EDITORIAL FOCUS

The extracellular matrix in early and advanced pulmonary arterial hypertension

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The extracellular matrix (ECM) is known to be of crucial importance for vascular development, homeostasis, and disease, and a review on the role of the ECM in pulmonary arterial hypertension (PAH) is a much needed contribution to the field. In an article recently published in the American Journal of Physiology-Heart and Circulatory Physiology, Thenappan et al. (9) elegantly described possible roles of early ECM changes in PAH pathogenesis.

In summary, the authors suggested that an initiating endothelial injury allows yet-unidentified circulating serum factors to enter the vessel wall to stimulate protease production, leading to the release of growth factors stored in the vascular ECM. The released factors can in turn induce cellular production of a proproliferative matrix, and the ECM turnover also produces bioactive proteolytic fragments. Mechanical cues from increased pulsatility and shear stress as well as loss of bone morphogenetic protein receptor 2 signaling and hypoxia can cause endothelial-to-mesenchymal transition, which is suggested to be one contributing mechanism for the increased collagen deposition and cross-linking seen in PAH. In addition, vascular stiffening further increases ECM deposition through feedback loops, involving the transcriptional coactivators YAP and TAZ as well as microRNAs. The activation of YAP and TAZ also has other, more direct effects on cell metabolism and proliferation, which will enhance vascular remodeling in PAH. Furthermore, elastin degradation is another early event in PAH that affects vascular compliance and cellular function. The tightly regulated balance between proteases and their inhibitors is discussed in the review as well as how inflammation can shift this balance.

Cells and the ECM closely interact, and any change in steady state involves changes in ECM function and composition (3). Figure 1 shows different types of biological effects of the ECM, some of which are described in detail in the review. Figure 1A shows how the ECM can have direct effects on cellular behavior through interactions with cell surface receptors like integrins. Stiffening of the ECM and altered mechanotransduction is an example of this type of process. Direct cell-ECM interactions can influence cell adhesion, migration, and proliferation.

There are also indirect effects of the ECM on cellular function. One example is how negatively charged proteoglycans, abundant in the vascular wall ECM, bind growth factors and either sequester or present the growth factors to their cognate receptors on the cell surface (Fig. 1B). Indeed, many factors central in PAH pathogenesis, like transforming growth factor-β, platelet-derived growth factor B, fibroblast growth factor 2, interleukin-6, bone morphogenetic proteins, and Wnt ligands, are heparin binding, and their bioavailability is therefore potentially regulated by proteoglycans in the ECM (1, 4, 6).

Another important indirect ECM effect is modulation of chemotactic gradients. This is of crucial importance during embryogenesis, where growth factors and morphogens direct the formation of organs and limbs. In diseased states with altered ECM turnover and increased production of growth factors, spatiotemporal signaling may influence cellular migration (Fig. 1C).

The three processes described above can all be modified by regulating ECM turnover, the balance between production and degradation. The type of matrix that is produced is of great importance. Some ECM components are considered to be part of a matrix that can keep cells in a quiescent differentiated state, whereas others induce activation and phenotypic changes leading to proliferation and shifts in the endogenous protein synthesis of the cell. As mentioned above, proteolytic turnover may also release sequestered factors and create bioactive ECM fragments.

In hypoxia-induced pulmonary hypertension, positioning of platelet-derived growth factor B in the peripheral lung creates a chemotactic gradient, as demonstrated by Sheikh et al. (7). In support of this, we have recently shown that the proteoglycan-binding domain of platelet-derived growth factor B is required to direct pulmonary vascular remodeling in mice (8).

ECM composition and modifications of matrix components also have the potential to influence recruitment of inflammatory cells. For example, hyaluronan (HA), which accumulates in the adventitia and in pleiform lesion in PAH, can be modified to form a pathological form of HA in which heavy chains from the serum-derived proteoglycan inter-α-inhibitor (IαI) are covalently attached to the HA backbone. The modified form of HA is more adhesive to leukocytes and may contribute to inflammation in PAH pathobiology (5).

Even though early processes are interesting and important, it is crucial to remember that most patients with PAH are diagnosed at an advanced disease state, beyond the early changes that are the focus of the review. Vascular stiffening is, of course, still highly important in the advanced stages, since pulmonary artery compliance correlates with right ventricular function and survival of the patient. However, the potential
roles of the ECM need to be expanded when advanced disease is discussed. Thenappan and colleagues (9) described how endothelial and smooth muscle proliferative lesions reduce vascular luminal area and increase pulmonary vascular resistance. This is true, but as Heath and Edwards (2) described already in 1958, the intimal reaction can be either cellular or fibrous and fibroelastic. They also stated that the fibrous and fibroelastic neointimas are more common with more advanced disease.

It is our impression, when examining human material from transplanted patients with PAH, that many of the lumen-reducing lesions are rich in ECM with very few cells, just as described by Heath and Edwards (2). The tempting idea of proteases as potential therapeutic targets must therefore be tested carefully, since most animal models do not adequately mimic advanced human disease.

We believe that the ECM plays different roles, depending on the position along the vessel and stage of PAH. What makes it so complex is that different types of vascular lesions are present within the same lung and even within the same vessel, as shown in Fig. 1D. Negatively charged glycosaminoglycan chains of proteoglycans are shown in blue and are seen in neointima, in between cells in the medium, and in the angiomatoid lesion. All three sites are found in the same artery from the same patient, and the roles of the proteoglycans may be very different at the different sites.

As Prof. Wight stated in a recent review, “The challenge is to distinguish between proteoglycan changes that cause disease and proteoglycan changes that result from the disease, because therapeutic strategies will differ upon primary or secondary causation” (10). This is of course true for all groups of ECM components and not only proteoglycans. Therefore, although challenging because of its diversity, the ECM contains numerous highly interesting targets for novel PAH therapies. Blockage of proteoglycan-binding regions and highly specific protease inhibitors are promising future possibilities for specific targeting in PAH pathogenesis. It is likely that several therapeutic strategies need to be combined in patients with advanced disease.

GRANTS

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AUTHOR CONTRIBUTIONS

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