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Dear APSR colleagues,

Cellular and molecular biological research helps us to understand biological process that regulate cell functions and networks between cells in organs and to translate these understandings into clinical approaches to treat diseases and to discover a novel treatment. Learning of the cellular and molecular biology in the lung is important for physicians, scientists, and trainees who are involved in the respiratory medicine. In this issue, we would like to highlight some important findings on recently published studies in this field and to upgrade our knowledge about the lung and the cellular and molecular biology.

Sincerely,

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Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer.

Authors: Hodgkinson CL, Morrow CJ, Li Y, et al.

Reference: Nat Med. 2014; 20(8): 897-903.

URL: <http://www.nature.com/nm/journal/v20/n8/full/nm.3600.html>

Comments: The authors analyzed tumorigenicity of circulating tumor cells (CTCs) from patients with small-cell lung cancer (SCLC). They collected CTCs (expressing epithelial cell adhesion molecule (EpCAM) and cytokeratins), and injected them into immune-compromised mice. Some of them formed tumor, and the resultant CTC-derived explants (CDXs) mirror the donor patient's response to platinum and etoposide chemotherapy. CDXs showed the similarity to the clinical diagnostic specimens in their morphology and expression of neuroendocrine markers. The authors also compared genomic profiles of CTCs isolated from patients to their corresponding CDXs. Whole genome sequence-based copy number aberration (CNA) analysis showed strong correlation between CTCs and the corresponding CDXs. Their CDX models, generated from sequentially available, minimally invasive clinical samples will help us understand SCLC biology and drug-sensitivity.

Bone marrow-derived stromal cells are invasive and hyperproliferative and alter transforming growth factor- α -induced pulmonary fibrosis.

Authors: Madala SK, Edukulla R, Schmidt S, et al.

Reference: Am J Respir Cell Mol Biol. 2014; 50(4): 777-86.

URL: <http://www.atsjournals.org/doi/abs/10.1165/rcmb.2013-0042OC>

Comments: The authors evaluated the contribution of fibrocytes to the progression of lung fibrosis, using the transforming growth factor (TGF)- α transgenic mouse model. Lung epithelial specific overexpression of TGF- α led to increased accumulation of GFP-tagged fibrocytes in the fibrotic lesions. Intravenous transfer of TGF- α -induced fibrocytes augmented the expansion of fibrotic lesions and collagen deposition after TGF- α overexpression. They showed that recruited fibrocytes express less collagen and α -SMA than resident stromal cells but express higher amounts of CD44 and are more invasive. Finally, coculture experiments of resident fibroblasts with fibrocytes showed that fibrocytes stimulated proliferation of resident fibroblasts. These findings elucidate a direct role for fibrocytes in modifying fibrotic lung disease.

Untargeted lipidomic analysis in chronic obstructive pulmonary disease. Uncovering sphingolipids.

Authors: Telenga ED, Hoffmann RF, Ruben t'Kindt, et al.

Reference: Am J Respir Crit Care Med. 2014; 190(2): 155-64.

URL: <http://www.atsjournals.org/doi/abs/10.1164/rccm.201312-2210OC>

Comments: This study describes untargeted lipidomic analysis in induced sputum of patients with chronic obstructive pulmonary disease (COPD), using liquid chromatography and mass spectrometry. More than 1,500 lipid compounds were identified in sputum. The class of sphingolipids was significantly higher expressed in smokers with COPD than smokers without COPD. At single compound level, 168 sphingolipids, 36 phosphatidylethanolamine lipids, and 5 tobacco-related compounds were significantly higher expressed in smokers with COPD compared with smokers without COPD. The 13 lipids with a high fold change between smokers with and without COPD showed high correlations with lower lung function and inflammation in sputum. Twenty (glyco)sphingolipids and six tobacco-related compounds were higher expressed in smokers without COPD compared with never-smokers. Two-month smoking cessation reduced expression of 26 sphingolipids in smokers with and without COPD. Expression of lipids from the sphingolipid pathway is higher in smokers with COPD compared with smokers without COPD. Considering their potential biologic properties, and the observed correlations with important clinical outcomes of COPD, these lipids may play a role in the pathogenesis of COPD. Lipidome analysis may become an important research tool that can lead to new drug targets and possible new biomarkers in COPD.

Cigarette Smoke–Induced Disruption of Bronchial Epithelial Tight Junctions Is Prevented by Transforming Growth Factor- β

Authors: Schamberger AC, Mise N, Jia J, et al.

Reference: Am J Respir Cell Mol Biol. 2014; 50(6): 1040-52.

URL: <http://www.atsjournals.org/doi/full/10.1165/rcmb.2013-0090OC>

Comments: Cigarette smoke exposure is suggested to impair tight junction integrity; however, detailed mechanisms were unclear. The authors showed that CSE decreased barrier function in bronchial epithelial cells showing down regulation of tight junction molecules such as ZO-1, ZO-2, and OCLD. TGF- β is the multifunctional cytokine and it is also able to rescue epithelial barrier functions. So they hypothesized that TGF- β might have protective functions on bronchial epithelium exposed to cigarette smoke. They showed that TGF- β 1 rescued barrier dysfunction, which was induced by CSE, through up-regulation of ZO-1, ZO-2, CLD4, and CLD6. TGF- β is a key mediator for pathogenesis of IP through fibro genesis; however, TGF- β has protective function in epithelial cells which exposed CSE.

Agonistic induction of PPAR γ reverses cigarette smoke–induced emphysema

Authors: Shan M, You R, Yuan X, et al.

Reference: J Clin Invest. 2014; 124(3): 1371-81.

URL: <http://www.jci.org/articles/view/70587>

Comments: Lung myeloid dendritic cells (mDCs) delivered from cigarette smokers activate Th1 and Th17 cells which play important role in developing emphysema. Peroxisome prolifer-

erator-activated receptor γ (PPAR γ) is expressed in APCs such as mDCs and negatively regulates their functions. The authors showed that a significant negative correlation between PPARG expression in mDCs and COPD severity as assessed by the reduced FEV1% in emphysema patients. Conditional knock out of PPAR γ mice spontaneously developed increased inflammation in airways and lung emphysema. Moreover, PPAR γ agonist reverses cigarette smoke-induced lung emphysema. The authors have previously shown that Spp1 gene, which encoding osteopontin (OPN), knock out mice develop attenuated lung inflammation and protected against emphysema induced by cigarette smoke. Spp1 and PPARG double knock out mice did not induced lung emphysema. Thus, OPN/PPAR γ axis is the important for developing lung emphysema.

IL-17 attenuates degradation of ARE-mRNAs by changing the cooperation between AU-Binding Proteins and microRNA16

Authors: Chowdhury S, Dijkhuis A, Steiert S, et al.

Reference: PLoS Genet. 2013; 9(9): e1003747.

URL: <http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1003747>

Comments: IL-17A enhances the production of pro-inflammatory mediators by attenuating decay of the encoding mRNAs. This article studies the mechanism of such attenuation by IL-17A. A major mRNA decay pathway is mediated by AU-rich-element (AREs) in the 3'-untranslated region and ARE-binding proteins (AUBPs) are involved in either mRNA degradation or stabilization. Recently, small non-coding RNA molecules, called microRNAs (miRs) have been implicated in mRNA degradation. This article elucidated that mRNA encoding for IL-8, GM-CSF and IL-6 assembled with various AUBPs in a novel ribonucleoprotein in the presence of miR16 and IL-17A attenuates miR16 expression and promotes the binding of stabilizing AUBPs over that of destabilizing AUBPs, reducing mRNA decay.

Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 mediates apoptosis during lung vascular permeability by regulating movement of cleaved Caspase 3

Authors: Damarla M1, Parniani AR, Johnston L, et al.

Reference: Am J Respir Cell Mol Biol. 2014; 50(5): 932-41.

URL: <http://www.atsjournals.org/doi/abs/10.1165/rcmb.2013-0361OC>

Comments: Apoptosis is a key pathologic feature in acute lung injury. The activation of p38 mitogen-activated protein kinase (MAPK) is linked to the initiation of the apoptotic cascade and the MAPK-activated protein kinase (MK) 2 is one of p38 MAPK's immediate downstream effectors. This article show that LPS induces apoptosis in lung via p38 MAPK-MK2-HSP27 signaling cascade and MK2 plays a critical role in the development of apoptosis and pulmonary vascular permeability, and its effects on apoptosis are in part related to its ability to regulate nuclear translocation of cleaved caspase 3.

A comparative encyclopedia of DNA elements in the mouse genome.

Authors: Yue F, Cheng Y, Breschi A, et al.

Reference: Nature. 2014; 515(7527): 355-64.

URL: <http://www.nature.com/nature/journal/v515/n7527/full/nature13992.html>

Comments: The laboratory mouse shares the majority of its protein-coding genes with humans, making it the premier model organism in biomedical research, yet the two mammals differ in significant ways. To gain greater insights into both shared and species-specific transcriptional and cellular regulatory programs in the mouse, the Mouse ENCODE Consortium has mapped transcription, DNase I hypersensitivity, transcription factor binding, chromatin modifications and replication domains throughout the mouse genome in diverse cell and tissue types. These results illuminated the wide range of evolutionary forces acting on genes and their regulatory regions, and provide a general resource for research into mammalian biology and mechanisms of human diseases.

Reconstructing lineage hierarchies of the distal lung epithelium using single-cell RNA-seq.

Authors: Treutlein B, Brownfield DG, Wu AR, et al.

Reference: Nature. 2014; 509(7500): 371-5.

URL: <http://www.nature.com/nature/journal/v509/n7500/full/nature13173.html>

Comments: Recently, single-cell RNA-seq has emerged as a new powerful approach for characterizing the cell types present in a mixed population. Although bronchial tree transform during development into a densely packed honeycomb of alveolar air has been studied by marker expression analysis and fate-mapping, the mechanisms that control the progression of lung progenitors along distinct lineages into mature alveolar cell types are still incompletely known, in part because of the limited number of lineage markers and the effects of ensemble averaging in conventional transcriptome analysis experiments on cell populations. Using this single-cell genomics approach, Treutlein B et al. defined progenitors and lineage hierarchies, and identify lineage-specific regulatory factors.

Generation of alveolar epithelial spheroids via isolated progenitor cells from human pluripotent stem cells.

Authors: Gotoh S, Ito I, Nagasaki T, et al.

Reference: Stem Cell Reports. 2014; 3(3): 394-403.

URL: [http://www.cell.com/stem-cell-reports/fulltext/S2213-6711\(14\)00235-5](http://www.cell.com/stem-cell-reports/fulltext/S2213-6711(14)00235-5)

Comments: This study demonstrates methods to induce and isolate alveolar epithelial

progenitor cells from human induced pluripotent stem cells. Carboxypeptidase M (CPM) was identified as a surface marker of alveolar epithelial progenitor cells and used for isolating “ventralized” anterior foregut endoderm cells (VAFECs). CPM-positive cells isolated from VAFECs differentiate into alveolar epithelial cells, using a 3D coculture system with fetal human lung fibroblasts. Moreover, 3D coculture differentiation of CPM-positive cells formed spheroids with lamellar-body-like structures and an increased expression of surfactant proteins compared with 2D differentiation. Methods to induce and isolate alveolar epithelial progenitor cells using CPM and consequently generate alveolar epithelial spheroids would aid human pulmonary disease modeling and regenerative medicine.

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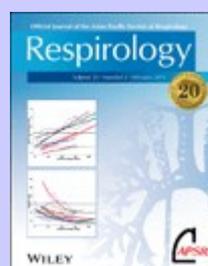
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