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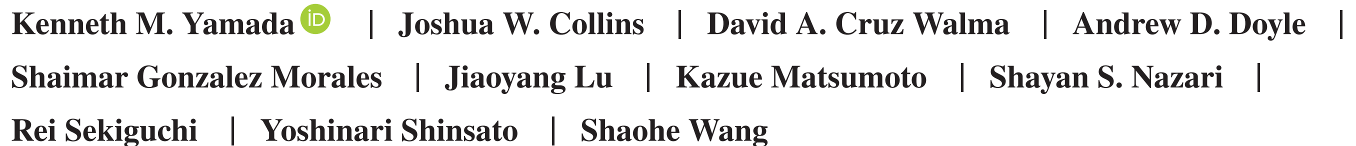
REVIEW ARTICLE

Extracellular matrix dynamics in cell migration, invasion and tissue morphogenesis



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Summary

This review describes how direct visualization of the dynamic interactions of cells with different extracellular matrix microenvironments can provide novel insights into complex biological processes. Recent studies have moved characterization of cell migration and invasion from classical 2D culture systems into 1D and 3D model systems, revealing multiple differences in mechanisms of cell adhesion, migration and signalling—even though cells in 3D can still display prominent focal adhesions. Myosin II restrains cell migration speed in 2D culture but is often essential for effective 3D migration. 3D cell migration modes can switch between lamellipodial, lobopodial and/or amoeboid depending on the local matrix environment. For example, "nuclear piston" migration can be switched off by local proteolysis, and proteolytic invadopodia can be induced by a high density of fibrillar matrix. Particularly, complex remodelling of both extracellular matrix and tissues occurs during morphogenesis. Extracellular matrix supports self-assembly of embryonic tissues, but it must also be locally actively remodelled. For example, surprisingly focal remodelling of the basement membrane occurs during branching morphogenesis—numerous tiny perforations generated by proteolysis and actomyosin contractility produce a microscopically porous, flexible basement membrane meshwork for tissue expansion. Cells extend highly active blebs or protrusions towards the surrounding mesenchyme through these perforations. Concurrently, the entire basement membrane undergoes translocation in a direction opposite to bud expansion. Underlying this slowly moving 2D basement membrane translocation are highly dynamic individual cell movements. We conclude this review by describing a variety of exciting research opportunities for discovering novel insights into cell-matrix interactions.

KEYWORDS

3D culture, basement membrane remodelling, branching morphogenesis, cell migration, extracellular matrix, invasion

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1 | INTRODUCTION

The extracellular matrix is now acknowledged to be a key regulator of a wide range of cell biological processes, including signalling and tissue remodelling. Although numerous, elegant biochemical and cell biological studies have documented key roles played by extracellular matrix molecules in embryonic development, tissue remodelling and disease, there have been fewer studies involving direct real-time visualization of the dynamic interactions of cells and tissues with the extracellular matrix. Others and we have recently applied increasingly powerful live-cell and live-tissue fluorescence microscopy technologies to try to identify novel and unexpected cell-matrix interactions in development and malignancy. This short review will highlight approaches that have yielded altered or new understanding of complex tissue processes. Its focus will be on examples chosen from research from our own laboratory, but we emphasize that there are a number of other outstanding studies in this research area (eg see the following Ref.[1-14]).

2 | MOVING INTO THE THIRD DIMENSION

Many important insights have been gained using regular cell culture on flat two-dimensional surfaces of glass or plastic, which can be termed "2D culture." However, work during the past couple of decades has moved the study of cell-matrix interactions—and even the development of early organ primordia—into 3D tissue culture to attempt to understand the complex events that occur in vivo at the molecular and microscopic physical level. Such 3D tissue models provide insights into the mechanisms of 3D cell migration, embryonic development and pathology. This approach permits the application of many of the same powerful technologies used in regular 2D cell culture, including transfection to increase or decrease the expression of a specific protein, antibody inhibition studies and analyses of the biological effects of interactions of cells with different types of extracellular matrix molecules in various topologies (reviews include the following Reference.[15-25]

3 | 1D MIGRATION

Besides 2D and 3D cell culture, however, the use of "1D" systems has proven to be surprisingly relevant to studies of functional cell interactions with the fibrillar structures characteristic of interstitial matrix. As depicted in Figure 1, it has been known for many decades that cells readily migrate along matrix fibrils using a process known as "contact guidance".[26] When viewed in cross section, the migration of a cell along a fibril can be modelled as 1D migration, though such in vitro "1D" lines usually have a width of 1-2 μm. On such 1D substrates, cells form long, continuous cell-matrix adhesions and

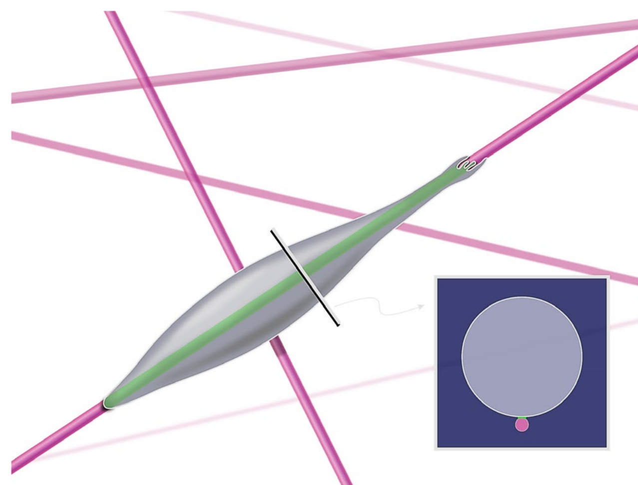

FIGURE 1 Cell migration on matrix fibres resembles one-dimensional (1D) migration. A cell translocating along a single fibre or fibril has a very small region of contact (see the inset), which can be mimicked by engineering very narrow 1D lines on a cell culture surface and coating them with a matrix protein confined to that line [Colour figure can be viewed at wileyonlinelibrary.com]

exhibit hyperactive lamellipodial activity[27,28] that can be accompanied by unusual fin-like membrane protrusive waves.[29] Not surprisingly, many of the cell biological characteristics of cell migration along a 1D substrate can closely mimic the behaviour of cells in 3D matrix, but not on flat 2D substrates (Figure 2). These similarities in morphology and cell dynamics may well be due to the capacity of simple 1D model systems to mimic at least partially the fibrillar nature of the interstitial

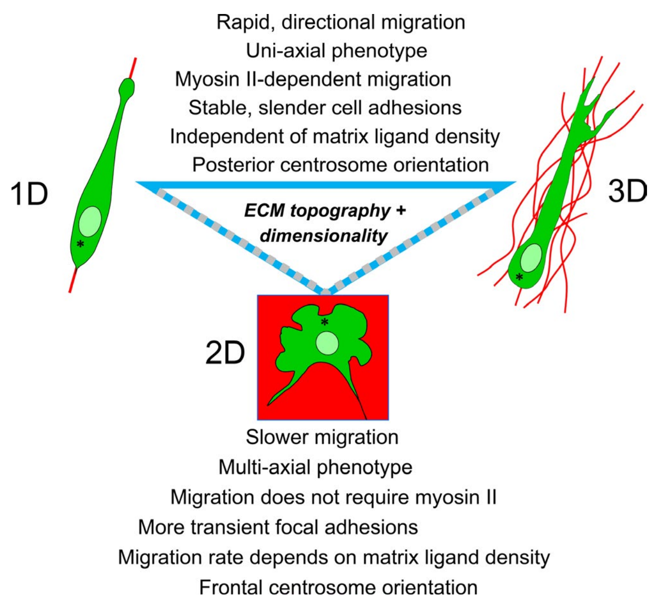

FIGURE 2 Direct comparisons of cells migrating in 1D, 2D and 3D models in vitro. Many specific cell biological behavioural features of fibroblasts migrating within a fibronectin-rich 3D cell-derived matrix are mimicked by migration of these cells on fibronectin-coated 1D lines, but not migration on 2D glass substrates coated with fibronectin or with serum proteins. Figure re-drawn from Doyle et al[28] [Colour figure can be viewed at wileyonlinelibrary.com]

matrix. Similarities between 1D and 3D systems include individual cell morphology, mode of cell migration, orientation of the centrosome and dependence on non-muscle myosin II.[28] Importantly, these studies also identify cell-matrix adhesions that closely resemble classical focal adhesions characterized in 2D cultures that are used by migrating cells on both 1D and 3D matrices. In fact, the number of focal adhesions and the level of activated β1 integrins can be even higher in cells migrating in 3D collagen matrix than on a 2D substrate.[27]

4 | MODES OF 3D CELL MIGRATION

There are multiple modes of migration by cells in various different 3D extracellular matrix environments. For example, primary human fibroblasts, which are flat and spread out on 2D substrates, often use lamellipodial migration characterized by large, flat lamellipodia driven by actin polymerization. These same cells in 3D collagen gels use tiny, multiple lamellipodia with filopodia. In contrast, when these cells migrate in a 3D cell-derived matrix, they switch to 3D "lobopodial" migration[30] (Figure 3). A number of normal human immune cells can migrate by a mode of migration that resembles the locomotion and morphology of an amoeba, a process termed amoeboid migration; some tumour cells can also use this mode of migration (reviewed by Ref.[2,31-33]

A recently described mode of migration occurs in a confining or constricting 3D matrix that induces lobopodial migration. This migration mode is characterized by protrusion of a blunt leading edge of the cell devoid of classical actin-driven lamellipodia, and it depends on differential intracellular pressure driven by a "nuclear piston".[30,34] In the lobopodial mode of migration (Figure 4), a cell is embedded within an extracellular matrix that produces an elongated cell with its plasma membrane pressed close to the nucleus to seal off the anterior from the posterior regions of the cell. This diffusion barrier/hydraulic pressure seal appears to require either very close nucleus-plasma membrane apposition or an extensive membranous vesicular barrier. Although not characterized in detail, the mechanism by which the nucleus is pulled forward to pressurize the anterior portion of the cell appears to be via myosin II linked to vimentin intermediate filaments, which are in turn anchored to the nucleus by nesprin-3.[34]

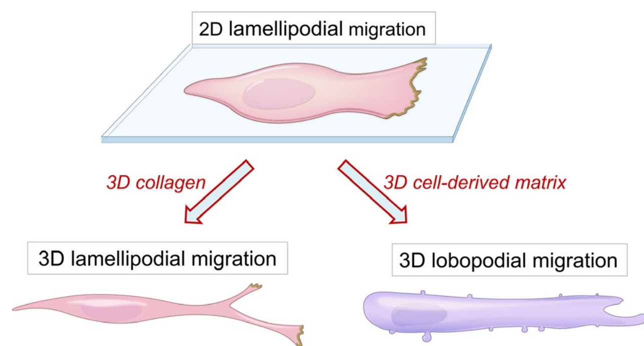

FIGURE 3 Cell morphologies in 2D vs 3D collagen or 3D cell-derived matrix environments. Cells such as human fibroblasts that migrate on flat substrates are flattened in morphology and display lamellipodia at their leading edge, which promote migration by actin polymerization and cell protrusion. The same cell type in 3D collagen gels become spindle-shaped and display multiple tiny lamellipodia at the tip of extending cell processes at the leading edge. In 3D cell-derived matrix, however, these cells have a more tubular shape with lateral blebs and a leading edge that lacks lamellipodia as they migrate using lobopodial migration. Cells can be switched from lobopodial to lamellipodial migration by mild proteolysis of the cell-derived matrix. Figure re-drawn from Petrie et al[30] [Colour figure can be viewed at wileyonlinelibrary.com]

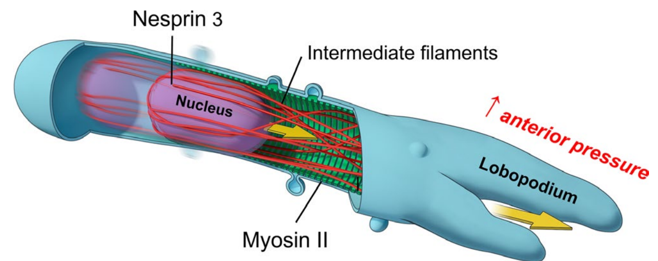

FIGURE 4 Nuclear piston 3D cell migration. Human fibroblasts migrating within a confining 3D cell-derived matrix switch to lobopodial migration, a migration mode in which the nucleus can serve as a piston. The nucleus is pulled forward by myosin II contractility via vimentin intermediate filaments that link to nesprin-3 on the nucleus. This pulling forward of the nucleus pressurizes the anterior end of the cell to protrude a lobopodial process. New cell-matrix adhesions then form at the cell anterior to anchor the cells, and the cycle can repeat with another round of nuclear piston movement [Colour figure can be viewed at wileyonlinelibrary.com]

5 | CANCER

The malignant counterpart of normal human fibroblasts, fibrosarcoma cells, fails to undergo nuclear piston migration in a cell-derived matrix until their protease activity is inhibited for stabilization of the adjacent extracellular matrix.[35] In fact, treatment of cell-derived matrix with proteases can abolish lobopodial migration by normal human fibroblasts.[30] Experimentally enhancing expression of the protease MT1-MMP to promote local proteolysis at only 3-4 times normal levels will cause loss of lobopodial migration by these normal human cells. Inhibition of MMPs restores normal lobopodial migration to these protease-overexpressing cells.[35] Thus, cells can switch their modes of migration depending on the level of proteolytic activity affecting cell interactions with locally adjacent extracellular matrix.

Invasion of human tumour cells into extracellular matrix has been studied extensively by many laboratories. Local invasion of these cells can be facilitated by microscopic cellular

extensions termed invadopodia (Figure 5). These filopodia-like cell processes often contain the MT1-MMP protease for digestion of local extracellular matrix.[36,37] Real-time imaging reveals that these microscopic processes are highly dynamic,[38] which may account for their ability to degrade zones of matrix in their vicinity. Interestingly, besides being regulated by oncogenes and Rho GTPase activity, invadopodia can be induced dramatically by merely elevating the concentration of local fibrillar collagen matrix to a local concentration of 15 mg/mL or higher.[39] This induction can surprisingly also occur with normal human fibroblasts in serum-free medium in vitro. Although the complex regulation of invadopodia remains to be characterized further, this phenomenon of invadopodia induction by high-density collagen involves a complex series of changes in protein phosphorylation, including phosphorylation of the integrin-associated regulator kindlin-2.[39]

It has been known for many years that normal cells will

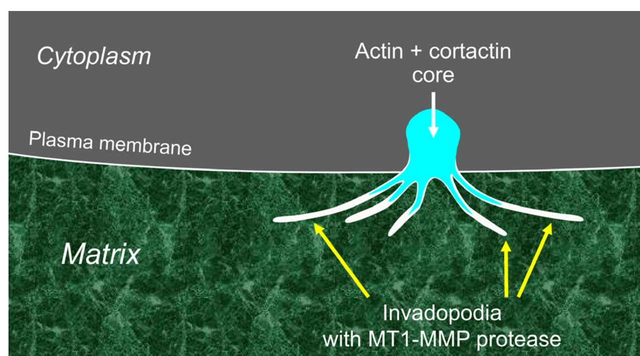

FIGURE 5 Invadopodia: dynamic micro-invasive structures. Invadopodia are generated from an actin-cortactin core at the plasma membrane and are used by cancer cells to degrade the extracellular matrix locally to promote invasion. The protease MT1-MMP is expressed on the thin, filopodia-like processes, which can degrade the matrix proteins and structures that they touch [Colour figure can be viewed at wileyonlinelibrary.com]

often migrate towards regions of increasing stiffness in a process termed "durotaxis".[40] A recent study reveals that a variety of human tumour cells can also undergo durotaxis as efficiently as normal human fibroblasts and that the efficiency of durotaxis can be greatest at regions of low matrix stiffness.[41] Another interesting feature of durotaxis is that it appears to be most efficient as a collective cell process, perhaps because a gradient of stiffness can be detected most efficiently by combining weak stiffness signals over a larger distance spanning multiple cells.[42]

6 | BRANCHING MORPHOGENESIS

A particularly complex series of cell-matrix interactions occurs during embryonic development of multiple organs in the highly dynamic process termed branching morphogenesis.[43-49] This process converts a simple single epithelial bud to highly branched structures that greatly enhance epithelial surface area to provide sufficient exchange of gases in lungs, produce copious saliva by salivary glands and excrete litres of urine by kidneys. Branching morphogenesis involves both subdivision of an initial single epithelial bud by the formation of clefts or additional buds and the outward expansion of the newly formed branches of the organ (Figure 6). One striking feature of this type of development of early embryonic organs is the transient acquisition of cell motility by initially quiescent epithelial bud cells.[50,51] This high level of cell migratory activity during the process of branching morphogenesis may be important to permit tissue plasticity in analogy to the physical process of jamming and unjamming observed

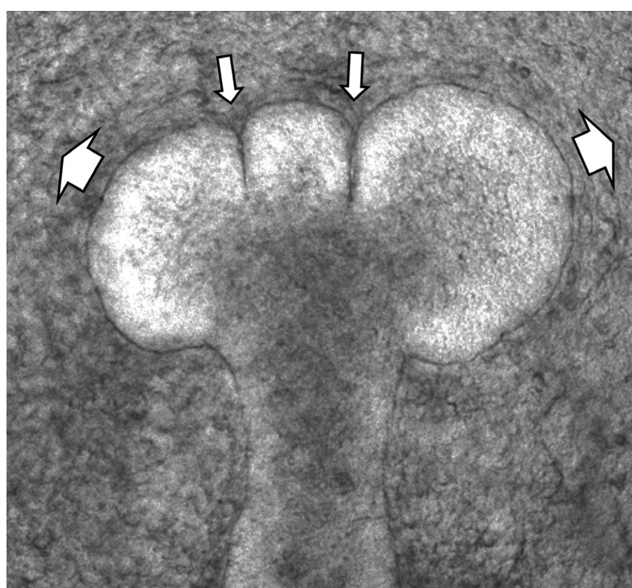

FIGURE 6 Early step of mammalian branching morphogenesis. This example shows a mouse salivary gland with two forming clefts (narrow arrows) and forming buds expanding outward (wide arrows) into the surrounding mesenchyme

during expansion of the early embryonic axis.[52] In addition, however, this high level of cell motility combined with cell-cell adhesive interactions can contribute to tissue self-organization. For example, completely dissociated and separated epithelial cells (Figure 7A,B) can self-aggregate if provided with a 3D Matrigel matrix and growth factors, eventually forming organoids with bud-like protrusions (Figure 7C).[53] These buds display nearly identical patterns of cell adhesion molecules and F-actin as never-dissociated epithelial buds. This process of self-assembly has been extended to salivary gland tissue engineering, as well as numerous organoid models, including mini-brains and mini-guts.[54-58] These approaches may permit tissue engineering and regenerative therapy. From the point of view of matrix biology, however, much remains to be learned about the specific contributions

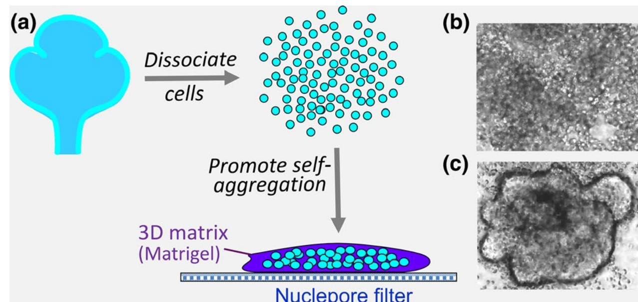

FIGURE 7 Self-assembly of dissociated epithelial cells into bud-like organoid structures. A, Isolated embryonic salivary gland epithelia were dissociated into single cells and then cultured within a small 3D Matrigel microenvironment on a nuclepore membrane filter. Phase-contrast time-lapse microscopy shows rapid self-aggregation of the initially dissociated cells (B) into clusters that merge into large aggregates, from which bud-like structures protrude (C) during a process of self-organization [Colour figure can be viewed at wileyonlinelibrary.com]

of matrix to organoid formation and how it can provide an appropriate niche in vivo.

7 | BASEMENT MEMBRANE DYNAMICS

Basement membranes are well-known structural features of many tissues, providing a substrate for epithelial cell attachment and organization, as well as separating epithelial and mesenchymal tissues.[59-62] The basement membrane provides a well-known barrier to epithelial (carcinoma) cell invasion, and a classical feature of malignancy is tumour cell invasion across the basement membrane. Although this process is thought to involve proteases, physical force by a cellular process against the basement membrane can also contribute to cellular invasion across the basement membrane.[63-65]

One puzzle in developmental biology has been how tough, sheet-like basement membrane barriers can be transiently transformed into sufficiently flexible sheets during embryonic development in order to permit rapid local tissue expansion without tissue mixing, for example, during the outward expansion of buds during branching morphogenesis (Figure 8A,B). Degradation of basement membrane proteins and proteoglycans by hydrolytic enzymes has been known for many decades to produce thinning of the basement membrane to allow local tissue expansion,[66,67] but exactly how this process is mediated was not clear. Direct examination of basement membrane structure and dynamics during active branching morphogenesis reveals a dramatic process of proteolytic and actomyosin-dependent generation of numerous microscopic perforations or holes in the region of the basement membrane located at the tip of an expanding bud. These perforations generate a lace-like meshwork (Figures 8C and

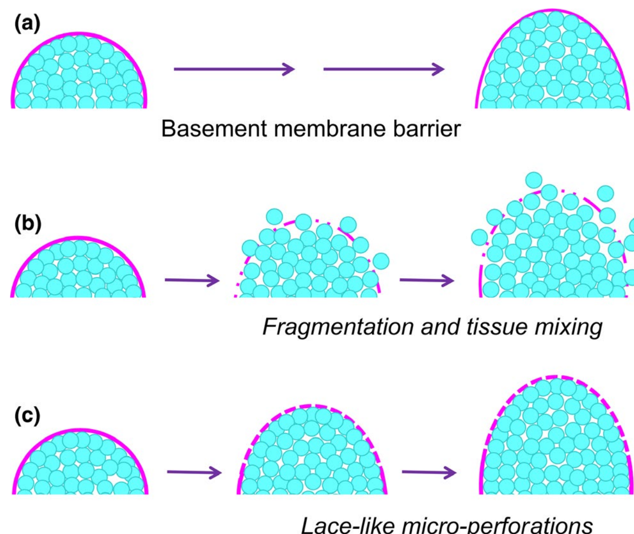

FIGURE 8 The challenge of embryonic tissue expansion within a confining basement membrane. A, The basement membrane barrier between epithelial and mesenchymal tissues must be able to expand along with bud expansion or extension during branching morphogenesis. B, Although degradation and thinning of the basement membrane are known to occur, absence of a controlled process would lead to tissue fragmentation and mixing of the highly motile epithelial cells into the surrounding mesenchyme—but this mixing does not occur in vivo. C, Basement membranes can become flexible by the formation of numerous microscopic holes or perforations that produce a lace-like meshwork of basement membrane that can expand while still confining the epithelial cells [Colour figure can be viewed at wileyonlinelibrary.com]

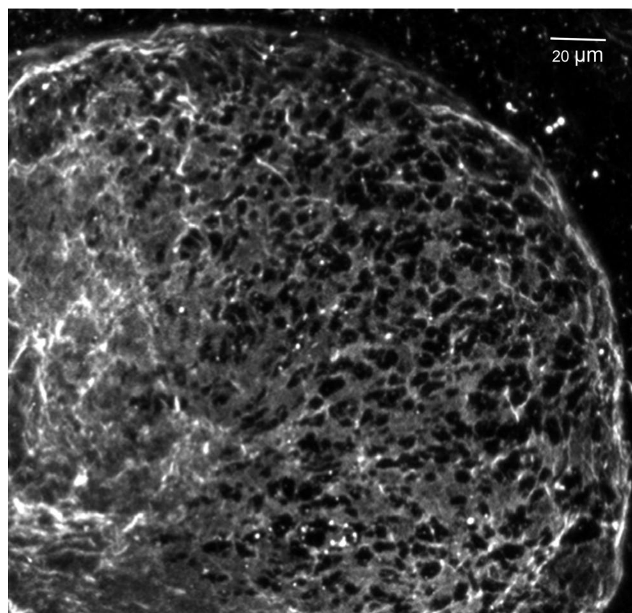

FIGURE 9 Perforated basement membrane meshwork at a bud tip. This image shows an embryonic salivary gland bud that was expanding towards the right with its basement membrane stained for collagen IV (light grey). Note the intact basement membrane on the left that becomes perforated by numerous microscopic holes (black) towards the righthand tip of an expanding bud

9) that permits extensive local distensibility of the basement membrane as visualized directly by time-lapse confocal microscopy.[68] These basement membrane perforations vary considerably in size but often average only 1-2 μm^2 in area, which is considerably less than the 25 μm^2 average area of the adjacent epithelial cells. Because of the small size of these numerous perforations, the epithelial cells are restrained behind a highly flexible basement membrane.

Intriguingly, however, the epithelial cells very frequently extend cellular blebs or elongated processes up to 5 μm in length through the perforations towards the surrounding mesenchyme cells. These highly active, extending and retracting cell processes may contribute to formation or maintenance of the perforations,[68] but they may also correspond to the previously described direct contacts between epithelial and mesenchymal cells through the basement membrane (basal lamina).[69,70] In fact, a classical analysis of epithelial-mesenchymal interaction reported that such close cell-cell interactions may be required for successful development, in addition to the currently extensively studied growth factor interactions known to be involved in branching morphogenesis.[71]

The embryonic basement membrane, however, undergoes bulk translocation. In embryonic salivary glands, the basement membrane moves as a seemingly intact structure replete with the perforations in a direction opposite to that of bud expansion. Buds expand outward at approximately 5 μm/h, whereas the basement membrane translocates in the opposite direction towards the secondary duct at a rate of approximately 7-8 μm/h (Figure 10). Both the formation of basement membrane perforations and the rearward translocation of the entire basement membrane require general MMP-associated proteolytic activity and myosin II-dependent actomyosin contractility.[68] A major puzzle involves how this global translocation of basement membrane is driven, since local cell motility is not obviously directional so as to provide motive forces to help move the basement membrane.

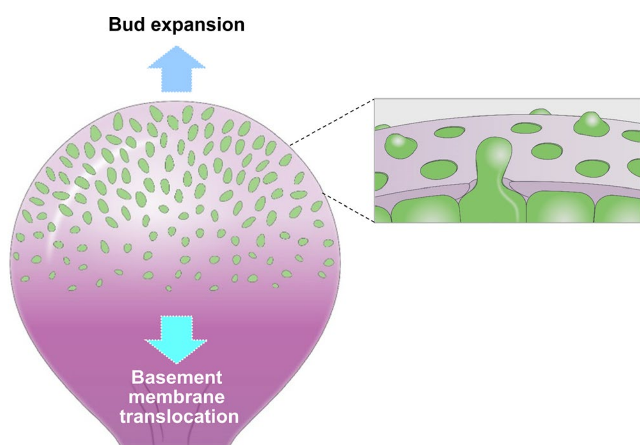

FIGURE 10 Basement membrane dynamics during embryonic branching morphogenesis. As buds expand outward, the basement membrane is perforated by numerous microscopic holes through which epithelial cell blebs and elongated processes protrude towards the mesenchyme. Concurrently, the entire basement membrane translocates backward towards the secondary duct [Colour figure can be viewed at wileyonlinelibrary.com]

8 | FUTURE CHALLENGES AND OPPORTUNITIES

Direct visualization of cell-extracellular matrix interactions involving single cells or tissues has provided novel insights into otherwise puzzlingly complex processes. The combination of direct real-time visualization and a variety of biochemical, biophysical and genetic approaches promises to open new avenues of research for understanding multiple complicated biological processes. In the following section, we suggest a series of intriguing future avenues of research into cell-matrix interactions. These and many other exciting opportunities should provide novel insights for many decades into the future.

8.1 | Migration, invasion and matrix assembly

Recent investigations have characterized differing modes of 3D migration, for example, amoeboid, mesenchymal and lobopodial. However, the field will need to examine in-depth the spatiotemporal dynamics of cells as they interact with their surrounding matrix microenvironment, in order to characterize the biophysics and biomechanics associated with these modes of migration. In addition, because contractility is known to be required for rapid 3D cell migration by numerous cell types, it will be important to understand how differences in cell interactions with different types of extracellular matrix affect cellular mechanosensing and mechanotransduction during 3D cell migration.

The diversity of protein composition and architecture in different types of 3D matrix can alter cell adhesion, mechanosensing/mechanotransduction and cell migration or invasion. Comparing in vivo matrix molecular components and architecture of different tissues and then developing increasingly complex and realistic in vitro 3D models will be important for understanding the roles of different types of matrix and their biophysical properties in biological processes. One example involves the known effects of matrix density on increased risk for breast cancer.[72-76] Because local tissue invasion initiates tumour progression and metastasis, further elucidation of cell interactions with the basement membrane will be informative. For example, how are local dynamics of basement membrane and associated extracellular matrix involved in the transformation of carcinoma in situ into invasive carcinoma?

8.2 | Organ morphogenesis

Work from our own and other laboratories has demonstrated extensive basement membrane remodelling during normal branching morphogenesis of mammalian organs during embryonic development. However, it remains unclear how cells regulate the production and assembly of new basement membrane for the coordinated surface expansion of epithelium during organ branching. An interesting future direction will be to examine how basement membrane components are produced and secreted using live imaging approaches. CRISPR/Cas-mediated genetic perturbations will likely help to clarify regulatory mechanisms of this process. A related question for both developing and adult tissues is how basement membranes accumulate such substantial levels of fibronectin immediately at the surface facing mesenchymal tissues. Live imaging of cell interactions with basement membranes should clarify this and other questions about cell-basement membrane interactions.

Additional approaches to understanding the mechanisms of branching morphogenesis will include increasingly in-depth characterizations of RNA regulatory biology. For example, transcriptomic approaches will be valuable, including single-cell sequencing to characterize the diverse cells of different early embryonic organs and their capacity to secrete specific matrix proteins as they self-organize during development into complex, functionally distinct tissues and organs. MicroRNAs have also emerged as important regulators during branching morphogenesis,[44] but also in cancer initiation/progression[78]; some miRNAs may be implicated in both processes. Their roles in extracellular matrix remodelling during branching morphogenesis and cancer progression are poorly understood. Direct comparisons of these biological processes should provide new mechanistic insights and potential therapeutic approaches to targeting matrix remodelling in different diseases.

We previously implicated the protein BTBD7 in branching morphogenesis,[79] but the extent of its functions and their molecular mechanisms remains unclear. BTBD7 is part of a large group of >200 BTB/POZ domain-containing proteins encoded by the human genome that serve central biological roles ranging from organogenesis, gastrulation and stem cell differentiation to ribonucleotide damage responses and cell cycle regulation.[80-83] Determining the function of BTBD7 and the mechanisms through which it regulates cellular phenotypes, such as partial epithelial-mesenchymal-transition (EMT), should open new insight into its role in cell-matrix interactions and organ development.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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