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Heterotypic Control of Basement Membrane Dynamics During Branching Morphogenesis

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Abstract

Many mammalian organs undergo branching morphogenesis to create highly arborized structures with maximized surface area for specialized organ function. Cooperative cell-cell and cell-matrix adhesions that sculpt the emerging tissue architecture are guided by dynamic basement membranes. Properties of the basement membrane are reciprocally controlled by the interacting epithelial and mesenchymal cell populations. Here we discuss how basement membrane remodeling is required for branching morphogenesis to regulate cell-matrix and cell-cell adhesions that are required for cell patterning during morphogenesis and how basement membrane impacts morphogenesis by stimulation of cell patterning, force generation, and mechanotransduction. We suggest that in addition to creating mature epithelial architecture, remodeling of the epithelial basement membrane during branching morphogenesis is also essential to promote maturation of the stromal mesenchyme to create mature organ structure. Recapitulation of developmental cell-matrix and cell-cell interactions are of critical importance in tissue engineering and regeneration strategies that seek to restore organ function.

Keywords

branching morphogenesis; cell-matrix adhesions; cell-cell adhesions; heterotypic; mechanotransduction; tissue engineering

Introduction

Branching morphogenesis creates organs having a large internal surface area for specialized organ function within a compact space. Many mammalian organs undergo branching morphogenesis, including the lungs, kidneys, pancreas, prostate, submandibular salivary glands (salivary glands), and mammary glands. During branching morphogenesis, the basement membrane orchestrates many epithelial cell behaviors, including cell proliferation,

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cell polarization, and migration that require dynamic cell-matrix adhesions with the basement membrane (Costantini and Kopan, 2010; Daley and Yamada, 2013; Gray et al., 2010; Hsu and Yamada, 2010; Kim and Nelson, 2012; Sequeira et al., 2010; Warburton et al., 2010; Yurchenco, 2011). Basement membranes are dense interconnected protein and glycoprotein networks associated with the basal epithelial surfaces that form boundaries between the epithelial and mesenchymal tissue compartments and have structural, mechanical, and chemical signaling properties that influence their associated epithelia. Integrins are the principal cell surface basement membrane receptors that mediate basement membrane assembly and cell-matrix adhesion, and basement membrane assembly is initiated by assembly of a laminin scaffold requiring integrin β1 function on the basolateral epithelial cell membrane. A collagen IV lattice is cross-linked to the laminin-based scaffold via nidogen and other proteins, including agrican and perlecan (Aumailley et al., 2000; Li et al., 2003; Yurchenco, 2011). Other diverse proteins and proteoglycans are then differentially integrated into basement membranes to confer tissue-type and physiology-dependent compositions that impact morphogenesis and subsequently, homeostasis.

Although most studies have focused on the epithelial cell population during branching morphogenesis, there is a growing appreciation of the interdependent nature of the epithelial and stromal compartments during organogenesis. Assembly, remodeling, and maintenance of basement membranes requires the cooperation of both the epithelial and mesenchymal tissue compartments at the boundary interface, and aberrations of basement membrane in disease states can originate in either tissue compartment. In this review, we discuss how heterotypic cell control of basement membrane dynamics regulates adhesions to drive branching morphogenesis, and how mechanical properties of the assembled matrices impact morphogenesis. We suggest that in addition to creating mature epithelial architecture, remodeling of the epithelial basement membrane during branching morphogenesis is also essential to promote maturation of the stromal mesenchyme and facilitate organization of the mesenchymal fibroblasts, vasculature, and innervation with the arborized epithelial structure. Finally, we discuss how recapitulation of this heterotypic cell control of basement membrane is an important consideration in effective tissue engineering and regenerative medicine approaches.

Epithelial-stromal interactions sculpt basement membranes at tissue interfaces

Tissue recombination experiments, where the epithelium and mesenchyme of branched organs are separated and recombined, have demonstrated a requirement for mesenchyme in branching morphogenesis (Gittes et al., 1996; Lawson, 1974). Although isolated epithelia can undergo limited branching in the absence of mesenchyme, this mesenchyme-free epithelial growth requires integrin-mediated adhesion to basement membrane proteins together with exogenous growth factors that substitute for the mesenchyme (Koyama et al., 2009; Nogawa and Takahashi, 1991). In vivo, epithelial-mesenchymal cooperation is required to orchestrate basement membrane assembly and remodeling during embryogenesis (see Fig. 1) (reviewed in (Yurchenco, 2011). In the developing kidney (Lee et al., 1993), lung (Thomas and Dziadek, 1994), pancreas (Crisera et al., 2000), mammary gland (Keely et

al., 1995), and salivary gland (Kadoya et al., 1995), the stromal mesenchyme cells synthesize laminin that is required for assembly of the epithelial basement membrane at the epithelial-stromal interface and to drive epithelial integrin-mediated organ-dependent epithelial cleft formation and ductal morphogenesis (Crisera et al., 2000). Additionally, stabilization and retention of the basement membrane at the epithelial-stromal interface is facilitated by nidogen that is secreted solely from the mesenchyme that condenses around the epithelium and is required for branching morphogenesis in several organs (Ekblom et al., 1994; Kadoya et al., 1997). Stromally produced growth factors can also promote regulated adhesion of epithelial cells with the nascent basement membrane during branching morphogenesis, and epithelial integrin binding to laminin is required for stromal HGF-induced mammary gland morphogenesis (Klinowska et al., 1999; Yang et al., 1995), and stromal FGF-induced salivary gland morphogenesis (Rebustini et al., 2007).

Remodeling of the basement membrane at the epithelial-stromal interface is required for branching morphogenesis

Continual basement membrane remodeling is required for branching morphogenesis, where dynamic changes in the composition and spatial distribution of the basement membrane modulate the activities of the basement membrane-adherent epithelial cells. Incorporation of fibronectin into basement membrane is essential for branching morphogenesis in the salivary gland (Sakai et al., 2003) and lung (De Langhe et al., 2005). In the developing salivary gland, fibronectin drives the formation of narrow clefts between epithelial cells of premature buds that are required for the formation of nascent proacinar and ductal structures (Larsen et al., 2006; Sakai et al., 2003), which form through replacement of epithelial cell-cell adhesions with cell-matrix adhesions as basement membrane is translocated rearward towards the ducts, accumulating at the base of clefts and in newly forming ducts (Harunaga et al., 2014; Hsu et al., 2013; Larsen et al., 2006). Fibronectin promotes cell proliferation and cleft progression in an integrin-dependent signaling cascade that creates a feed-forward mechanism for cleft progression, requiring active integrin β1 on the epithelial cell membrane (Daley et al., 2009; Daley et al., 2011; Sakai et al., 2003). The rapid synthesis and turnover of basement membrane has been highlighted by time-lapse imaging studies in which labeled basement membrane proteins can be tracked over time (Harunaga et al., 2014; Hsu et al., 2013; Larsen et al., 2006). The mechanisms through which rapid basement membrane remodeling occurs remain poorly understood. However, it is clear that matrix metalloproteases (MMPs) produced by the epithelium and the mesenchyme contribute to basement remodeling, promote epithelial invasion and epithelial-mesenchyme transition (EMT), and are required for branching morphogenesis in diverse organs (Bruni-Cardoso et al., 2010; Oblander et al., 2005; Rebustini et al., 2009; Tan et al., 2014; Wiseman et al., 2003). In addition to structural remodeling of the basement membrane, another important consequence of protease activity is to liberate bioactive fragments of structural proteins and growth factors from the basement membrane, as with MMP15-dependent liberation of the collagen IV NC1 fragment, which activates signaling in the epithelial cells to promote salivary gland branching (Rebustini et al., 2009), and many other examples (Horejs et al., 2014; Koshikawa et al., 2010; Loffek et al., 2011; Maller et al., 2010; McCawley and Matrisian, 2001; Mott and Werb, 2004). Importantly, heterotypic control of cell adhesions

and basement membrane remodeling at the epithelial-mesenchymal boundary are also required for adult organ homeostasis, including maintenance of epithelial stem cell niches, as reviewed in (Glukhova and Streuli, 2013; Hsu et al., 2014; O'Brien and Bilder, 2013). Understanding the mechanisms required to maintain organ homeostasis are significant since defective basement membrane and extracellular matrix (ECM) homeostasis is a contributing factor to many diseases, including cancer and fibrotic diseases (Cox and Erler, 2011).

Spatiotemporal control of epithelial cell-cell adhesions creates critical cell subpopulations during morphogenesis

Branching morphogenesis and the establishment of mature organ structure require complex spatio-temporal regulation of cell-cell adhesions (Hsu and Yamada, 2010; Nelson and Gleghorn, 2012; Walker et al., 2008). Cell-cell adhesions confer integrity and functional coupling in mature epithelial cells; however, these adhesions are dynamically coordinated during branching morphogenesis. Recent studies indicate that a transient loss of cell-cell adhesions is required at specific times in specific cells during the course of branching morphogenesis. In the embryonic salivary gland, a discreet loss of epithelial cell adhesion occurs at the base of progressing clefts in response to fibronectin-induced activation of btbd7. Btbd7 induces a partial EMT including transcriptional activation of slug/snail2 and stimulation of a transient loss of E-cadherin containing adhesions to allow for redistribution of the epithelial cells and the basement membrane at the base of the nascent clefts (Onodera et al., 2010). In the mammary gland, the tip cells of the end buds also undergo a partial EMT during branching (Lee et al., 2011), and precisely timed repression of the EMT by the transcription factor, ovo-like zinc finger 2 (Ovol2), is critical for proper epithelial morphogenesis (Watanabe et al., 2014). Additionally, luminal epithelial cells migrate collectively through the mammary myoepithelial cell layer to initiate new branches (Ewald et al., 2008), and FGF-2 stimulated branching in an vitro model of mammary epithelial branching requires disruption of desmosomal cell-cell adhesions, which can be inhibited by activation of aryl hydrocarbon receptor (AHR) (Basham et al., 2013). In embryonic lung epithelium, tight junctions and adherens junctions, maintained by Scribble, are required for normal morphogenesis (Yates et al., 2013). However, tight junctions are generally formed at the apical surfaces at late stages of branching morphogenesis both as a requirement for tubulogenesis of the ducts (Zegers, 2014) and to stimulate epithelial cell polarity and subsequent epithelial cell function (reviewed in (Garrido-Urbani et al., 2014; Gonzalez-Mariscal et al., 2014; Rodriguez-Boulan and Macara, 2014). Thus, delineation of the molecular controls regulating cell-cell adhesions and how these adhesions synergize with cell-matrix adhesions for organogenesis and homeostasis is an important and active area of current research.

Topology and compliance of the basement membrane and extracellular matrix regulate branching morphogenesis

Several lines of evidence indicate that the topology and compliance of ECM and basement membranes facilitate cell adhesion-based forces that sculpt organ form (see Fig. 2). In mammary gland development, stromal collagen fiber alignment can dictate patterning of the

branching epithelium by creating local anisotropy and directing epithelial branching (Brownfield et al., 2013). Although previous studies indicate the mesenchyme cells position the fibers (Grinnell, 2003; Hieda and Nakanishi, 1997), cell culture studies with the non-invasive mammary epithelial cell line, MCF-10A, show that these epithelial cells themselves can also organize a supplied collagen matrix and subsequently respond to the organized matrix (Barnes et al., 2014). In vivo, heterotypic cell interactions may be required for fiber orientation. Interestingly, ductal structures formed adjacent to the anisotropic fibers and acinar structures near the isotropic fibers (Barnes et al., 2014), suggesting fiber structure and forces imparted by the assembled matrix can regulate cell differentiation. How matrix receptors recognize the isotropic and anisotropic matrix is not fully understood. However, Rho/ROCK-mediated contraction was reported not to be required for sensing collagen fiber orientation, but instead was implicated in enhancing collagen I fiber orientation, which would reinforce branching directional decisions (Brownfield et al., 2013). In several branching organs, thinning or transient disruption of the basement membrane at the epithelial tip invading the surrounding stroma is compromised, allowing the basement membrane structural integrity to create directional forces that guide epithelial expansion and branch orientation (Gjorevski and Nelson, 2011; Harunaga et al., 2014; Hsu et al., 2013; Hsu and Yamada, 2010). These studies reflect current interests in elucidating the mechanisms by which ECM and basement membrane dynamics are transduced to create morphogenetic forces, and how such forces control organ development and homeostasis.

One way that ECM and basement membrane dynamics participate in generation of morphogenetic forces is by modulating micro-environmental compliance. Extracellular compliance controls cell phenotype via integrin and focal adhesion signaling and regulation of cell contractility (Discher et al., 2005; Engler et al., 2006; Pelham and Wang, 1997). In the developing salivary gland, branching morphogenesis and epithelial differentiation were shown to be inhibited by culture of submandibular gland organ explants on gels of aberrantly high stiffness/low compliance (Miyajima et al., 2011; Peters et al., 2014a). The mechanisms driving these compliance-mediated differences in glandular development are unknown, but significant differences in the organization of the ECM and basement membrane were observed in glands cultured at low vs high compliance (Peters et al., 2015). The hippo effector protein, Yap, which is known to be mechanosensitive (Low et al., 2014), is critical in forming airway epithelium in the developing lung (Mahoney et al., 2014), whereas activation of the hippo effector, Taz, is required for ductal morphogenesis in the salivary gland (Enger et al., 2013). Aberrant extracellular stiffness disrupts branching behavior of mammary cells in 3D cultures (Chaudhuri et al., 2014; Gomez et al., 2010; Wozniak et al., 2003), and is associated with cancer progression (Chaudhuri et al., 2014; Paszek and Weaver, 2004; Rubashkin et al., 2014).

Recent work indicates that one mechanism through which cells respond to stiffness is through regulation of the activation state and levels of integrins (Friedland et al., 2009; Huebsch et al., 2010; Puklin-Faucher and Sheetz, 2009; Schwartz, 2010). Loss of activated integrin β1 was detected at the periphery of the salivary gland epithelium in developing glands grown at aberrantly low compliance that was associated with a decrease in myoepithelial differentiation, consistent with integrin β1 functioning as a compliance sensor in branching morphogenesis (Peters et al., 2015). Recent work reveals that integrin

endocytosis and the recycling of integrins back to the cell surface can be controlled by microenvironmental stiffness (Du et al., 2011; Huebsch et al., 2010) to regulate the number of available integrins, which may occur in branching organs. In the related process of sprouting angiogenesis, dynamin 2 (DNM2)-regulated endocytosis of vascular endothelial growth factor receptor 2 (VEGFR2) is required for endothelial focal adhesion and integrin β1 turnover, in that loss of VEGFR2 turnover prevents focal adhesion disassembly and causes accumulation of integrin β1 at sites of failed angiogenesis (Lee et al., 2014). In isolated fibroblasts sensing compliance via fibronectin, αv-class integrins were found to activate a GEF-H1-RhoA pathway that is coupled to the formin mDia1 but not to non-muscle myosin type II, and α5β1 integrins activated a RhoA-ROCK-non-muscle-myosin II pathway (Schiller et al., 2013). Future studies will need to elucidate the interplay between these cellular mechanisms for compliance-mediated signaling and effects on cell phenotype. Since the properties of the ECM and basement membrane are impacted by the global mesenchymal tissue organization, studies that address the role of compliance in intact organs with native ECM and basement membrane assemblies will be essential to understand how modulation of the compliance of the ECM and basement membrane networks themselves affects branching morphogenesis and organ function.

Co-patterning of heterotypic cell populations is an inherent requirement of branching morphogenesis

A common emerging theme during morphogenesis is that heterotypic cell interactions at the basement membrane interface create co-patterning of different tissue types to promote mature tissue architecture. Stromal collagens are important for linking the basement membrane to the underlying stroma for tissue integrity during organogenesis in general (Yurchenco, 2011). For example, at the skin dermal-epidermal junction, dermal fibroblasts and epidermal keratinocytes cooperate to make basement membrane (Benny et al., 2014), and fibroblast contribution of collagen VII is particularly important for structural integrity. Co-patterning of interacting cell populations by shared basement membranes also contributes to establishment and maintenance of mature tissue architecture. For example, during angiogenesis, interaction of mesenchymal smooth muscle with endothelium stabilizes the endothelial basement membrane and cellular tube. Remodeling of the endothelial basement membrane and cellular architecture are required for sprouting angiogenesis, a process similar to epithelial branching morphogenesis (Loibl et al., 2014; Stratman et al., 2009). Innervation patterning and neurovascular co-alignment can also be promoted by shared basement membrane, as in the developing pancreatic islets where the vascular basement membrane is required to guide islet innervation (Reinert et al., 2014). Interestingly, recent data show that basement membranes are functionally asymmetric, with the epithelial side of the basement membrane being laminin-enriched, stiffer, and preferentially binding epithelial cells (Halfter et al., 2013). Implantation of basement membranes in vivo demonstrated that human basement membranes have an instructive role in organizing the neuronal cell and mesenchymal cell populations on opposite sides of an assembling spinal cord (Halfter and Yip, 2014). Whether asymmetric basement membrane assembly and adhesion is general mechanism for heterotypic cell population co-patterning in solid branching organs will be an interesting topic for future studies.

Several recent studies point to the interdependence of epithelial branching morphogenesis with mesenchymal cell subsets. As discussed previously, mesenchymal fibroblasts are essential for assembly and remodeling of the basement membrane and for production of growth factors that regulate epithelial cell behaviors, including cell adhesion for the elaboration of mature tissue architecture. Additionally, recent data reveal an instructive role for developing innervation in epithelial patterning. Acetylcholine signaling from parasympathetic innervation ingressing into maturing clefts expands the cytokeratin 5-positive epithelial progenitor cell population in the developing salivary gland and prostate (Knox et al., 2010). Parasympathetic innervation sustains this function in naïve (Knox et al., 2010) and damaged (Knox et al., 2013) adult salivary gland, suggesting that parasympathetic innervation is an important component of basal progenitor cell homeostasis. Parasympathetic innervation also controls ductal elongation and lumen formation in the developing salivary gland, via a distinct molecular cascade requiring vasoactive intestinal peptide (VIP) signaling (Nedvetsky et al., 2014). Interestingly, perfusion-independent vascular signaling is required for the development and co-patterning of the epithelium in several branched organs. In the embryonic pancreas, endothelial cells have an instructive role in epithelial differentiation and patterning (Lammert et al., 2001, 2003; Magenheim et al., 2011), and proper patterning of lung epithelium during branching morphogenesis requires vascular endothelium (Lazarus et al., 2011). Endothelial cells can also promote branching and partial EMT of mammary cells in a 3D in vitro assay, which is regulated by the receptor tyrosine kinase modulator sprouty-2 (Sigurdsson et al., 2013), while a role for endothelium in salivary gland branching has not yet been described. In liver, VEGFR2-expressing vascular endothelial cells are required for specification of the liver endoderm and expansion of the liver into the surrounding mesenchyme prior to the completion of vasculogenesis and onset of circulation (Matsumoto et al., 2001). Taken together, these data indicate that despite a conserved requirement for co-patterning of the epithelium and endothelium in branching morphogenesis, there are organ-specific differences in the epithelial-stromal co-patterning. Definition of the mechanisms driving co-patterning of the epithelium and stromal vasculature and nerves is a critical unmet need, and will likely require organ-specific considerations for therapeutic development.

Implications of heterotypic cell interactions in tissue engineering and regenerative medicine

To engineer a branched organ, three general strategies are possible to generate a compact organ containing a large surface area: 1) use a natural bifunctionally organized decellularized scaffold that contains inherent instructive signals, 2) engineer a complex scaffold that in some way replicates the complexity of the native organ using natural, synthetic, or a combination of materials, or 3) provide an environment in which the cells can self-organize and generate their own scaffold as they undergo the developmental program of branching morphogenesis or something resembling it. All three strategies and combinations of these strategies are being pursued by different groups with distinct approaches. Currently, natural, decellularized scaffolds out-perform any synthetic organ scaffolds for solid organ engineering (Faulk et al., 2014; Song and Ott, 2011). Such natural scaffolds include complex, spatially organized extracellular signals to stimulate cell-matrix adhesion, cell-cell

adhesion, and cellular self-organization of the diverse cell types required for mature organ function that engineers have not yet been able to fully recapitulate. Thus, stimulating heterotypic cell self-organization and matrix production in engineered constructs is a current goal of many tissue engineers. For example, recent work aimed at improving the quality of the basement membrane at the dermal/epidermal boundary in engineered skin revealed that it was the dermal fibroblasts that contributed the most to the enhanced basement membrane, and basement membrane production by these cells was in turn stimulated by natural scaffolds (Benny et al., 2014). Some combination of deliberate engineering and self-organization of heterotypic cell populations may ultimately succeed.

Current efforts in tissue engineering and regenerative medicine are increasingly focused on the need to support and maintain parenchymal tissue using the interacting stromal cell populations both for organ generation and for sustained organ function. With the recognition that multiple cooperating cell types are required for organogenesis and epithelial basement membrane assembly and remodeling, engineered scaffolds must promote survival and self-organization of both epithelial and mesenchymal cell populations, including the mesenchymal fibroblasts that support the epithelial-stromal interface and the integrated vasculature and innervation. Additionally, engineered scaffolds must provide an appropriate environmental compliance or stiffness to allow tensional homeostasis and regulation of integrin-based cell adhesions (Du et al., 2011; Huebsch et al., 2010) and support functional differentiation and retention of complex interacting cell populations (Bissell and Bilder, 2003; Hu et al., 2008; Peters et al., 2015). Ultimately, scaffolds that best support dynamic homotypic and heterotypic cell interactions and encourage the cells to deposit and remodel their own extracellular matrices and basement membranes may be required to engineer functional and sustainable organs. Eventual development of tissue-engineered constructs capable of long-term maintenance of homeostasis will require recapitulation of a niche for renewing progenitor cell populations (Dziasko et al., 2014; Fujiwara et al., 2011; Marthiens et al., 2010; Menezes et al., 2014). In regenerating tissues, similar considerations for strategies to promote recapitulation of the complex developmental programs and restoration of the microenvironment and progenitor cell niches are required.

Conclusion

Concepts and examples discussed here illustrate the importance of heterotypic cell control of basement membrane dynamics and cell adhesion for elaboration and maintenance of parenchymal cell function in branched organs. Additionally, we suggest that while branching morphogenesis has long been recognized to create patterned epithelial tissue, epithelial-stromal co-patterning is critical during organogenesis, and thus will be essential to create functional and effectively host-integrated neo-organs. These themes highlight the need to provide scaffolds of appropriate compliance with organized chemical signals to facilitate appropriately localized and dynamic remodeling of basement membrane and cell-matrix adhesions for effective therapeutic restoration of impaired organ function. Application of knowledge regarding control of basement membrane dynamics and cell patterning by heterotypic cell populations will enable improved tissue engineering and regenerative medicine approaches by defining the required cell populations and characteristics of their environments to both create organ architecture and to be able

maintain it. As the requirements for organ development and maintenance may be distinct, a significant future challenge will be to integrate knowledge of these processes into concrete strategies for effective organ regeneration and engineering.

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Highlights

Epithelial-stromal interactions sculpt basement membranes at tissue interfaces.

Adhesion dynamics create epithelial cell subpopulations during morphogenesis.

Basement membrane and extracellular matrix properties influence tissue architecture.

Heterotypic cell co-patterning is an inherent requirement of branching morphogenesis.

How basement membrane dynamics drive development can inform regenerative medicine.

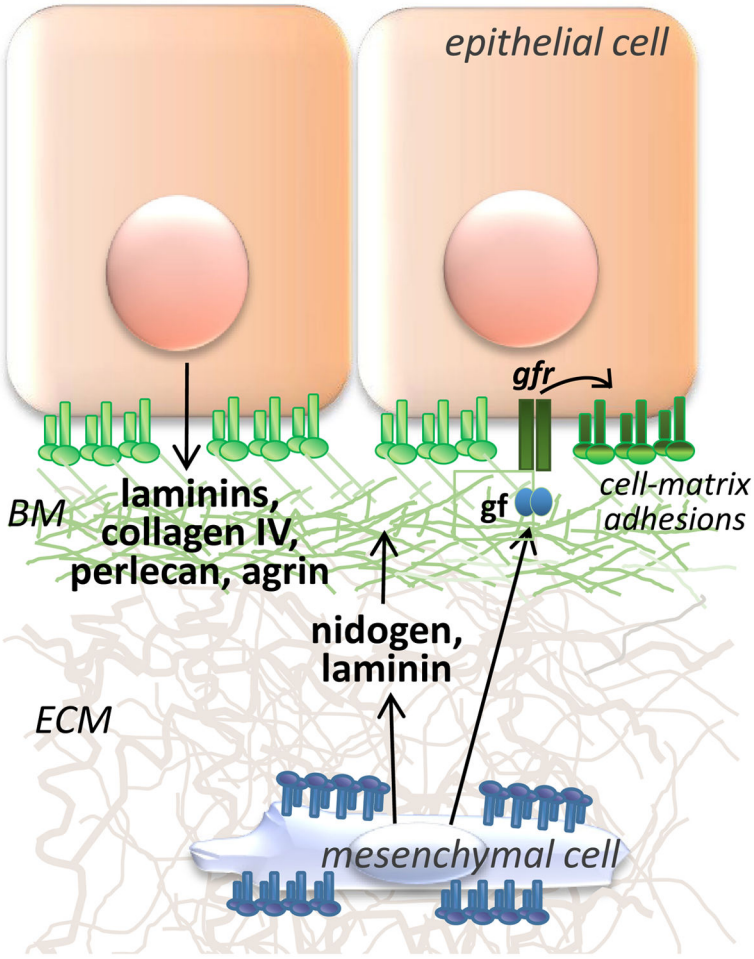

Fig. 1. Heterotypic cell contributions to basement membrane assembly

Epithelial cells produce a diverse group of basement membrane (BM) proteins (i.e. laminins, collagen IV, agrin, perlecan, etc) and other basement membrane components that are anchored to the cell membrane via integrins and other matrix receptor proteins. Mesenchymal cells, enclosed within and attached to their own ECM via integrins, synthesize some laminin and also nidogen that crosslinks laminins with collagen IV. Epithelial cell adherence to the assembled BM can be regulated by mesenchymal growth factors that activate epithelial growth factor receptors.

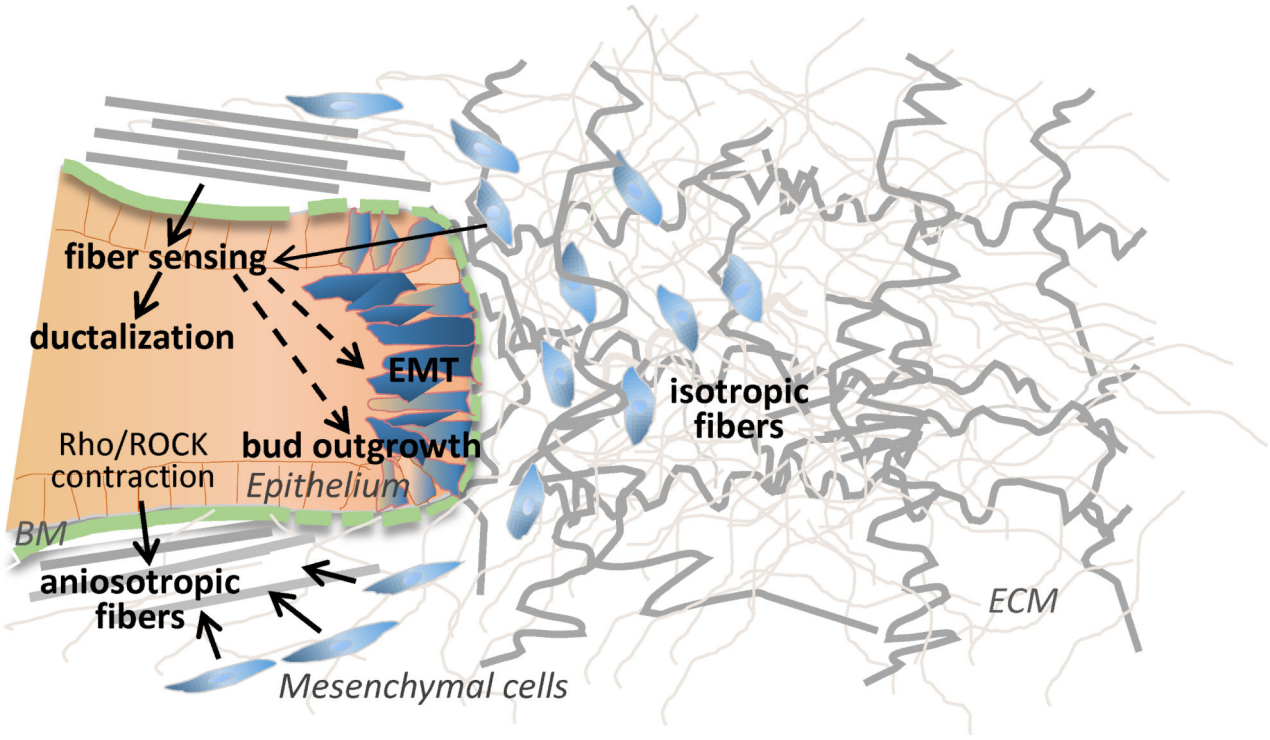

Fig. 2. Topology and compliance of the basement membrane and extracellular matrix regulate branching morphogenesis

In developing mammary gland, cells at the tip of an epithelial end bud extend into the surrounding anisotropic ECM and undergo a local EMT. Expansion and extension of the bud is facilitated by breaks in the basement membrane, as are detected in other branching organs. In a 3D mammary model system, axially aligned anisotropic collagen I fibers are sensed by the the epithelium and stimulate ductalization while isotropic fibers facilitate acinar formation and may also facilitate bud outgrowth and EMT (dotted lines). Mesenchyme cells can align ECM and epithelial cells can also contribute to fiber alignment through Rho/ROCK pathway-mediated contraction.