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The message from the matrix – should we listen more closely?

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The lung is the primary gas exchange organ of the human body. To achieve an effective gas exchange, the lung structure is morphologically divided into a micro-porous, parenchymal compartment (alveoli) and connecting airways. These connecting airways, the bronchi, starting from the alveoli upward, grow in diameter to finally form the bronchial tree and conjoin into the trachea. The extracellular matrix (ECM) of the lung is tailor-made to functionally support the gas exchange and efficient air transport. In the interstitium collagen mesh-works lend stabilizing characteristics to the ECM, while proteins like elastin confer elasticity to manage the expansion and contraction during tidal breathing. Rigidity, elasticity and structural compartmentalization was the long held, traditional belief of what the ECM contributed to lung function. Recent advances in understanding ECM-cell interactions however shine light on an alternative, arguably equally important function of the ECM proteins.

In 2010, Ott and colleagues explanted lungs from mice, decellularized the tissue and reseeded these scaffolds with epithelial and endothelial cells to generate functional bio-artificial lungs (1). To illustrate functionality of their reseeded bio-artificial lungs, they implanted them into recipient mice and attached them to the blood circulation. The lungs provided oxygenation of the organism for up to 6 h post transplantation. Clearly, homing of epithelial

and endothelial cells and their attachment to the ECM was sufficient to provide functionality, which suggests the existence of cues in the ECM, that guide specific cells types to their respective compartments. Although, this is in itself was quite remarkable, it still perpetuates the concept of the ECM as a passive, structural support for maintaining lung (cell) function. Excitingly, Kawai *et al.* recently established for the first time, that embryonic stem cells engrafted into decellularized lung matrices, began expressing markers of differentiation towards alveolar type I and II cells as well as club cells, when cultured at an air-liquid interface (2). These studies open the door on alternative roles for the ECM in the lung.

The question that arises is, is the ECM of the lung instructive for cell differentiation? Does the lung ECM provide functional compartments (niches) supporting specific cell function? First evidence to answer these questions were elegantly presented by Burgstaller and colleagues, who reseeded decellularized lungs slices with murine and primary human fibroblasts. Dependent on the location to which the fibroblasts migrated, cell morphology, gene expression and protein phosphorylation were significantly altered, suggesting that the fibroblasts responded directly to the functional compartment or niche they resided within (3). This leaves room for speculation as to how the ECM achieves such a feat. The necessity

for specific ECM proteins to direct cell differentiation functionality has been appreciated in other research fields including tendon repair (4) and the bone marrow (5). The ECM may contribute explicit cues via different routes including but not limited to stiffness of the matrix, accessibility of integrin binding sites, growth-factor binding sites and matrikines (small bioactive fragments that are released from ECM by proteolytic cleavage), with the latter being tightly interwoven with lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), lymphangiomyomatosis, cystic fibrosis (6-10) and recently Andriani and colleagues reported an association with non-small cell lung cancer (11).

The ECM is a dynamic structure that undergoes constant remodeling, through both synthesis of new components and degradation of existing constituents. During aging (12,13) and (lung) disease the balance between synthesis and degradation of the ECM can become disrupted leading to potentially pathological outcomes; for example, emphysema (matrix destruction) in COPD or fibrosis in IPF or around the small airways in COPD. In lung cancer the ECM bed around the tumor is also remodeled, potentially in a manner advantageous to the tumors (14). As the microenvironmental landscape of the ECM within the lung changes the cellular niche, which plays a central role in directing the response of cells that reside within that location, is impacted. The resultant aberrant signals and environmental cues are emerging as key players in disease progression. There is an emerging urgent need for developing tools (both diagnostic and prognostic) that facilitate the monitoring of active ECM changes, separating tissue formation, tissue degradation, and ECM signals in simple non-invasive technologies.

Collagens are among the most abundant proteins, with type I collagen being the most abundant protein, while type II, III, IV, V, VI, IX and XI are all in the list of the top 20 proteins in the body (15). In total there are 28 collagens, derived from 46 distinct genetic chains, each with its own structure and function (16). Very simplistically, the fibrillar collagens (type I, II, III, V and XI) can be considered fibroblast collagens, embodying the main constituents of the interstitial matrix (15). These collagens are mainly structural, supporting the tissue 3-dimensional structure. They are very dense, and are the main collagens in fibrotic accumulations in tissues and around tumors. In the basement membranes directly beneath epithelial or endothelial cells specialized networking collagens are found, predominantly type IV and VIII (17). These collagens allow

for diffusion of oxygen and other nutrients in specialized tissues. Some of the networking collagens are vital for optimal tissue repair response processing of the basement membrane ECM, whereas the fibrillar collagens, may be dangerous collagens adversely accumulating within interstitial spaces (15). Clearly, during tissue remodeling an altered composition of collagens, but also localization of collagens, may affect tissue function. Replacing a specialized networking basement membrane collagen with a crude fibrillar fibroblast collagen, both changes the distribution of proteins but also the function of the surrounding cells.

During tissue remodeling, the small fragments of these collagens (as well as fragments from laminins and elastins) which are released into the circulation (matrikines), may potentially serve as biomarkers for disease (18). With regards to tissue turnover mediated by proteolytic protein degradation during pathological settings of the interstitial ECM, MMP mediated degradation fragments of type I, III, VI collagens have been both shown to be upregulated during exacerbations in COPD (19,20), related to decline of lung function [forced expiratory volume in one second (FEV1)] in COPD (21), as well being prognostic for progression of IPF (10). Andriani and colleagues have now also reported the potential of matrikines in aiding diagnosis of non-small cell lung cancer (11).

Collagens are not just collagens, as they are emerging as important signaling molecules. Importantly, these matrikine fragments are cryptic, meaning that their signaling function is realized only after the protein undergoes processing by degradation during tissue remodeling. These signals are dormant in the tissue, only being activated upon release, as the intact parent molecule does not provide known signaling function.

Type IV collagen: in each of the 6 sub-chains of type IV collagen fragments containing the non-collagenous (NC)1 domain have been shown to be highly anti-angiogenic, targeting the function of epithelial and endothelial cells. As a consequence, these matrix fragments are recognized to be not only a structural part of the ECM of the basement membrane, but also part of essential tissue signaling homeostasis; these fragments are known as arresten, canstatin, tumstatin, terastatin, pentostatin and hexastatin. Tumstatin in the most well investigated to date (6,8,17).

Type VI collagen. The pro-peptide of type VI collagen, is now also recognised as a collagen hormone known as endotrophin. It is produced by fibrotic fibroblasts and associated with insulin resistance. Endotrophin levels have been shown to be predictive of mortality (19) and

exacerbations (9) in COPD patients, to predict response to insulin sensitizers in type 2 diabetes patients (13), and related to outcome (death) in many malignant oncologies (22).

Type VIII collagen. The pro-peptide of type VIII collagen is also known as vastatin. Vastatin has been shown to be as potent as endostatin in its anti-angiogenic effects on endothelial cells, and to exhibit anti-migratory effects on epithelial cells (23).

Type XV collagen. While it has been recognized as existing, much less is known about the NC1 domain of type XV collagen, Restin. While holding potent anti-migratory effects, much still remains to be understood about the tissue expression, pathological relevance and exact role of this matrikine (24).

Type XVIII collagen. Probably the most famous fragment of a collagen, endostatin is also a fragment originating from the NC domain of type XVIII collagen. It is currently thought to be the most anti-angiogenic fragment produced endogenously in the body, and also has similar anti-migratory effects on epithelial cells (25). Its potential importance in mechanisms underlying lung diseases has also been identified (26)

Taken together, this impressive list of signaling fragments released during tissue remodeling with clear effects on the surrounding cells, may play important roles in the initiation and progression of disease. The cells are clearly listening to the matrix, as, possibly, should biomarker developers and those striving to develop new drugs targeting lung pathologies.

Some of these collagen fragments have already been revealed to provide capacity to segregate COPD patients into different phenotypic groupings and have shown potential for identifying those patients who are actively progressing, i.e., experiencing a decreased lung function and increased exacerbations (27). There is an immediate need to understand tissue remodeling in relation to tissue functional loss, with the ultimate goal of monitoring reversal of this impairment. Given that the ECM changes with aging it will be important to understand what is the aging related signature and what is an indication of a pathological process in the lung.

Markers are needed to help select the patients in most need of treatment, and to provide informed decisions about which patients to include in clinical trials, thereby allowing drug developers shorter and smaller studies to identify efficacious treatments for restoring lung function already in phase II studies (27). Such biomarkers are ideal candidates for personalized health care approaches,

allowing for early diagnosis, prognosis of patients in need of treatment and to define the best treatment regimen on a personalized basis, prediction of responders to a given treatment, and lastly allowing a monitoring tool for patents, making sure that an early surrogate of clinical efficacy is presented to patients, as described under the BEST guidelines developed by the FDA.

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Footnote

Conflicts of Interest: Dr. Karsdal declares that he is a full-time employee and stock holder of Nordic Bioscience, a company engaged in the discovery, development and commercialization of biomarkers. The other authors have no conflicts of interest to declare.

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