Mechanistic overlap between chronic lung injury and cancer: ERS Lung Science Conference 2017 report

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The aims of the European Respiratory Society (ERS) Lung Science Conference (LSC) are three-fold: to present the very best of international lung science research; to highlight new discoveries likely to have an impact on the future of respiratory medicine; and to encourage debate and interaction between emerging investigators and established leaders in the field. The 15th ERS LSC, held in Estoril, Portugal, on March 23–26, 2017, was focused on the mechanistic overlap between chronic lung injury and cancer. Epidemiological studies have shown increased risk of lung cancer development in individuals with chronic obstructive pulmonary disease (COPD) as an independent risk factor [1, 2]. Studies dating back to 1977 had already made the link and concluded that "lung cancer and COPD share a common familial pathogenetic component associated with pulmonary dysfunction" [2]. More recent studies have confirmed this pathogenetic overlap with the observation that common bronchial epithelial gene expression signatures exist for (ex)-smoking and squamous cell lung cancer [3]. Emerging evidence suggests that progressive lung scarring in the context of idiopathic pulmonary fibrosis (IPF) similarly represents a risk factor for lung carcinogenesis, although causality remains to be definitively established [4], Given that chronic lung diseases such as COPD and IPF occur more frequently in elderly individuals, and that the hallmarks of ageing are closely linked with the hallmarks of cancer development [5], such an overlap is perhaps not entirely surprising. Nonetheless, only limited genetic and mechanistic studies on the specific overlap between chronic lung disease and cancer have been reported, underscoring the urgent need for further scientific investigation in this area. The 15th ERS LSC was entirely dedicated to this topic, aiming to foster scientific interactions in order to move this exciting and rapidly evolving concept forward, with a view to developing effective therapeutic approaches for the many patients affected.

To set the stage for the conference, Gary Anderson (University of Melbourne, Melbourne, Australia) opened proceedings with a thought-provoking lecture on targeting the lung cancer–inflammation nexus,

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with a particular focus on insights gleaned from recent research using Src family kinase mutants to redirect macrophage phenotypes that not only promote and sustain cancer but can also cause primary disease. A key take-home message emerging from this field is that mutations that cause cancer also trigger and shape inflammation. Conversely, inflammatory events, such as pneumonia, early on in the disease process of a patient with chronic lung disease, may predispose to loss of lung function and lung cancer development later in life.

Pathological and mechanistic disease similarities were also the main topic of the first scientific session, in which Sam Janes (University College London, London, UK) discussed the concepts of molecular imprinting in lung cancer development and ongoing work from his laboratory focusing on defining the epigenetic and genetic signature of pre-invasive cancer lesions, in order to determine the natural history of these lesions, their cellular origin, and the key pathogenetic steps in cancer evolution.

Barry Stripp (Cedars-Sinai Medical Center, Los Angeles, CA, USA) followed up on the concept of the importance of abnormal repair processes leading to remodelling of the distal lung. Much evidence indicates that initiation and/or progression of chronic lung disease is linked to progenitor cell dysfunction. However, our current understanding of the nature of the epithelial progenitor cells that regenerate damaged airways of the human lung and alveoli and the mechanisms that regulate their behaviour during critical stages of repair or pathological remodelling is still evolving. Recent work from Barry Stripp's laboratory in the setting of IPF has shed important light on how epithelial progenitor cell dysfunction contributes to defective repair, focusing on the potential roles of altered p53 signalling as a common mechanistic link between chronic lung disease and lung cancer.

In line with this topic of shared pathways of abnormal repair in lung cancer and chronic lung disease, Carla Kim (Boston Children's Hospital, Boston, MA, USA) presented recent work from her laboratory focused on the identification of lung stem cells in lung cancer. It is now recognised that multiple stem and progenitor subpopulations participate in the repair process in the lung. In a mini-review in this issue of the *European Respiratory Review* (*ERR*), Kim [6] elaborates further on this topic, by describing the molecular pathways involved in stem cell biology as well as novel organoid models that allow the investigation of the mechanisms by which stem cells interact with endothelial and mesenchymal cells in their niche.

Related to this topic, Georgios Stathopoulos (University of Patras, Rio, Greece) discussed the role of airway and distal lung progenitor cells in tissue repair and disease, describing progenitor cell subpopulations and their hierarchy in the lung. Recent discoveries into the plasticity of gene expression profiles, as well as localisation of airway and alveolar progenitors, raise discussion of how these populations contribute to tissue repair in chronic lung disease. This topic is also discussed in greater detail in the mini-review by Spella *et al.* [7] in this issue of the *ERR*.

Diseases associated with chronic lung injury and lung cancer also share an important immunological component that is characterised by a failure of the immune system to adequately restore normal tissue homeostasis. Marie-Caroline Dieu-Nosjean (Cordeliers Research Centre, Paris, France) discussed the potential role of tertiary lymphoid structures in lung cancer development. Tertiary lymphoid structures are characterised by the presence of T-cells, proliferating B-cells and mature dendritic cells, and are found both in tumours and in inflamed and infected tissues. The link between the presence of tertiary lymphoid structures and lung cancer outcomes was discussed. The presence of mature dendritic cells is associated with better survival, whereas regulatory T-cell infiltration of nonsmall cell lung cancer is associated with worse outcomes. Karim Vemaelen (Ghent University, Ghent, Belgium) discussed a closely related subject of how immune corruption is a key hallmark of the tumour microenvironment. A picture is now emerging that the phenotypical and functional heterogeneity of the pulmonary dendritic cell system can also have an impact on the fate of lung tumours. While conventional dendritic cells seem able to mount anti-tumoral immune responses, inflammatory monocyte-derived dendritic cells represent a plastic population with the potential to exert tumour-supporting functions.

Given the importance of the stromal microenvironment in dictating stem cell biology, tissue repair and lung cancer, epithelial–mesenchymal interactions was another key topic discussed during this conference. Saverio Bellusci (Justus-Liebig University of Giessen, Giessen, Germany) described how mesenchyme-derived fibroblast growth factors contribute to lung development from the initial stages of lung budding to supporting airway progenitor cells, including club cells, during airway repair in response to injury. The reactivation of developmental epithelial–mesenchymal transition-like programmes in adult cells is further recognised to underlie several pathologies in addition to cancer. This topic was discussed by Angela Nieto (Institucio de Neurociencias, Alicante, Spain), with a particular emphasis on the concept of intermediate epithelial–mesenchymal transition states, where cells express both epithelial and mesenchymal markers, and from which they can revert to the original state or move towards a more mesenchymal phenotype.

This concept may be particularly relevant to the pathogenesis of IPF, where interfering with this process may present several opportunities for therapeutic intervention.

Translation of basic biology to therapeutic applications is key to the development of clinical impact in this field. We have only just begun to understand the mechanistic overlap between lung injury and lung cancer, indicating the need for novel models and therapeutic targets to modify disease. Robert Vries (Hubrecht Institute, Utrecht, the Netherlands) addressed the potential of organoids to serve as models to further our understanding of stem-cell-driven tissue regeneration. Also discussed was the future application of organoid technology to aid the discovery of novel therapeutic approaches and adopt a personalised medicine approach, by linking patient-specific functional profiles of investigational compounds in organoid assays to modification of clinical outcomes in the patient.

The potential re-positioning of immune checkpoint inhibitors from the cancer setting to COPD was discussed by Tom Wilkinson (University of Southampton, Southampton, UK). This concept is further explored in a mini-review article in this issue of the *ERR*, where Wilkinson [8] describes how T-cells from COPD patients express loss of cytotoxic functions and how immune checkpoints may be involved.

Endoplasmic reticulum stress has been implicated in a number of chronic lung diseases, as well as lung cancer. Stefan Marciniak (University of Cambridge, Cambridge, UK) demonstrated how endoplasmic reticulum stress pathways play crucial roles in tumour progression and explored how cancer cells may become dependent on endoplasmic reticulum stress pathways, opening up new avenues for novel therapeutic approaches in lung cancer and chronic lung disease. These concepts are explored in greater detail in the mini-review by Marciniak [9] in this issue of the *ERR*.

Richard Marshall (GlaxoSmithKline, Stevenage, UK) provided an integrated perspective of basic disease mechanisms, and addressed some of the more pragmatic challenges associated with transferring preclinical success to clinical trials and refining approaches to accelerate the clinical development of novel therapeutic agents, with a particular focus on adopting an experimental medicine approach to robustly explore mechanism and target engagement.

In the final talk, Felix Hermann (Apceth Biopharma, Munich, Germany) described the potential of cell therapy for chronic lung diseases. The mini-review by Geiger *et al.* [10] in this issue of the *ERR* elaborates on the potential of mesenchymal stem cell therapy in COPD, acute respiratory distress syndrome, IPF, pulmonary hypertension and bronchopulmonary dysplasia. Although the therapeutic application of (genetically modified) mesenchymal stem cells is still at an early stage, it is noteworthy that the progression from preclinical studies to clinical trials has now been achieved in several disease areas.

A key aspect of the LSC is to provide a platform for emerging investigators to present their work to an international audience. The scientific standard of these presentations was again exceptionally high and the selection of prize winners challenging. Next year, on March 8–11, 2018, the LSC will focus on the role of the extracellular matrix in lung disease and regeneration. Rachel Chambers (University College London, London, UK), together with the LSC 2018 programme coordinators Clare Lloyd (Imperial College, London, UK), Melanie Koenigshoff (University of Colorado, Denver, CO, USA) and Silke Meiners (Helmholtz Zentrum, Munich, Germany), have already established 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 the LSC community.

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