Hiding in Plain Sight: The Basement Membrane in Pulmonary Vascular Remodeling

Initially described by William Bowman in 1840, the basement membrane (BM) is a specialized form of extracellular matrix (ECM) with multiple functions, including cell anchoring, mechanotransduction, immunomodulation, and signaling (1). Although BMs are similarly composed of laminins, type IV collagen, nidogen, and proteoglycans, the proportion of these components can differ depending on the tissue location and can be influenced by local factors such as mechanical stress, cellular turnover, and signaling activity. Thus, the biochemical profile of BM is largely tissue specific and tailored to optimally support the biological functions of the cells in its jurisdiction. Pathological changes in the composition and integrity of the BM are a common feature of diseases such as Alport syndrome, Goodpasture syndrome, and cancer, in which loss of BM integrity results in cell loss, extravasation of intravascular components, inflammation, and reduced cell regeneration (2). In this issue of the *Journal*, Jandl and colleagues (pp. 104–117) present exciting evidence that sheds light on the BM as a not-so-silent player in pulmonary arterial hypertension (PAH)-associated vascular remodeling, and provides new insight into the mechanisms by which BM pathology results in abnormal cell behavior and loss of homeostasis (3).

The architecture of the lung BM is unique and complex. In the lung, the BM of airway epithelium and blood vessels have unique properties that are finely tuned to the dynamic changes in intrathoracic pressures, oxygen tension, cardiac output, and acid–base balance associated with pulmonary physiology. Thus, it is no surprise that changes in the composition of the BM in airways and blood vessels can have adverse functional consequences and contribute to the pathobiology of respiratory diseases. For instance, one of the hallmarks of airway remodeling in asthma and chronic obstructive pulmonary disease is thickening of the airway reticular BM stemming from changes in the local production of BM molecules and reduced turnover (4). However, although chronic obstructive pulmonary disease and asthma exhibit similar pathological changes, they differ with regard to the composition of the BM, likely owing to differences in inflammatory responses and environmental exposures (5). Loss of BM integrity is considered a major tipping point in the natural history of lung fibrotic disorders (6). As mentioned in the first paragraph, the BM is responsible for directing the timing of cell proliferation, immune cell recruitment, and resolution of repair responses after epithelial or vascular injury. Without the signaling cues of the BM, there is a lack of oversight, which leads to progressive loss of epithelial cells, disruption of the alveolar-capillary membrane, and a switch toward profibrotic responses that culminates in parenchymal destruction (7). PAH is associated with progressive changes in the cellular composition of the vessel wall that culminate in irreversible luminal obstruction, *in situ* thrombosis, and perivascular fibrosis. A close examination of affected vessels reveals pathological changes in ECM structures, such as fragmentation of the elastic lamina (8), increased perivascular deposition of ECM components (9), and accumulation of fibroblasts (10). Besides creating a stranglehold on the vessel, the ECM also harbors growth factors and inflammatory mediators that perpetuate the cellular growth within vascular lesions. Based on recent studies showing how elastase production by local smooth muscle cells can alter ECM integrity and contribute to vascular remodeling (11), there are plans for a National Institutes of Health–sponsored clinical study using elafin (an elastase inhibitor) as a potential therapy for PAH. These studies demonstrate that the ECM is a prime target for novel PAH therapies, and support the need for efforts to understand how changes in the composition and integrity of the ECM contribute to the natural history of vascular remodeling in PAH.

Using well-established imaging techniques, Jandl and colleagues performed a comprehensive characterization of the structure, composition, and function of the pulmonary arterial BM of healthy donors and patients with PAH. Similar to what is seen in airway diseases, the BM of PAH lesions was found to be thicker and fragmented than that of healthy donors. At a molecular level, the composition of the BM was found to vary in relation to vessel size, with collagen IV being predominant in small vessels and laminin being more abundant in larger vessels. Experiments using patient-derived pulmonary artery endothelial cells (PAECs) seeded on surfaces coated with either laminin or collagen IV revealed significant activation of the YAP/TAZ pathway in PAH endothelial cells that correlated with the strength of adhesion and formation of tight junctions, a critical step in the establishment of the endothelial barrier. Interestingly, knockdown of COL4A5 and LAMC1 (genes for collagen IV and laminin, respectively) in PAECs had opposing effects on barrier formation, as COL4A5-deficient PAECs demonstrated a lower density of VE-cadherin in tight junctions compared with LAMC1-deficient PAECs, which exhibited significantly higher VE-cadherin expression. In light of these findings, the authors concluded that changes in the composition of the BM are a major feature of the vascular pathology of PAH and can disrupt the normal behavior of endothelial cells by interfering with barrier formation and local adhesion.

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This is the first in-depth study of the BM in PAH, and the authors should be commended for their robust approach to addressing how changes in BM composition are linked to the abnormal behavior of PAH PAECs in culture. Their study opens exciting opportunities to further elucidate how the BM interacts with the genetic and signaling landscape of endothelial cells during the initiation and progression of vasculopathy. In particular, the role of YAP/TAZ in the endothelial response to collagen IV and laminin is an important observation that fits within the current paradigm of how changes in the biomechanical properties of the ECM can influence the genetic activity and local behavior of smooth muscle and endothelial cells within remodeled vessels (12). It is worth speculating about whether changes in the local composition and/or integrity of the BM could also trigger more dramatic changes in vascular cells, such as induction of endothelial-to-mesenchymal transdifferentiation, pericyte detachment and hyperplasia, metabolic switch, and senescence (13–15). In light of the growing efforts to carry out deep phenotyping of samples from patients with PAH, assessments of the ECM and BM should be undertaken, as the development of experimental models to mimic the lung environment will require a comprehensive understanding of how the composition of the BM can influence cell behavior independently of growth factors or potential therapeutic agents. With the advent of novel technologies such as synchrotron-based lung imaging and three-dimensional printing (16, 17), it is now possible to go beyond molecular and genetic studies to model the actual environment in which the cells carry out their activities.

In light of the complexity underlying the ECM–cell interaction, it is worth considering whether our current PAH paradigm should start including a "matrix code" to help us conceptualize the close biological connections between cells and their immediate extracellular environment as we seek novel targets for therapeutic development. ■

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