

APSR RESPIRATORY UPDATES



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Dear APSR colleagues,

Understanding of the cell and molecular biology of the lung helps clinical respiratory medicine and is important for physicians, scientists, and trainees who are involved in the development of respiratory medicine. Cellular and Molecular biological research will reveal the biological processes that regulate the function of lung cells, translate the understandings into clinical approaches to cure the respiratory disease, and lead to the discovery and development of novel treatment for untreatable diseases. Recently, the methods with cellular and molecular biology are widely used as the tools for the diagnosis and treatment, and thought to be closely related with the clinical medicine. In this issue, we would like to highlight some important findings on recently-published respiratory cellular and molecular biological reports in international journals in order to heighten new knowledge of our specialty, including fibroblasts, epithelial and endothelial cell functions, inflammation, tissue remodeling and fibrosis, cell signaling, siRNA, miRNA, and stem cell biology in respirology.

Sincerely,

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Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, TOKYO, JAPAN

Endothelial Cells Are Central Orchestrators of Cytokine Amplification during Influenza Virus Infection

Authors: Teijaro JR, Walsh KB, Cahalan S, et al.

Reference: Cell 2011; 146: 980-991

URL: [http://www.cell.com/abstract/S0092-8674\(11\)00941-X](http://www.cell.com/abstract/S0092-8674(11)00941-X)

Comments: This study demonstrates that pulmonary endothelium can play a central role in regulating both the recruitment of innate immune cells into the lungs and the excessive proinflammatory cytokine and chemokine production during influenza virus infection. Sphingosine-1-phosphate (S1P)₁ receptor agonist suppressed early proinflammatory cytokine and chemokine production and innate immune cells recruitment during Influenza virus infection. Administration of an S1P₁ agonist suppressed early innate cytokine and chemokine production and significantly improved survival to lethal infection with influenza virus in wild-type mice. S1P₁ receptor was expressed on pulmonary endothelium and lymphocytes, but not on pulmonary epithelial cells. However, S1P₁ agonists also suppressed the virus-induced cytokine storm in lymphocyte-deficient mice, suggesting that pulmonary endothelium is a key regulator of influenza virus-induced cytokine storm. In support of this, pulmonary endothelial cells purified from virus-infected mice showed decreased chemokine production when the mice had received S1P₁ agonists. The authors suggest that the modulation of endothelium with a specific agonist could be a useful strategy for preventing virus-induced immunopathology during influenza virus infection.

Lung Natural Helper Cells Are a Critical Source of Th2 Cell-Type Cytokines in Protease Allergen-Induced Airway Inflammation

Authors: Halim TYF, Krauss RH, Sun AC, et al.

Reference: Immunity 2012; 36: 451-463

URL: [http://www.cell.com/immunity/abstract/S1074-7613\(12\)00085-4](http://www.cell.com/immunity/abstract/S1074-7613(12)00085-4)

Comments: This study shows that the lung contains innate lymphocytes termed lung natural helper (LNH) cells in normal mice and that NHL cells play a critical role as T-cell-independent source of Th2 cell-type cytokines in protease allergen-treated lungs. LNH cells were characterized with Lin⁻ c-kit^{+lo} Sca-1⁺ CD25⁺ CD127⁺ cells. LNH cells rapidly produced large amount of Th2 cell-type cytokines in response to IL-33 and costimulation with IL-2, IL-7, or thymic stroma lymphopoietin (TSLP). Intranasal administration of protease allergen papain induced eosinophil infiltration and mucus hyperproduction in the lung of wild-type and Rag1^{-/-} mice that have LNH cells, but not in Rag2^{-/-} Il2rg^{-/-} mice that lack LNH cells. LNH cells depletion inhibited papain-induced airway inflammation in Rag1^{-/-} mice whereas adoptive transfer of LNH cells enabled Rag2^{-/-} Il2rg^{-/-} mice to respond to papain. Treatment of lung explants with papain induced IL-33 and TSLP production by stroma cells and IL-5 and IL-13 production by LNH cells. Thus, the authors conclude that LNH cells are critical early source of IL-5 and IL-13 in protease allergen-induced airway inflammation.

Multipotent Capacity of Immortalized Human Bronchial Epithelial Cells

Authors: Delgado O, Kaisani AA, Spinola M, et al.

Reference: PLoS ONE 2011; 6: e22023 (1-8)

URL: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0022023>

Comments: This study describes that human bronchial epithelial cells (HBECs) display characteristics of multipotent stem cells of the lung. While the adult murine lung utilizes multiple compartmentally restricted progenitor cells during homeostasis and repair, much less has been known about the progenitor cells from the human lung. Translating the murine stem cell model to humans is hindered by anatomical differences between species. These HBECs expressed markers indicative of several epithelial types of the adult lung when experimentally tested in cell culture. When cultured in three different three-dimensional (3D) systems, subtle changes in the microenvironment resulted in unique responses including the ability of HBECs to differentiate into multiple central and peripheral lung cell types. These new findings indicate that the adult human lung contains a multipotent progenitor cell whose differentiation potential is primarily dictated by the microenvironment. The HBEC system is not only important in understanding mechanisms for specific cell lineage differentiation, but also for examining changes that correlate with human lung diseases including lung cancer.

Reprogramming of Mouse and Human Cells to Pluripotency Using Mature MicroRNAs

Authors: Miyoshi N, Ishii H, Nagano H, et al.

Reference: Cell Stem Cell 2011; 8: 633-638

URL: [http://www.cell.com/cell-stem-cell/abstract/S1934-5909\(11\)00221-9](http://www.cell.com/cell-stem-cell/abstract/S1934-5909(11)00221-9)

Comments: This study demonstrates the possibility of reprogramming mice and human cells to pluripotency by direct transfection of mature double-stranded microRNAs (miRNAs). Induced pluripotent stem cells (iPSCs) can be directly generated from fibroblast cultures by expression of only a few defined factors, such as Oct4, Sox2, Klf4, and c-Myc. Since the initial description of this approach, numerous studies have described modifications of the original protocol using alternative methods, including removable PiggyBac transposons, episomal systems, and Sendai virus. miRNA expression in mouse embryonic stem cells (ESCs), mouse iPSCs, and adult mouse adipose stromal cells (mASCs) were analyzed to identify candidate miRNAs for reprogramming activity, and a combination of mir-200c plus mir-302 s and mir-369 s family miRNAs was transfected to mASCs from the *Nanog* promoter-driven green fluorescent protein (GFP) reporter mice. Since mouse and human cells were successfully reprogrammed to pluripotency, the reprogrammed cell was termed as miRNA-induced pluripotent stem cells (mi-iPSCs). Because this reprogramming method does not require vector-based gene transfer, the authors hope that mi-iPSC generation will eventually prove to be of significant benefit for both biochemical research and clinical regenerative medicine.

Activation of Canonical Wnt Signaling Is Required for TGF- β -mediated Fibrosis

Authors: Akhmetshina A, Palumbo K, Dees C, et al.

Reference: Nature communications 2012; 3: 735 (1-12)

URL: <http://www.nature.com/ncomms/journal/v3/n3/full/ncomms1734.html>

Comments: The authors demonstrate a novel link between TGF- β and the canonical Wnt pathway. They showed enhanced expression of Wnt proteins and decreased expression of the Wnt antagonist Dickkopf-1 in tissue samples from human fibrotic diseases. Wnt signaling stimulated the differentiation of resting fibroblasts into myo-fibroblasts, increased the release of extracellular matrix components *in vitro* and induced fibrosis *in vivo*. Transgenic overexpression of Dickkopf-1 inhibited fibrosis. Of particular interest, they demonstrated on multiple experimental levels that TGF- β activates the canonical Wnt pathway by decreasing the expression of Dickkopf-1 via p38 as major molecular mechanism. These results indicate that the interaction of the canonical Wnt pathway and TGF- β has a key role in the pathogenesis of fibrotic diseases, and inhibition of the canonical Wnt pathway might be a novel approach to prevent the profibrotic effects of TGF- β signaling.

Aclidinium Inhibits Human Lung Fibroblast to Myofibroblast Transition

Authors: Milara J, Serrano A, Peiro T, et al.

Reference: Thorax 2011 doi:10.1136/thoraxjnl-2011-200376

URL: <http://thorax.bmj.com/content/early/2011/09/28/thoraxjnl-2011-200376.full.pdf>

Comments: This paper describes the possible role of aclidinium, a new long-acting muscarinic antagonist, on human fibroblast to myofibroblast transition. The authors showed carbachol, a cholinergic agonist, increased collagen type I and α -SMA mRNA and protein expression in human lung fibroblasts as well as TGF- β 1. Carbachol-induced myofibroblast transition was mediated by an increase in ERK1/2 phosphorylation, RhoA-GTP formation and downregulation of cAMP levels. Aclidinium was shown to inhibit these effects. They also showed that muscarinic receptor activation shared the common downstream pathways with TGF- β 1. Furthermore, aclidinium inhibited the common phenotypic alterations of myofibroblasts such as increased cell proliferation and migration. The authors conclude that, in addition to its bronchodilatory activity, aclidinium may play a role in regulating fibrotic remodelling in chronic inflammatory diseases such as asthma and COPD.

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Development and Preclinical Efficacy of Novel Transforming Growth Factor- β 1 Short Interfering RNAs for Pulmonary Fibrosis

Authors: D'Alessandro-Gabazza CN, Kobayashi T, Boveda-Ruiz D, et al.

Reference: American journal of respiratory cell and molecular biology 2012; 46: 397-406

URL: <http://ajrcmb.atsjournals.org/content/46/3/397.long>

Comments: This study demonstrates that intratracheal administration of aerosolized short interfering (si) RNAs targeting TGF- β 1 is efficacious in two different models, bleomycin-induced and TGF- β 1-overexpressing pulmonary fibrosis. Administration of aerosolized siRNA against TGF- β 1 in bleomycin-induced pulmonary fibrosis mice significantly inhibited TGF- β 1 lung expression and lung fibrosis compared with mice treated with scrambled siRNA or vehicle alone. Aerosolized human-specific siRNAs also efficiently inhibited pulmonary fibrosis and improved lung function, and prolonged survival in human TGF- β 1 transgenic mice. Mice showed no off-target effects after intratracheal administration of siRNA. These results suggest the applicability of these novel siRNAs as tools for treating pulmonary fibrosis in human.

Participant of miR-200 in Pulmonary Fibrosis

Authors: Yang S, Banerjee S, De Freitas A, et al.

Reference: American Journal of Pathology 2012; 180: 484-493

URL: [www.journals.elsevierhealth.com/periodicals/ajpa/article/S0002-9440\(11\)00989-8/fulltext](http://www.journals.elsevierhealth.com/periodicals/ajpa/article/S0002-9440(11)00989-8/fulltext)

Comments: This paper shows that microRNAs (miRs)-200 family members participate importantly in fibrotic lung disease through the inhibition of TGF- β 1-induced epithelial mesenchymal transition (EMT) by miR-200 family members. miR-200a, miR-200b, miR-200c were significantly down-regulated in the lungs of mice with experimental lung fibrosis. Levels of miR200a and miR-200c were reduced in the lungs of patients with idiopathic pulmonary fibrosis. miR-200 had greater expression in alveolar epithelial cells (AECs) than in lung fibroblasts, and the AECs from bleomycin-induced pulmonary fibrosis mice had diminished expression of miR-200. The miR-200 family members inhibited TGF- β 1-induced EMT of AECs and diminished the fibrogenic activity of TGF- β 1 in lung fibroblasts from mice with experimental lung fibrosis and from patients with IPF. Indeed, the introduction of miR-200 into lung diminished experimental pulmonary fibrosis in mice. The authors suggest that restoring miR-200 expression in the lungs may represent a novel therapeutic approach in treating pulmonary fibrotic disease.

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The Tumor Necrosis Factor Family Member LIGHT Is A Target for Asthmatic airway remodeling

Authors: Doherty TA, Soroosh P, Khorram N, et al.

Reference: Nature Medicine 2011; 7: 596-604

URL: <http://www.nature.com/nm/journal/v17/n5/full/nm.2356.html>

Comments: This study describes that the TNF family member LIGHT is essential for airway remodeling in several mouse models of chronic asthma. TNF family member LIGHT was expressed on lung inflammatory cells after allergen exposure. Pharmacological inhibition of LIGHT using a fusion protein between the IgG Fc domain and lymphotoxin β receptor (LT β R) reduced lung fibrosis, smooth muscle hyperplasia and airway hyperresponsiveness in mouse model of chronic asthma, despite having little effect on airway eosinophilia. LIGHT-deficient mice also showed a similar impairment in fibrosis and smooth muscle accumulation. Blockade of LIGHT suppressed expression of lung TGF- β and IL-13, cytokines implicated in airway remodeling in humans, whereas exogenous administration of LIGHT to the airway induced fibrosis and smooth muscle hyperplasia. The authors suggest that LIGHT may be a relevant target for suppressing fibrosis and smooth muscle hyperplasia.



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IL-17A Produced by $\alpha\beta$ T Cells Drives Airway Hyper-responsiveness in mice and Enhances Mouse and Human Airway Smooth Muscle Contraction

Authors: Kudo M, Melton AC, Chen C, et al.

Reference: Nature Medicine 2012; 18: 547-555

URL: <http://www.nature.com/nm/journal/v18/n4/full/nm.2684.html>

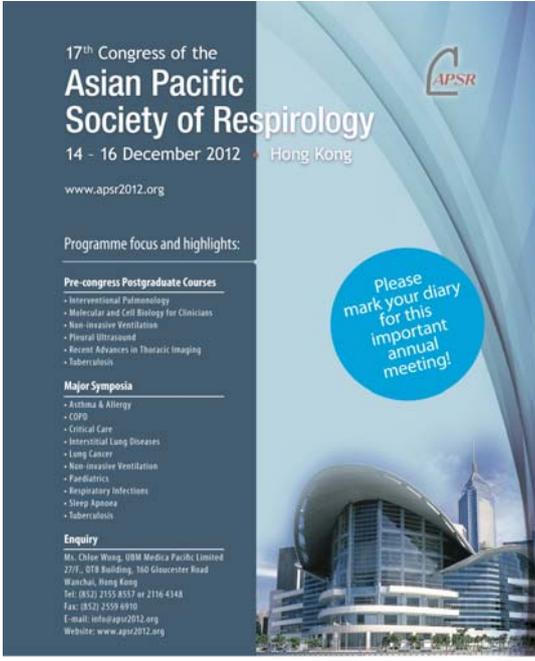
Comments: This study demonstrates that IL-17A produced by Th17 cells contributes to allergen-induced airway hyper-responsiveness through direct effects on airway smooth muscle. Mice lacking the $\alpha\beta 8$ integrin on the dendritic cells did not generate Th17 cells in the lung and were protected from airway hyper-responsiveness in response to house dust mite and ovalbumin sensitization and challenge. IL-17A, but not IL-17F or IL-22, enhanced contractile force generation of airway smooth muscle through NF- κ B, RhoA and ROCK2 signaling cascade. Mice lacking integrin $\alpha\beta 8$ on dendritic cells showed impaired activation of this pathway after ovalbumin sensitization and challenge, and the diminished contraction of the tracheal rings in these mice was reversed by IL-17A. The authors conclude that the $\alpha\beta 8$ integrin, IL-17A, NF- κ B and downstream of this pathway could be attractive targets for improved treatment of allergic asthma.

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