Cell–matrix interactions in lung disease and regeneration: ERS Lung Science Conference 2018 report

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Imbalances in cell–matrix interactions perturb normal cell function and contribute to a range of respiratory diseases, including those associated with abnormal lung development, acute lung injury, pulmonary fibrosis, airway remodelling and cancer http://ow.ly/AVXi30k3QPT

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The extracellular matrix (ECM) is essential for the maintenance of tissue architecture, anchoring cells and sustaining normal tissue function. Cells sense and functionally respond to their physical three-dimensional (3D) environment by translating ECM interactions, as well as mechanical forces and deformations, into subsequent cell signalling events. Imbalances in these reciprocal interactions between cells and their ECM perturb normal cellular function and contribute to a diverse range of respiratory diseases, including those associated with abnormal lung development, acute lung injury, pulmonary fibrosis, airway remodelling and cancer [1]. The aim of the European Respiratory Society (ERS) Lung Science Conference (LSC) 2018 was to provide a state-of-the-art review of current understanding of the role of the perturbations of cell–matrix interactions as determinants of cell fate and function across the spectrum of respiratory diseases and lung regeneration. The conference took place on March 8–11, 2018 in Estoril, Portugal, and was regarded as an outstanding forum for the discussion of novel scientific concepts on cell–matrix interactions as well as their dysregulation in lung disease.

The stage for the conference was set by Paul Noble (Cedars-Sinai Medical Center, Los Angeles, CA, USA), who gave the opening lecture and presented his expert view on the interaction of Toll-like receptor 4 with the ECM component hyaluronic acid and how this cell–matrix interaction shapes renewal of alveolar epithelial type II cells in the lung [2]. His seminal work establishes hyaluronic acid not only as an immune regulator but also as a regulator of stem cell renewal.

In the first scientific session, which was focused on matrix remodelling in lung disease, Tracy Hussell (University of Manchester, Manchester, UK) introduced the concept of training of cells by ECM cues with a particular focus on the interactive relationship between bronchial basal cells with their basement membrane in chronic obstructive pulmonary disease (COPD) and in response to lung infection.

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Importantly, cellular training appears not to be substantially mediated by soluble factors but rather relies on definitive cues provided by the instructive matrix [3]. Tracy Hussell's group demonstrated that inflammatory processes as well as virus infections alter the composition of the basement membrane in the bronchial epithelium, such as the expression of hyaluronic acid. As a consequence, basal cells respond by increased proliferation and expression of matrix components and immune cells are attracted. This topic is discussed in greater detail in the accompanying mini-review in this issue of the *European Respiratory Review* (*ERR*) by Hussell *et al.* [4].

Martin Kolb (McMaster University, Hamilton, ON, Canada) stressed the impact of mechanical tension acting in combination with altered biochemical signals as a key driver of altered cell behaviour and fibrogenesis in the lungs of patients with idiopathic pulmonary fibrosis (IPF). With his provocative statement that "breathing is bad for you", Martin Kolb proposed that not only matrix stiffness but also the mechanical sensing of cells activates the profibrotic cytokine transforming growth factor (TGF)-β and attracts mast cells to the site of mechanical stress [5]. Targeting the mechanosensing machinery may thus represent an innovative conceptual approach for the development of novel therapeutic approaches in IPF [6]. This topic is discussed in greater detail in the accompanying mini-review in this issue of the *ERR* by Upagupta *et al.* [7].

Danielle Park from Erik Sahai's group (The Francis Crick Institute, London, UK) presented the concept of cancer cell invasion along defined ECM structures. Using fraction-force microscopy, her work revealed a reciprocal relationship between fibroblasts and the matrix in shaping the alignment of ECM molecules and at the same time being shaped by defined ECM structures.

The second scientific session of the conference focused on matrix–cell interactions. Kristian Riesbeck (Lund University, Malmö, Sweden) explored how pathogens hack into the ECM by binding to ECM components to influence the host response to infection. One prominent example is the binding of microbes to vitronectin, which allows them to escape detection and killing by the complement system [8]. This topic is also discussed in greater detail in the accompanying mini-review in this issue of the *ERR* by Paulsson and Riesbeck [9].

Robert Snelgrove (Imperial College London, London, UK) focused on the major matrikine, Pro-Gly-Pro (PGP), an ECM-derived neutrophil chemoattractant, which has been implicated in multiple chronic lung diseases ranging from COPD and cystic fibrosis to asthma. Failure of the PGP-hydrolysing enzyme leukotriene A_4 hydrolase to efficiently degrade PGP augments neutrophilic responses to bacterial infections and drives epithelial proliferation and remodelling in these diseases. This topic is discussed in greater detail in the accompanying mini-review in this issue of the *ERR* by Patel and Snelgrove [10].

Yuval Rinkevich (Comprehensive Pneumology Center, Munich, Germany) presented novel data on specialised fibroblasts in a skin wound-healing model [11]. Using sophisticated lineage tracing and live-imaging methods, his group was able to identify different types of mouse embryonic fibroblasts that possess divergent wound-healing capacities: while early embryonic fibroblasts are able to completely resolve skin wounds, fibroblasts from later developmental stages lose this capacity and instead contribute to scar formation. Notably, once the wound-healing fibroblasts are transplanted onto adult scars, they lose their ability for wound healing and form scars instead, highlighting the importance of the instructive matrix in the formation of scar tissue. These data thus elucidate a cell intrinsic pathway of wound healing, which might be exploited to switch fibrotic/scarring responses into regenerative responses in the context of chronic lung disease.

The third scientific session focused on the concept of how the ECM instructs cells. Bernhard Wehrle-Haller (University of Geneva, Geneva, Switzerland) explored the concept of mechanosensing at a molecular level, focusing on how the architecture and mechanical properties of the ECM are transformed into biochemical information controlling cell adhesion, migration and survival [12]. In this model, a mechanosensory switch mediates recruitment of adhesion molecules that are anchored to the matrix. Tensile forces influence integrin signalling *via* signalling adapter proteins, such as paxillin. This signalling network controls the actin cytoskeleton of the cell as well as its adhesive and motile functions. Lysine acetylation links cellular metabolism and adhesion, *via* regulation of β1 integrin.

Michael Beers (University of Pennsylvania, Philadelphia, PA, USA) asked the provocative question "When is an epithelial cell an alveolar epithelial cell?" [13]. He addressed this by first reviewing the literature on the experimental approaches investigators have taken to determine the particular properties that define the specialisation of this type of pulmonary epithelial cell. These approaches include the generation of engineered alveolar epithelial cells from induced pluripotent stem cells, as well as *in vivo* approaches using reporter or inducible mutant mice. Michael Beers further proposed that the alveolar epithelial cell is a Jekyll and Hyde cell, in that it is both the defender of the alveolar niche but also a driver of disease.

He outlined the specialised phenotype that facilitates this diversity in function. The alveolar epithelial cell phenotype is linked to surfactant metabolism as well as the synthesis, processing and storage of diverse cargo in unique lysosomal-related organelles.

As the pre-dinner speaker, Peter Friedl (Radboud University, Nijmegen, the Netherlands) provided fascinating and entertaining insights into cell–matrix interactions using state-of-the-art imaging approaches with a major focus on the mechanisms underlying cell migration, particularly during tumour invasion, using organotypic cultures [14]. His superb images, generated by two-photon microscopy, showed how cellular and subcellular structures can be studied during tumorigenesis and thereby visualised the dynamic progression of cancer *in vivo*. Peter Friedl's work emphasises the importance of studying cell–matrix interactions to understand basic biological concepts.

The fourth scientific session focused on novel bioengineering approaches to reconstruct the matrix in the lung. Generating systems to study human lung cells *ex vivo* has long been a challenge. Ramon Farré (University of Barcelona, Barcelona, Spain) talked about how investigators are taking advantage of novel 3D printing technology to fabricate synthetic lungs. The concept of bioprinting is generally well established, and allows printing of a cell suspension into a tissue construct in the presence or absence of a tissue support. For lungs, however, it is still in its infancy. Given the structural complexity of the lung as an organ, this is perhaps not surprising. Nevertheless, substructures of the lung have been developed using this technique. An air–blood barrier has been engineered, comprising layers of endothelial cells and epithelial cells with a basement membrane, as a precursor to an advanced 3D lung model that would enable high-throughput screening for drug efficacy and toxicity testing in the future [15]. Ramon Farré stressed how cell function differs in a 3D system compared to a 2D system, emphasising the need for systems that enable cells to be grown in 3D. Ideally these systems would incorporate the mechanical stimuli that pulmonary cells face, such as ventilation stretch and sheer stress.

An alternative method of studying lungs *ex vivo* was presented by Darcy Wagner (Lund University, Lund, Sweden), who discussed how acellular scaffolds from complex organs such as the lung are being used as a vehicle for study of cell–matrix interactions. There are major hurdles to be overcome before decellularisation is routine, with the challenge of scaling up the procedure to produce an acellular human lung. However, decellularisation of human cadaver lungs retained ECM architecture, and using 3D bioprinting and decellularised lung together with thermography analysis confirmed preservation of airways and vascular routes. This topic is discussed in greater detail in the accompanying mini-review in this issue of the *ERR* by Gilpin and Wagner [16].

The final session explored novel therapeutic strategies to modulate ("drugging") the matrix. Morten Karsdal (Nordic Bioscience, Herlev, Denmark) introduced the concept of neoepitopes of matrix molecules serving as novel prognostic biomarkers for monitoring disease progression in diseases associated with the excessive deposition of matrix, including IPF, as well as in diseases associated with tissue destruction, such as COPD. Morten Karsdal argued that these biomarkers may provide better diagnostic tools for identifying specific phenotypes of patients who progress to develop either emphysema or fibrosis in response to a specific pathological driver. As well as their application in clinical trials, these biomarkers will enable a deeper understanding of the essential ECM–cell interactions following tissue injury and the development of chronic respiratory disease.

The final presentation of the meeting was given by Gisli Jenkins (University of Nottingham, Nottingham, UK), who focused on the recent impact of major multi-institutional genome-wide association studies in both confirming known genetic risk factors for the development of IPF, as well as identifying novel genetic variants associated with IPF susceptibility. Gisli Jenkins highlighted novel insights on some of the key profibrotic signalling pathways underlying the development of progressive fibrosis, in particular in terms of integrin-mediated TGF-β1 activation pathways. The identification of the novel genome-wide significant signal of association with IPF susceptibility near *AKAP13* (A-kinase anchoring protein 13), a Rho guanine nucleotide exchange factor regulating activation of RhoA, highlighted the prospect of targeting the RhoA pathway in patients with IPF [17].

The conference also highlighted the advances in proteomic technologies to resolve the dynamics of ECM remodelling and signalling in a time- and space-resolved manner. Several oral and poster presentations by early career researchers focused on phospho-proteomic analysis of mechanosensing and interactome analysis of the pulmonary basement membrane (Herbert Schiller's group), time- and space-resolved proteomics of the ECM in the lung (Gunilla Westergren-Thorsson's group), and changes in the proteome upon influenza infection or in COPD lungs, in mesenchymal cells of the lung as well as in cancer cells. Among those, Catharina Müller (Lund University, Lund, Sweden) was awarded the LSC 2018 William MacNee Award for her presentation on mass-spectrometry approaches in transplanted lungs coupled with laser-capture microdissection. The oral presentation prize talk was awarded to Marco Nikolic from Emma

Rawlins' group (University of Cambridge, Cambridge, UK), who presented his novel data on the development of genetically modifiable 3D organoid culture of human embryonic lung stem cells to study human lung development *in vitro*. As in previous years, the poster sessions were again of an excellent scientific standard, well-attended and very lively. The selection of eight distinguished poster prize winners proved very challenging to the judges.

Collectively, this year's LSC highlighted the importance of the local 3D ECM niche in influencing cellular behaviour and dysfunction in lung disease. Cell–matrix interactions are delicately fine-tuned by mechanosensing and signalling pathways that need to be considered when studying the diseased lung. The past years have led to tremendous technological advancements with regard to the proteomic dissection of components and crosslinking of the ECM, even down to defined tissue structures, as well as in the area of *in vivo* imaging of defined cell types and alignment of matrix structures. These recent advances have not only identified matrix components as drivers of lung diseases but also highlighted the prospect of therapeutically targeting these changes, as well as their potential exploitation as novel biomarkers. This work is allowing a more comprehensive understanding of the 3D interplay between cells and their surrounding matrix, and how this delicate interaction is disturbed in disease but can be potentially targeted for therapy.

Next year, the 17th ERS LSC will take place on March 7–10, 2019, and will focus on "Mechanisms of acute exacerbation of respiratory disease" (www.ersnet.org/congress-and-events/mechanisms-of-acute-exacerbation-of-respiratory-disease). Rachel Chambers (University College London, London, UK) and the LSC 2019 Programme Coordinators, Ken Bracke (Ghent University, Ghent, Belgium), Toby Maher (Imperial College, London, UK) and Benjamin Marsland (Monash University, Melbourne, Australia), are already working on an exciting programme with an excellent line-up of keynote speakers. We encourage you to contribute to excellence in respiratory science by submitting abstracts and joining us and the LSC community in Estoril next March.

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