embryonic stem cells (Xiong et al., 2017) and enhances branching morphogenesis of the mouse salivary gland (Patel et al., 2007). Notably, heparanase promotes not only development but also tumor progression in the mammary gland (Boyango et al., 2017). This illustrates an example of the same mechanism mediating both development and disease.

Perlecan—Perlecan is a secreted heparan sulfate proteoglycan that is a potential linker of laminin and collagen IV networks (Figure 2C). Perlecan is a large (> 200 nm), evolutionarily old (> 550 million years) ECM protein (Farach-Carson et al., 2014). Both epidermal keratinocytes and dermal fibroblasts express perlecan (Sher et al., 2006). Perlecan binds multiple growth factors and basement membrane components including laminin and collagen IV (Battaglia et al., 1992). By sequestering growth factors such as FGF7, perlecan promotes keratinocyte survival and differentiation (Sher et al., 2006). Furthermore, perlecan interacts with integrin $\alpha 2\beta 1$, α -dystroglycan, and fibrillin-1; fibrillin-1 generates microfibrils that anchor the epidermal basement membrane to the papillary matrix (Herzog et al., 2004; Woodall et al., 2008). Perlecan and agrin establish collateral associations between basement membrane proteins and cell surface receptors by linking nidogen and laminin to integrins, dystroglycan, and sulfated glycolipids. The chain of bound proteins involving dystroglycan is termed a dystrophin-glycoprotein complex that extends from basement membrane proteins to F-actin through dystroglycan and dystrophin/utrophin (Yurchenco, 2011).

Perlecan is indispensable for formation of the epidermal basement membrane (Costell et al., 1999). Perlecan is especially important in corneal epithelial development (Inomata et al., 2012) and maintenance of basement membrane integrity in regions with high mechanical stress, including the contracting myocardium and expanding brain vesicles (Costell et al., 1999). Moreover, perlecan has a distinct role in tissue development independent of other core basement membrane proteins. Though the basement membrane is absent in cartilage, perlecan is expressed in cartilage and helps to mediate cartilage development (Yoshizaki and Yamada, 2013).

FRAS/FREM

Located in the sublamina densa, FRAS1, FREM1, and FREM2 form a ternary complex known as the Fraser complex (Petrou et al., 2008). This protein complex controls stabilization of cell-matrix adhesions during embryonic development. Deficiency in FRAS1, FREM1, or FREM2 is the etiological origin of Fraser syndrome, which manifests as hidden eyes (cryptophthalmos), syndactyly, embryonic skin blistering, and renal agenesis or dysplasia with water transport deficits. Loss of *Fras1* in mice leads to arrest of ureteric bud growth owing to severe deficiency of glial cell line-derived neurotrophic factor (GDNF)—the inducer of the budding of ureteric buds from the Wolffian duct (Pitera et al., 2008).

The importance of this protein complex in embryonic development is linked to the spatially and temporally restricted expression of the basement membrane protein nephronectin, which is a ligand for integrin $\alpha 8 \beta 1$ (Sato et al., 2009). The Fraser complex anchors nephronectin to the ureteric bud basement membrane and therefore stabilizes its binding to integrin $\alpha 8 \beta 1$ (Kiyozumi et al., 2012). Nephronectin-null mice frequently display renal agenesis or hypoplasia (Linton et al., 2007) whereas $\alpha 8$ -integrin mutations in humans can cause renal agenesis associated with compromised epithelial-mesenchymal interaction (Humbert et al., 2014). These studies reveal bound basement membrane and transmembrane receptor proteins that act in concert to direct spatiotemporal orchestration of mammalian organogenesis.

Spatial and Temporal Variations in Basement Membrane Thickness and Composition

Conventional transmission electron microscopy measurements made with desiccated tissues estimate basement membrane thickness to be less than 100 nm (Bluemink et al., 1976; Cutler, 1977; Lehtonen, 1975). These measurements are most likely gross underestimations. More realistic measurements by atomic force microscopy on hydrated chick, mouse, and human basement membranes identify their thickness to be at least twice as thick (Jayadev and Sherwood, 2017). The basement membrane requires sufficient thickness to allow network formation by laminin molecules (80 nm in length) and collagen IV molecules (400 nm in length). Variations in basement membrane thickness most likely result from differences in tissue hydration levels and inherent tissue and species differences (Candiello et al., 2010; Halfter et al., 2015).

Basement membrane density and thickness vary across time and space. Fibril-like aggregation of collagen IV in the embryonic mouse salivary gland becomes increasingly denser and thicker over time [see (Harunaga et al., 2014)]. Even though electron microscopy measurements on desiccated tissues likely underestimate the thickness of basement membranes, findings from classical studies consistently demonstrate region-specific variations. In developing lung (Bluemink et al., 1976), kidney (Lehtonen, 1975), mammary gland (Paine and Lewis, 2017), and submandibular salivary gland (Bernfield and Banerjee, 1982; Cutler, 1977), the basement membrane adjacent to regions of active growth and tissue expansion is thinner and discontinuous compared to the relatively static regions away from the bud tip.

Interestingly, the thinner basement membrane at the actively growing regions of the salivary gland exhibits micro-perforations through which epithelial bleb-like protrusions commonly extend (Harunaga et al., 2014). This observation is consistent with classical electron microscopy studies of the embryonic lung (Bluemink et al., 1976), kidney (Lehtonen, 1975), tooth (Burgess and Katchburian, 1982; Slavkin and Bringas, 1976), and salivary gland (Bernfield and Banerjee, 1982). These studies capture direct epithelial-mesenchymal contact through perforations, with cytoplasmic protrusions extending from epithelial or mesenchymal cells. As discussed below, the spatial specificity of this observation of cell interactions associated with active growth supports the idea that direct cellular contact may be a mode of epithelial-mesenchymal interaction.

This regional difference in basement membrane thickness coincides with the level of ECM turnover in the embryonic mouse submandibular gland. The basement membrane at active branching regions is subject to extensive remodeling. Glycosaminoglycans are degraded much more rapidly at the distal end bud region than in the interlobular clefts (Bernfield and Banerjee, 1982). Local alterations in the mechanical compliance of the basement membrane may also account for the regional differences in its morphological appearance. Tissue morphogenesis and patterning are controlled by both molecular signals and alterations in the mechanical compliance of the basement membrane as they respond to cellular forces (Mammoto and Ingber, 2010). Changes in cytoskeletal tension mediated by Rho-signaling through Rho-associated kinase have a profound impact on embryonic lung development. Inhibiting cellular tension results in disruption of the basement membrane, blood vessels, and bud formation, whereas increasing cell tension enhances lung branching and capillary development (Moore et al., 2005). Thus, increased mechanical compliance and distensibility associated with enhanced degradation and the outward expansive force from the growing organ may underlie thinning of the basement membrane at regions of active growth.

Mammary Gland Basement Membrane Composition and Density

Basement membrane composition and density vary within the developing mammary gland. During puberty, the terminal end bud emerges at the tip of the mammary duct (Sternlicht, 2006). The terminal end bud is the regulatory control point for proliferation, branching, angiogenesis, and pubertal branching morphogenesis (Huebner et al., 2014; Paine and Lewis, 2017). The tip of the terminal end bud represents the active site of branching morphogenesis, whereas the neck of the terminal end bud is the site of ductal morphogenesis

and tissue stabilization (Silberstein and Daniel, 1982). Cells in the terminal end bud show spatially limited and reversible reductions in intercellular adhesion and polarity (Ewald et al., 2012), which correlate with a high degree of morphological plasticity in the region. Basement membrane accumulation towards the neck of terminal end buds contributes to sculpting of the elongating ducts by constriction (Jayadev and Sherwood, 2017). The basement membrane at the bulbous tip of the terminal end bud is very thin (104 nm), while it is thicker in the neck region of the bud (1.4 μ m) (Paine and Lewis, 2017). The thin basement membrane at the tip of the terminal end buds consists primarily of laminin, collagen IV, and hyaluronic acid. In contrast, the basement membrane at the neck of the terminal end bud is thicker, forming a more defined meshwork of LM-111 and LM-332, collagen IV, and heparan sulfate proteoglycans (Fata et al., 2004; Keely et al., 1995). The variations in basement membrane composition and thickness of the terminal end bud likely facilitate epithelial-mesenchymal interaction and morphogenesis.

Laminin Expression in Development and Sjogren's Syndrome

Present in skin, kidney, lung, thymus, brain, gastrointestinal tract, and lung, LM-332 (laminin-5) displays uneven spatial and temporal distribution throughout the epithelial basement membrane. LM-332 is enriched within hemidesmosomes, but its expression decreases during hair morphogenesis (Nanba et al., 2000). Time-dependent expression of different types of laminin is also observed in the subendothelial basement membrane. The subendothelial basement membrane provides a substrate for β -cells in pancreatic islets, podocytes in renal glomeruli, and alveolar epithelial cells in the lung (Hallmann et al., 2005). Two main laminin isoforms, LM-411 and LM-511 (laminin-10), are commonly present in the subendothelial basement membrane. When the basement membrane undergoes active remodeling during embryonic angiogenesis, LM-411 is the predominant laminin expressed in the vascular endothelial basement membrane. LM-511 emerges postnatally when the subendothelial basement membrane is stabilized (Hallmann et al., 2005). These time- and space-specific expression patterns of laminin suggest distinct functions for each isoform during development.

Laminin expression in the embryonic mouse submandibular salivary gland varies temporally and spatially. The salivary gland at embryonic day 13, which marks the onset of active branching, shows expression of laminin α 1 and α 5 surrounding the distal end bud and α 1, α 3, and α 5 chains along the duct (Kadoya and Yamashina, 2005). This laminin distribution changes later in embryonic development, when α 2 and α 4 emerge adjacent to the end bud, while α 3 increases around myoepithelial cells that surround acini, the saliva-secreting units.

The basement membrane of labial salivary glands in individuals with Sjogren's syndrome shows structural disorganization and altered expression of collagen IV and laminin (Molina et al., 2006). The epithelial acinar basement membrane of Sjogren's syndrome patients can display reduced laminins (LM-111 and LM-211), accompanied by decreased integrin (α 1 β 1 and α 2 β 1) receptors that bind to laminin (Laine et al., 2008). Basement membrane disorganization may be associated with loss of structural integrity and atrophy of salivary acini, ductal cell hyperplasia, and impaired secretory function. Lack of basement membrane integrity makes the salivary gland more susceptible to lymphocytic invasion in Sjogren's

syndrome patients (Hayashi, 2011; Molina et al., 2006). Thus, basement membrane structure and composition are greatly altered in disease, suggesting that the basement membrane plays an important role beyond development.

Glomerular and Retinal Capillary Basement Membrane Thickness

Two basement membranes (retinal pigment epithelial and choroid) in Bruch's membrane maintain integrity of the retinal pigment epithelium, which separates the retina from the choriocapillaris (Figure 1B) (Strauss, 2005). Retinal pigment epithelium supports photoreceptor health, and disruption of its integrity is often a disease manifestation. Age-dependent thickening of the basement membrane is associated with pathology in the retina, but not in the kidney. In the kidney, thickening of the glomerular basement membrane during aging does not affect hydraulic permeability of the glomerular capillary wall (Neumann et al., 2004). In contrast, age-related thickening of retinal capillary basement membranes is likely linked to senile retinopathies (Nagata et al., 1986). Retinal vascular basement membrane thickening is associated with human microaneurysms during aging—a hallmark of retinal vascular disease. Small microaneurysms show basement membrane thickening and up-regulation of collagen IV, laminin, fibronectin, nidogen, and perlecan. On the other hand, large microaneurysms display loss of basement membrane integrity and increases in MMP-9 and plasminogen activator inhibitor-1 (Lopez-Luppo et al., 2017).

Other conditions linked to ocular basement membrane thickening are diabetes mellitus and drusen accumulation. Diabetic retinopathy is associated with basement membrane thickening, stiffening, and compositional changes (To et al., 2013). With aging, progressive accumulation of drusen comprised of cellular debris can overwhelm removal and result in thickened basement membrane (Salvi et al., 2006). Basal laminar drusen primarily accumulates in the macular area. With progressive accumulation, drusen is associated with the development of age-related macular degeneration.

Ocular basement membranes have sidedness. The inner epithelial face of the human adult ocular basement membrane is two-fold stiffer than the outer stromal side (Halfter et al., 2013). Laminin is enriched on the stiffer inner epithelial-facing side, whereas collagen IV is enriched on the stromal side, with a distinct distribution of the C and N-terminal domains in the basement membrane. This unique sidedness of basement membrane structure may lead to spatial and temporal variations in levels of susceptibility to basement membrane thickening and degradation. Biological implications of basement membrane sidedness in development and aging remain to be identified.

Glomerular Basement Membrane Composition

Along with their adjacent organs, basement membranes undergo dramatic transformation throughout development, with altered composition and structure. For instance, laminin and collagen isoforms switch during progression from embryonic development to adult stages in the human glomerular basement membrane. The basement membrane during kidney development is formed by the stage-specific assembly of a common laminin $\gamma 1$ and different α and β subunits (Skorecki et al., 2015). Components of the fetal glomerular basement membrane include collagen $\alpha 1$ and $\alpha 2(IV)$ and laminin $\alpha 1$ and $\beta 1$, which are gradually

replaced by collagen $\alpha 3$ - $\alpha 5$ (IV) and laminin $\alpha 5$ and $\beta 2$ subunits (Abrahamson et al., 2013; Harvey et al., 1998; Miner et al., 1997). This developmental switch in collagen and laminin isoforms is crucial for kidney development and maturation. Laminin $\alpha 5$ -mutant mice show glomerular basement membrane breakdown and renal agenesis or defective glomerulogenesis because of a failed transition from laminin $\alpha 1$ to $\alpha 5$ (Miner and Li, 2000). A laminin $\gamma 1$ loss-of-function mutation in the murine ureteric bud causes renal agenesis as a result of failure of basement membrane formation and compromised integrin-based and growth factor-based (FGF2, WNT11, and GDNF/RET) signaling pathways (Yang et al., 2011). Laminin $\beta 2$ mutation is the etiological cause of Pierson syndrome, which is characterized by neurological, ocular, and renal deficits (Miner et al., 2006).

Dental Basement Membrane Composition

During tooth morphogenesis, the dental basement membrane undergoes dynamic structural and chemical transformation involving degradation and calcification. Epithelial and mesenchymal cells in the tooth bud differentiate into their respective secretory cells (ameloblasts and odontoblasts) along the basement membrane (He et al., 2010). Many basement membrane proteins show site-specific expression in the embryonic day 16.5 mouse tooth bud. Laminin subunits $\alpha 5$ and $\beta 1$, collagens IV and XVIII, nidogen-1, perlecan, agrin, and other proteins are widely expressed throughout the basement membranes of the tooth bud and oral epithelium (Figure 3A) (Manabe et al., 2008). Laminin $\gamma 1$ and nidogen-2 are expressed specifically around the entire tooth bud (Figure 3B). FRAS1 and FREM1 are localized to the basement membrane subjacent to the inner enamel epithelium (Figure 3C). Other proteins such as netrin-1 show a gradient expression pattern along the inner enamel epithelium; the expression level of netrin-1 is highest adjacent to the primary enamel knot, from which it gradually declines laterally (Figure 3D) (Manabe et al., 2008).

A similar gradient pattern is found in odontoblast differentiation. Odontoblast differentiation follows a spatial gradient that begins adjacent to the enamel knot and proceeds in a direction away from the enamel knot (Bloch-Zupan et al., 2012). Gradients of SHH and BMP are thought to regulate cell proliferation and differentiation (Li et al., 2015; Seppala et al., 2017). By binding to heparan sulfate proteoglycans, netrin-1 may modulate morphogen gradients (Manabe et al., 2008).

As ameloblasts and odontoblasts secrete enamel and dentin matrices, respectively, the basement membrane is degraded and replaced with interdigitations of calcified enamel and dentin (Sahlberg et al., 1992; Thesleff et al., 1981). This interface forms the dentin-enamel junction, which joins two unique matrices that have different biomechanical properties (Chun et al., 2014). Composed of mineralized connective tissue, dentin is similar to bone in its composition and nanostructure. On the other hand, enamel primarily consists of hydroxyapatite and represents the hardest tissue in the body (Gibson et al., 2001). Accordingly, the dentin-enamel junction serves as a crack-arrest barrier for the brittle enamel, preventing the two distinct matrices from dislodging (Imbeni et al., 2005). However, how the dentin-enamel junction, which is devoid of a basement membrane, establishes the effective adhesion needed to withstand enormous occlusal loads is not completely understood. The extent of basement membrane degradation in teeth—whether it is complete

or partial—has been questioned because presence of collagen IV and VII at the dentin-enamel junction has been reported in adult teeth (McGuire et al., 2014a; McGuire et al., 2014b). The dentin-enamel junction becomes a vulnerable site for enamel delamination in irradiated teeth of head and neck cancer patients, where radiation likely affects biochemical and structural integrity at the dentin-enamel junction. Further research is required to identify detailed mechanisms maintaining the integrity of the dentin-enamel junction in health and post-irradiation.

Basement Membranes in Tissues Surrounding Teeth

A tooth is surrounded by supporting dento-gingival tissues that consist of junctional epithelium, basement membranes, and gingival fibers (Newman et al., 2011). Oral gingival and junctional epithelia surrounding the tooth are associated with three distinct basal laminae (Figure 1D; 4A). The oral gingival epithelium basement membrane consists of typical basement membrane components, including collagen IV, nidogen, LM-332 (laminin-5), LM-311 (laminin-6), LM-321 (laminin-7), LM-511, and LM-521 (laminin-11) (Oksonen et al., 2001). Located adjacent to the tooth surface, the junctional epithelium is sandwiched between two unique basement membranes: the internal and external basal laminae. The internal basal lamina mediates attachment to the tooth surface, whereas the external basal lamina attaches to the gingival connective tissue (Figure 4B) (Newman et al., 2011). Compared to the oral gingival epithelium, the junctional epithelium contains relatively few desmosomes and less E-cadherin, with wide intercellular spaces permissive for leukocyte migration (Hatakeyama et al., 2006). The internal and external basal laminae undergo continuous rapid remodeling because the adjacent junctional epithelium displays high turnover as a means of defense against bacterial infection (Dabija-Wolter et al., 2013). Forming an epithelial attachment to the tooth surface through basal laminae, the junctional epithelium serves as the first line of defense against bacterial plaque; its disruption and detachment below the cemento-enamel junction signify initiation of periodontitis (Kinane, 2001; Marks et al., 1994). The composition of the external basal lamina—collagen IV, LM-332, LM-311, and LM511, and nidogen-1—is similar to that of the oral gingival epithelium (Oksonen et al., 2001), whereas the internal basal lamina is primarily comprised of LM-332 and collagen VIII (Larjava et al., 2011). These differences in composition suggest that the two types of basal lamina may derive in part from different cell populations and may have evolved along different pathways to function in their unique local microenvironments.

Basement Membrane Micro-Perforations

Although composed of a structurally dense sheet of interwoven networks, basement membranes in some tissues have micro-perforations. A combination of covalent and noncovalent forces coalesce the interconnected laminin and collagen IV meshwork into a molecular sieve with pores (Kalluri, 2003). Pores or micro-perforations in the basement membrane exist in a wide range of shapes and sizes (5 nm–8 μ m in diameter) (Hironaka et al., 1993; Takeuchi and Gonda, 2004). The size and form appear to be spatially and temporally determined. Proper sizes of basement membrane pores or micro-perforations are

crucial for regulation of permeability and intercellular interactions – and in certain tissues, permissibility for cell migration.

Alterations in basement membrane pore size can be a pathological manifestation. For instance, disruption/enlargement of the extremely tiny (~5-10 nm in diameter) (Hironaka et al., 1993) pores of the glomerular basement membrane is the underlying cause of proteinuria in the kidney disease Alport's syndrome, which results from collagen IV mutations (Barker et al., 1990; Longo et al., 2002).

Basement membrane micro-perforations are normal physiological findings in bronchial airway (0.75-3.85 μm in diameter) (Howat et al., 2001) and in the intestinal villi and lymph nodules of ileal Peyer's patches (~1-8 μm in diameter) (Takeuchi and Gonda, 2004). Basement membrane micro-perforations in these tissues facilitate lymphocyte migration, especially in the small intestine, where the abundance of micro-perforations corresponds to the degree of lymphocytic infiltration.

The transient presence of basement membrane micro-perforations in the embryonic mouse submandibular salivary gland correlates with the time and location of maximal epithelial expansion (Harunaga et al., 2014). Micro-perforations are most prominent at the beginning of the active branching phase, when cell proliferation and repetitive clefting and branching substantially increase the organ surface area (Figure 5). The tip of the end bud has both the largest size and density of micro-perforations. The largest micro-perforations (4 μm in diameter) are still smaller than the size of a cell. With 90% of the micro-perforations being even smaller (<2.5 μm in diameter), they are not permissive to cell transmigration. Both the size and density of micro-perforations dramatically decrease further away from the tip. Micro-perforations eventually disappear towards the equator of the bud, which is a site of basement membrane accumulation (Figure 5). Protease and myosin II-dependent global translocation of the basement membrane occurs rearward toward the duct, in a direction opposite to epithelial outgrowth. The long axis of the oblong micro-perforations is oriented parallel to the presumptive pulling force that drives global basement membrane translocation. Fibril-like basement membrane aggregates have varying thickness and direction, but their general orientation also runs parallel to the long axis of the end bud. Thus, the general orientation of fibril-like basement membranes also coincides with the axis of the basement membrane translocation (Harunaga et al., 2014), which suggests a possible link between pore shape, orientation of fibril-like deposition, and global basement membrane translocation.

Consistent with findings of classical electron microscopy studies on epithelial-mesenchymal inductive interactions (Bluemink et al., 1976; Cutler, 1977; Lehtonen, 1975), cellular protrusions from basal epithelial cells are observed exclusively at the tip of the end bud in the embryonic mouse lung and submandibular gland. The protrusions appear to expand the basement membrane micro-perforations as they protrude as far as 5 μm beyond the basement membrane (Harunaga et al. 2014). Individual micro-perforations undergo local dilation and contraction, a process dependent on actomyosin-mediated rapid physical distortion of subjacent cells and protease activity. Unlike *C. elegans* anchor (uterine) cell invasion, which involves physical widening of a gap by the cell and laminin accumulation at the edge of the

gap (Hagedorn et al., 2013; Matus et al., 2014), the mouse submandibular salivary gland does not exhibit basement membrane displacement or accumulation around the periphery of the micro-perforation. Micro-perforations in the salivary gland basement membrane are not enlarged to a size sufficient to permit cell crossing. Rather, the salivary gland basement membrane as a whole becomes distensible in response to cellular forces; the amount of distensibility and the size of perforations are just sufficient for extension of cellular processes (Harunaga et al., 2014). Similarly, epithelial-mesenchymal cell contact is found during tooth morphogenesis. Differentiating ameloblasts lining the inner enamel epithelium extend cellular processes through the basement membrane, which penetrate into developing uncalcified dentin (Burgess and Katchburian, 1982). Cytoplasmic processes from odontoblasts in the tooth bud mesenchyme subsequently penetrate the basement membrane to contact preameloblasts (Slavkin and Bringas, 1976). A series of reciprocal inductions between the two apposed tissues is essential for sequential differentiation of the epithelial and mesenchymal cells into their respective matrix-secreting cells (Simmer et al., 2010). In addition to growth factors secreted by the oral epithelium (Tucker and Sharpe, 2004), this cellular contact may be another mechanism of cross-tissue interactions. The implications of direct cell-cell contact, the detailed mechanisms of micro-perforation formation in mammalian organs, the function(s) of micro-perforations, and the source of global basement membrane translocation are important research questions to be explored in future studies.

Basement Membrane Transmigration and Invasion

Basement Membrane Transmigration

Basement membranes in many tissues are a permissive substrate for certain migrating cells. In tissues where leukocyte trafficking is prevalent, such as in lymph nodes, the basement membrane has pre-existing gaps at specific locations that facilitate routine cell transmigration (Nourshargh and Alon, 2014). Neutrophils can migrate between the circulation and the subendothelial space in response to injury. Upon sterile thermal hepatic injury, neutrophils migrate from the vasculature into the subendothelial space and then later reverse-migrate back into the circulation (Wang et al., 2017). However, the basement membranes of many other tissues contain pores that are substantially smaller than the diameters of cells in physiological conditions. Consequently, enlargement of basement membrane pores is required for cells to traverse the barrier, by means of expansion, disassembling, stretching, proteolytic breakdown, or finding regions with reduced density and cross-linking (Rowe and Weiss, 2008; Wang et al., 2006). Nonetheless, many cells frequently transmigrate through basement membranes during embryonic development, such as during gastrulation (Nakaya et al., 2008), and disease, as in inflammatory disease (Sorokin, 2010) and metastatic cancer (Steeg, 2003).

Transmigration through mammalian basement membranes is often not solely a simple mechanical process. Rather, it may evoke molecular signaling that alters gene transcription in transmigrating cells. During leukocyte trafficking, leukocytes traverse beyond the endothelium and through the vascular basement membrane (Nourshargh and Alon, 2014). Their vascular wall breaching involves extensive alterations of both the migrating leukocytes and the matrix components through reciprocal signaling. Breaching of the vascular wall and

basement membrane prime the transmigrating leukocytes for clearing pathogens and neoplastic cells with enhanced survival and increased effector functions (Nourshargh et al., 2010). Though the mechanistic role of the basement membrane in the priming process has yet to be elucidated, cell transmigration through the basement membrane is most likely a combined molecular and mechanical process that is tightly regulated during development and leukocyte transmigration, which becomes dysregulated in disease.

Basement Membrane Invasion during Tumor Progression

Normal developmental processes are often hijacked during tumor progression. Reduced epithelial cell polarity, EMT, and attenuation of intercellular and cell-matrix adhesion during tumor progression partially recapitulate developmental processes (Ewald et al., 2012; Tanos and Rodriguez-Boulán, 2008). While tumor progression and normal morphogenetic processes may share some regulatory mechanisms, what clearly differentiates tumor progression from developmental processes is transcriptional dysregulation. Because the basement membrane serves as a barrier against malignant cell dissemination, basement membrane breaching and dysregulation are hallmarks of many malignant tumors (Nguyen-Ngoc et al., 2012). Tumor progression involves alterations of ECM along with transcriptional and post-transcriptional acquisition of invasive cellular machinery by tumor cells (Ozanne et al., 2006).

Invadopodia are membrane-associated F-actin based structures that can help mediate cell invasion through surface expression of proteolytic enzymes that locally degrade ECM (Gimona et al., 2008). Cellular manifestation of invadopodia can be a part of normal morphogenetic processes such as axon guidance (Santiago-Medina et al., 2015) and can also be induced in non-malignant cells by a dense fibrillar collagen matrix (Artym et al., 2015). However, acquisition of invadopodia by tumor cells reflects a transcriptional and signaling switch. Malignant cells often insert invadopodia into the basement membrane for local degradation as they establish adhesion to the underlying stroma (Friedl and Wolf, 2003). Transcriptional and signaling switches confer on tumor cells the ability to extend invadopodia, perforate, and invade through the basement membrane. The invasive cells can destroy the basement membrane as they invade with local protease activity, consistent with a prominent characteristic of tumor histology: a reduction or complete absence of the basement membrane (Tosios et al., 1998). The presence of such basement membrane-invasive cells portends a poorer prognosis (Hanahan and Weinberg, 2000).

This invasive behavior of neoplastic cells may initially be attenuated or blocked by basement membranes. The barrier function of basement membranes derives from its tightly cross-linked matrix and niche formation that prevents carcinoma cell dissemination. Both normal and malignant mammary epithelia initially form cellular protrusions and disseminate in a collagen I substrate (Nguyen-Ngoc et al., 2012). However, a striking difference arises in subsequent behavior of these cells. Malignant mammary epithelium continues to disseminate without organizing structured basement membranes. On the other hand, normal mammary epithelium ceases to disseminate as it progressively organizes basement membranes. Deletion of P-cadherin, an adhesion gene that is downregulated in breast carcinoma cells, induces epithelial cell dissemination into collagen I but not in Matrigel. These findings

demonstrate that the malignant epithelium preferentially disseminates in collagen I and suggest that breaks in basement membranes may induce invasion (Nguyen-Ngoc et al., 2012).

Normal non-malignant epithelial cells depend on pro-survival signaling from laminin that defines their niche (Chiarugi and Giannoni, 2008). Leaving their ECM niche can result in apoptosis due to lack of survival signaling. Thus, remaining in contact with their natural niche is crucial for basal epithelial cell survival. However, tumor cells that undergo malignant transformation can survive outside of their niche by actively altering their transcription pattern and basement membrane composition. Malignantly transformed cells can overexpress the basement membrane protein they depend on or alter their intrinsic integrin signaling to adjust to a foreign ECM (Chiarugi and Giannoni, 2008). For example, a mechanism commonly employed by carcinoma cells is overexpression of LM-332—a mechanism observed in esophageal, colon, and squamous cell carcinomas (Marinkovich, 2007). Survival signals from LM-332 can enable carcinoma cells to leave their natural niche and metastasize. Furthermore, angiogenesis is stimulated by laminin and perlecan, providing essential nutrients and oxygen for survival of disseminated cancer cells.

While invasive tumor cells may have enhanced survival, invasion and proliferation can be mutually incompatible cell states as demonstrated in mice (Gil-Henn et al., 2013) and *C. elegans* (Sherwood and Sternberg, 2003). The *C. elegans* model of basement membrane invasion utilizes a hermaphrodite developmental process in which anchor cells transmigrate through juxtaposed uterine and ventral epidermal basement membranes to initiate uterine-vulval connection (Sherwood and Sternberg, 2003). Transcription factor *nhr-67/tlx*-directed G1 cell-cycle arrest is required for invadopodia formation, pro-invasive gene transcription, and basement membrane invasion (Figure 6) (Matus et al., 2015). G1 cell-cycle arrest promotes the expression of FOS-1A (the vertebrate FOS proto-oncogene) in *C. elegans*. FOS-1A in turn triggers a transcriptional cascade; through transcription factors HLH-2 (E proteins) (Schindler and Sherwood, 2011) and EGL-43 (EVII) (Rimann and Hajnal, 2007), FOS-1A regulates pro-invasive genes, including CDH-3 (protocadherin), HIM-4 (hemicentin), ZMP-1 (MMP) (Sherwood et al., 2005), MIG-6 (papilin), and F-actin (Schindler and Sherwood, 2011). This requirement for cell-cycle arrest is partially echoed in a developmental process underlying mammalian tooth morphogenesis. Throughout incisor placode and bud morphogenesis, a subset of non-proliferative epithelial cells remains in the G1 phase (Ahtiainen et al., 2016). These cells localize to the emerging enamel knot that exhibits restricted expression of SHH, BMP, FGF, and cyclin-dependent kinase inhibitor P21. The neighboring epithelial cells surrounding this non-proliferating emerging enamel knot contribute to the growth of the tooth bud (Ahtiainen et al., 2016).

C. elegans anchor cell transmigration takes place in two stages: first, the generation of initially tiny basement membrane perforations by small invadopodia, and second, subsequent local gap enlargement by proteolysis and physical force from a large cellular protrusion (Figure 6). Deciphering the mechanism of the second stage that clears a path for tissue entry is important because of its similarity to tumor cell transmigration and invasion during cancer metastasis. The first stage involving invadopodia formation is dependent on integrin, which promotes netrin receptor (DCC) localization to the anchor cell membrane in contact with the

basement membrane (Hagedorn et al., 2009 ; Hagedorn et al., 2013). Netrin-DCC signaling directs the second stage via creation of a single large cellular protrusion through the exocyst and SNARE-mediated fusion of lysosomal membranes to fuel local plasma membrane expansion (Naegeli et al., 2017). This outward expansion of the invasive protrusion is anchored and promoted by F-actin and dystroglycan, which form a diffusion barrier at the neck of the protrusion. This transient large anchor cell protrusion and MMP protease activity expand the hole by a combination of local basement membrane displacement and degradation, enabling the cell to transmigrate (Naegeli et al., 2017).

Cell invasion in development and tumors can correlate with EMT (Micalizzi et al., 2010; Thiery et al., 2009). EMT is promoted by the transcription factors SNAIL, SLUG, TWIST, and ZEB1/2 (Hanahan and Weinberg, 2011). EMT in development is well-exemplified by neural crest cell migration. First induced in the ectodermal germ layer during gastrulation, neural crest cells undergo EMT involving SNAIL2, ZEB2, and TWIST after neural tube closure (Simões-Costa and Bronner, 2015). Upon acquisition of migratory behavior and transformation into multipotent progenitors, neural crest cells leave the central nervous system and migrate through the basement membrane along highly stereotypical paths. Along with EMT, degradation of the basement membrane by proteases is crucial for neural crest cell migration (Theveneau and Mayor, 2011). However, transcription factors alone do not specify invasive cellular behavior, since their effects on protease activity and invadopodia formation are indirect (Eckert et al., 2011; Jorda et al., 2005). In addition, EMT and invadopodia are not essential for all instances of basement membrane breaching. During development and metastatic carcinoma, cells can collectively migrate or invade through the basement membrane without undergoing complete EMT (Chui, 2013). Thus, additional mechanisms may as well regulate carcinoma cell invasion.

During tumor progression, dysregulation of proteases such as MMPs facilitate basement membrane degradation and invasion (Wiseman and Werb, 2002). However, clinical trials of MMP inhibitors have been largely unsuccessful. Some of the potential reasons relate to issues with drug specificity, side effects that limited amounts that could be tolerated, study design of clinical trials with respect to the stage of cancer, as well as study design of many initial *in vitro* preclinical studies. The initial *in vitro* studies using cancer cell lines that overexpress certain MMP family members may not accurately reflect *in vivo* dynamics, where the primary source of proteases in carcinoma is apparently non-neoplastic stromal cells (Madsen and Bugge, 2015; Nielsen et al., 2001). The cellular source of proteases indeed matters because the activity of released enzymes significantly differs between cell types (Kessenbrock et al., 2010).

The basement membrane initially physically separates neoplastic epithelial cells from nonmalignant stromal cells. The likelihood that the stromal cells are the major source of proteases in carcinomas raises a fundamental question: how do neoplastic epithelial cells initiate basement membrane breaching? One possibility is activation of stromal cells by inflammatory signals such as interleukins-6 and -8 from neoplastic cells. Another potential mechanism is localized loss of the adhesion receptor dystroglycan. Loss of dystroglycan in basal epiblast cells during chick gastrulation allows epiblast cells undergoing EMT to cross through the basement membrane into the developing embryo (Nakaya et al., 2011).

Additionally, mechanical forces may mediate basement membrane breaching. During post-implantation embryonic mouse development, localized constriction at the distal tip of the developing embryo by the surrounding maternal uterus appears to rupture the basement membrane. Basement membrane rupture in turn permits epiblast cell transmigration and initiation of establishment of the anterior-posterior axis (Hiramatsu et al., 2013). Similarly, tumor cell invasion may involve a combination of molecular signaling, degradation of basement membrane components, global mechanical hydrostatic force from the growing tumor, and local breaching force exerted by an invasive cellular protrusion. The mechanism of this initial basement membrane breaching remains a crucial gap in our understanding of tumor progression.

Perspectives and Future Directions

Advances in high-throughput omics and bioinformatics techniques have enabled the identification of novel ECM genes and proteins at unprecedented speed. However, the relevance of many of these newly discovered genes to development and disease remains to be unraveled. Accordingly, time-course proteomic and functional analyses of basement membrane proteins from embryonic development through adulthood and disease will help identify their roles in both development and disease.

In carcinoma progression, the basement membrane serves as an important barrier that spatially confines malignant epithelial cells prior to invasion. Identification of mechanisms underlying basement membrane invasion will provide valuable insight into cancer progression. One of the important topics that require further investigation is the source of specific ECM-degrading proteases and their contributions in initiation of basement membrane breaching. Also not clear is whether initial protease-induced breaks in the basement membrane are enlarged by tumor cell protrusions. For example, do tumor cells use cellular extensions that expand rapidly due to focal exocytosis of lysosomes to enlarge initially tiny basement membrane holes analogous to the mechanism used by *C. elegans* anchor cells? Another challenge will be the full elucidation of the biophysical, transcriptional, and post-translational changes affecting the basement membrane at different stages of cancer.

Identification of complex developmental and disease mechanisms will require a better understanding of not only molecular signaling but also biomechanical processes. Further investigations are needed to characterize the biophysical properties of the different basement membranes in relation to development and disease. If technically feasible, measurement of local stiffness versus tension within the basement membranes of embryonic tissues will provide valuable insight, which might be achieved by atomic force microscopy (Casuso et al., 2011) or fluorescence-resonance energy transfer measurements of tension sensors (Grashoff et al., 2010). The levels of stiffness or tension may well vary across developmental stages, throughout the body, and in different regions of the basement membrane within the same organ. Variations in tension, stiffness, and patterns of micro-perforation may alter the levels of cell adhesion, the extent of epithelial-mesenchymal interactions, patterns of cell migration, and/or the mode of tissue remodeling and morphogenesis. Live imaging of tissue explants will be valuable for structural and functional characterization of basement

membrane constituents in developing, mature, and pathological or genetically perturbed tissues. Temporally and spatially controlled gene perturbation will be crucial because many developmental and disease mechanisms are precisely controlled at the single-cell level.

The ultimate goal of future research will be to develop effective therapeutic approaches, e.g., to help prevent basement membrane breaching in cancer. Additional future therapeutic approaches could benefit individuals afflicted by conditions in which the basement membrane plays a pivotal role in pathogenesis and disease progression. For example, gene therapy for laminin $\alpha 2$ -deficient congenital muscular dystrophy (Qiao et al., 2005) and genetically modified epidermal stem cell therapy for epidermolysis bullosa (Hirsch et al., 2017; Mavilio et al., 2006) represent potentially promising future directions for the treatment of congenital disorders. Another recent advance in regenerative medicine research is laminin-guided human pluripotent stem cell differentiation into endothelial progenitor cells, e.g., using a fragment of LM-411 (Ohta et al., 2016). LM-411 found predominantly in the vascular endothelial basement membrane seems to instruct cell fate determination and differentiation into endothelial cells. Because some laminin isoforms are cell type-specific, this method may provide a means of guiding differentiation toward specific cell types when combined with chemical differentiation protocols. With its relevance to many developmental and disease processes, the basement membrane provides an exciting and vitally important area for further research.

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Figure 1. Schematics of basement membranes (BMs) in various tissues.

(A) Blood-brain barrier: endothelial and parenchymal BMs surround the brain capillary. (B) Eye: retinal pigment epithelium BM, choroid BM, and an intermediate collagenous zone comprise the Bruch's membrane. (C) Lung: endothelial and alveolar BMs merge to provide a site for gas exchange. (D) Tissues surrounding teeth: junctional epithelium adheres to the enamel via the internal basal lamina and to the mesenchyme via the external basal lamina. The oral gingival epithelium BM is adjacent to the oral epithelium. (E) Skin: cutaneous BM underlies basal epithelial cells. (F) Kidney: during development, endothelial and podocyte-derived epithelial BMs merge to form the glomerular BM. Figures are not drawn to scale.

Figure 2. Basic structure of the BM.

(A) Collagen IV network. (B) Laminin network. (C) Schematic representation of the BM with its major components.

Figure 3. The BM of embryonic mouse tooth bud.

(A) The basement membrane underlies the oral epithelium and surrounds inner and outer enamel epithelia of the enamel organ. The dental papilla lies beneath the inner enamel epithelium and gives rise to the dentin and pulp. (B) Laminin γ 1 and nidogen-2 are expressed around the tooth bud. (C) FRAS1 and FREM1 show a spatially specific expression pattern along the inner enamel epithelium. (D) A gradient expression pattern of netrin-1 is found subjacent to the primary enamel knot.

Figure 4. Basic structure of dental supporting basal laminae.
 (A) Schematic illustration of basal laminae around a tooth. (B) Desmosomes mediate intercellular adhesions. Hemidesmosomes mediate attachment of internal and external basal laminae to enamel and mesenchyme, respectively.

Figure 5. BM micro-perforations in embryonic mouse submandibular salivary gland. Micro-perforations are prominent at the tip of epithelial buds. These perforations gradually disappear towards the equator (dotted line). As the growing buds expand rapidly, the number of perforations peaks at embryonic day (E) 13.5. Basement membrane translocation away from the bud tip is accompanied by accumulation of fibril-like basement membrane proteins at the forming secondary duct.

Figure 6. Factors involved in *C. elegans* BM transmigration.

The first stage is initiated by cell cycle arrest and activation of a transcriptional cascade that lead to invadopodia formation. The second stage involves netrin-DCC signaling that directs growth of a single large cellular protrusion, allowing the anchor cell to breach the juxtaposed uterine and vulval basement membranes.