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Inside this issue: Recent Advance in Cell and Molecular Biology of Respiratory Disease

Articles selected and commented on by: **Dr. Hirotaka Matsuzaki, Naoya Miyashita, Kosuke Makita, Yasuhiro Yamauchi, and Takahide Nagase**. Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, TOKYO, JAPAN.

To advertise, subscribe a colleague or to unsubscribe please contact : Secretariat, Asian Pacific Society of Respirology, 2F, UK's Bldg. 2-29-3 Hongo, Bunkyo-ku, Tokyo 113-0033 Japan. Email: apsrinfo@theapsr.org

Brain-derived neurotrophic factor and airway fibrosis in asthma.

Authors: Freeman MR, et al.

Reference: Am J Physiol Lung Cell Mol Physiol. 2017; 313(2):L360-l70.

URL: https://www.physiology.org/doi/10.1152/ajplung.00580.2016

Comments: Recent studies have suggested that locally produced growth factors such as brain-derived neurotrophic factor (BDNF) have a role in mediating and modulating inflammation effects. The authors evaluated the profibrotic influence of BDNF in the context of asthma by examining expression, activity, and deposition of Extracellular Matrix (ECM) proteins in primary airway smooth muscle (ASM) cells isolated from asthmatic vs. nonasthmatic patients. Basal BDNF expression and secretion, and levels of the high-affinity BDNF receptor TrkB, were higher in asthmatic ASM. Exogenous BDNF significantly increased ECM production and deposition, especially of collagen-1 and collagen-3 and the activity of matrix metalloproteinases (MMP-2, MMP-9). Exposure to Tumor Necrosis factor (TNF)-α significantly increased BDNF secretion, particularly in asthmatic ASM, whereas no significant changes were observed with Interleukin (IL) -13. Chelation of BDNF reversed TNFα-induced increase in ECM deposition. Conditioned media from asthmatic ASM enhanced ECM generation in nonasthmatic ASM, which was blunted by BDNF chelation. These data suggest ASM as an inflammation-sensitive source of BDNF within human airways, with autocrine effects on fibrosis relevant to asthma.

A TNFRSF14-FcεRI-mast cell pathway contributes to development of multiple features of asthma pathology in mice.

Authors: Sibilano R, et al.

Reference: Nat Commun. 2016 Dec 16;7:13696.

URL: https://www.nature.com/articles/ncomms13696

Comments: The TNF superfamily member TNFSF14, via interactions with the receptor TNFRSF14, can support Th2 cell generation and longevity and promote airway remodeling in mouse models of asthma, but the mechanisms are incompletely understood. The study demonstrated that mouse and human mast cells (MCs) express TNFRSF14 and that TNFSF14:TNFRSF14 interactions can enhance IgE-mediated MC signaling and mediator production. In mouse models of asthma, TNFRSF14 blockade with a neutralizing antibody or genetic deletion of Tnfrsf14 diminished plasma levels of antigen-specific IgG1 and IgE antibodies, airway hyperreactivity, airway inflammation and airway remodeling. Finally, by analyzing two types of genetically MC-deficient mice after engrafting MCs that either do or do not express TNFRSF14, this study concluded that TNFRSF14 expression on MCs significantly contributes to the development of multiple features of asthma pathology.

Role of IL-17A in murine models of COPD airway disease.

Authors: Yanagisawa H, et al.

Reference: Am J Physiol Lung Cell Mol Physiol. 2017 Jan 1;312(1):L122-L130.

URL: https://www.physiology.org/doi/abs/10.1152/ajplung.00301.2016

Comments: Small airway fibrosis is a major pathological feature of chronic obstructive pulmonary disease (COPD) and is refractory to current treatments. Chronic inflammatory cells accumulate around small airways in COPD and are thought to play a major role in small airway fibrosis. This study demonstrated a role for IL -17A in airway fibrosis using mice deficient in the IL-17 receptor A (il17ra) Il17ra-deficient mice were protected from both airway inflammation and fibrosis in two different models of airway fibrosis that employ COPD-relevant stimuli. Antibody neutralization of IL-17RA or IL-17A confirmed that IL-17A was the relevant pathogenic IL-17 isoform and IL-17RA was the relevant receptor in airway inflammation and fibrosis. These results concluded that the IL-17A/IL-17 RA axis is crucial to murine airway fibrosis.

Inhibition of IL-13-induced periostin in airway epithelium attenuates cellular protein expression of MUC5AC.

Authors: Suzaki I, et al.

Reference: Respirology. 2017; 22(1):93-100.

URL: http://onlinelibrary.wiley.com/doi/10.1111/resp.12873/full

Comments: Serum periostin is increased in asthma and serves as a surrogate marker for IL-13 activity in the lungs. However, there are few studies evaluating periostin protein production from human airway epithelial cells. The authors investigated the secretion of periostin in normal human bronchial epithelial (NHBE) cells, using IL-13. They demonstrated that cultured human airway epithelial cells, in particular goblet cells, produce periostin and that this secretion is dominantly towards the basolateral membrane of the cells. Airway periostin production is regulated by both Janus kinase (JAK)/signal transducer and activator of transcription factor 6 (STAT6) and mitogen activated protein kinase kinase (MEK)/ extracellular regulated protein kinase (ERK) pathways. Inhibiting periostin attenuated IL-13-driven MUC5AC mucin secretion. These findings suggest NHBE cells are an important cell source of periostin production in Th2-derived inflammatory diseases.

ADAM10-mediated ephrin-B2 shedding promotes myofibroblast activation and organ fibrosis.

Authors: Lagares D, et al.

Reference: Nat Med. 2017 Dec;23(12):1405-1415.

URL: https://www.nature.com/articles/nm.4419

Comments: This study discovers a new molecular mechanism of tissue fibrogenesis with a combination of mouse models and clinical samples obtained from individuals with IPF, using molecular, functional and translational experiments. The authors demonstrated that ephrin-B2 in fibroblasts was a potent mediator of lung fibrosis. Then, they identified that soluble form of ephrin-B2, sEphrin-B2, was increased in the lung tissue and the BAL of mice in bleomycin-induced pulmonary fibrosis. The sEphrin-B2, composed of the ectodomain of ephrin-B2, induced fibroblast migration, invasion and myofibroblast differentiation by promoting α-smooth muscle actin (SMA) and type I collagen protein expression. Further, they identified that a disintegrin and metalloproteinase domain-containing protein (ADAM) 10 was responsible for ephrin-B2 ectodomain shedding in fibroblasts. ADAM10-mediated ephrin-B2 shedding contributed to the Transforming growth factor (TGF) -β-induced myofibroblast activation. And, they demonstrated that pharmacological inhibition of ADAM10 prevented ephrin-B2 shedding, myofibroblast formation and bleomycin-induced lung fibrosis. Furthermore, they observed that ADAM10-sEphrin-B2 signaling was upregulated in individuals with IPF. This study suggests that ADAM10-sEphrin-B2 signaling would be potential therapeutic targets for tissue fibrosis.

IL-17A deficiency mitigates bleomycin-induced complement activation during lung fibrosis.

Authors: Cipolla E, et al.

Reference: FASEB J. 2017 Dec;31(12):5543-5556.

URL: http://www.fasebj.org/doi/full/10.1096/fj.201700289r

Comments: IL-17A and complement (C') activation have each been implicated in the pathogenesis of idiopathic pulmonary fibrosis (IPF). This study investigated the role of IL-17A in regulating C' in lung fibrosis. IL-17A induced protein and mRNA regulation of C' components and the synthesis of active C' 3a in normal primary human alveolar type II epithelial cells. Wild-type mice subjected to IL-17A neutralization and IL-17A knockout (il17a-/-) mice were protected against bleomycin (BLEO)-induced fibrosis and collagen deposition. BLEO-induced local C' activation was attenuated in il17a-/- mice. RNAi-mediated gene silencing of il17a in fibrotic mice arrested the progression of lung fibrosis, attenuated cellular apoptosis and lung deposition of collagen and C' (C5b-9). This study concluded that limiting complement activation by neutralizing IL-17A is a potential mechanism in ameliorating lung fibrosis.

ASCL1 and NEUROD1 Reveal Heterogeneity in Pulmonary Neuroendocrine Tumors and Regulate Distinct Genetic Programs

Authors: Mark DB, et al.

Reference: Cell Rep. 2016; 16(5):1259-1272

URL: http://www.cell.com/cell-reports/fulltext/S2211-1247(16)30850-6

Comments: Small cell lung cancer (SCLC) is a high-grade pulmonary neuroendocrine tumor. The transcription factors ASCL1 and NEUROD1 play crucial roles in promoting malignant behavior and survival of human SCLC cell lines. The authors evaluated the heterogeneity in neuroendocrine lung cancer revealed by ASCL1 and NEUROD1 by analyzing bind distinct genomic loci, and regulating mostly distinct genes. They revealed that ASCL1 is present in mouse pulmonary neuroendocrine cells, and only ASCL1 is required in vivo for tumor formation in mouse models of SCLC. ASCL1 targets oncogenic genes including MYCL1, RET, SOX2, and NFIB while NEUROD1 targets MYC. ASCL1 and NEUROD1 regulate different genes that commonly contribute to neuronal function. ASCL1 also regulates multiple genes in the NOTCH pathway including DLL3. Together, ASCL1 and NEUROD1 distinguish heterogeneity in SCLC with distinct genomic landscapes and distinct gene expression programs. Thus, this may have therapeutic implications as a partial inhibition of ASCL1 may substantially attenuate tumor growth in humans.

MYC Drives Progression of Small Cell Lung Cancer to a Variant Neuroendocrine Subtype with Vulnerability to Aurora Kinase Inhibition.

Authors: Gurkan M, et al.

Reference: Cancer Cell. 2017; 31(2):270-285

URL: http://www.cell.com/cell-reports/fulltext/S2211-1247(16)30850-6

Comments: SCLC has historically been treated therapeutically as a homogeneous disease without molecular stratification. SCLC has a bad prognosis with no targeted therapies approved for treatment. Loss of the tumor suppressors RB1 and TP53 and MYC amplification are frequent oncogenic events in SCLC. The authors developed an MYC-driven genetically engineered mouse model that recapitulates key features of human SCLC. Surprisingly, this model mimics a human SCLC subtype characterized by “variant” morphology, high NEUROD1, and low expression of neuroendocrine genes including ASCL1. Targeted drug screening revealed that MYC-driven SCLC is uniquely sensitive to Aurora kinase inhibitors, which dramatically improves chemotherapy response in vivo. These data identify molecular features for patient stratification and uncover a potential targeted treatment approach for MYC-driven SCLC.

Periostin promotes epithelial-mesenchymal transition via the MAPK/miR-381 axis in lung cancer.

Authors: Hu WW, et al.

Reference: Oncotarget. 2017; 8(37):62248-60.

URL: https://doi.org/10.18632/oncotarget.19273

Comments: Periostin has been implicated in the metastatic process of many cancers. However, little is known about the mechanisms involved in periostin-induced epithelial-mesenchymal transition (EMT) and metastatic progression in lung cancer. This study revealed that recombinant periostin induces the EMT process by a shift in expression of cancer cells from epithelial (E-cadherin) to mesenchymal phenotypes (N-cadherin, vimentin, and Twist) in lung cancer cells through the p38/ERK pathway. Moreover, authors demonstrated that periostin regulates EMT by repressing microRNA-381 (miR-381) expression, which is the only microRNA that targets the 3'-untranslated region segments of both Twist and Snail. These findings indicate that changes in periostin expression in lung cancer may serve as a therapeutic target for the treatment of lung cancer metastasis.

NQO1 inhibits proteasome-mediated degradation of HIF-1α.

Authors: Oh ET, et al.

Reference: Nat Commun. 2016; 7:13593

URL: https://www.nature.com/articles/ncomms13593

Comments: Overexpression of NQO1 is associated with poor prognosis in human cancers including breast, colon, cervix, lung and pancreas. But, the molecular mechanisms underlying the pro-tumorigenic capacities of NQO1 have not been fully elucidated. The authors analyzed a previously undescribed function for NQO1 in stabilizing HIF-1α, a master transcription factor of oxygen homeostasis that has been implicated in the survival, proliferation and malignant progression of cancers. They demonstrate that NQO1 directly binds to the oxygen-dependent domain of HIF-1α and inhibits the proteasome-mediated degradation of HIF-1α by preventing PHDs from interacting with HIF-1α. NQO1 knockdown in human colorectal and breast cancer cell lines suppresses HIF-1 signaling and tumor growth. High NQO1 expression levels correlate with increased HIF-1α expression and poor colorectal cancer patient survival. Their insight into PHDs-mediated oxygen sensing machinery in cancer leads to a discovery of a regulator of HIF-1α stabilization that may open up an avenue for anti-cancer therapeutic strategies.

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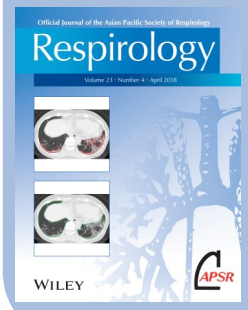

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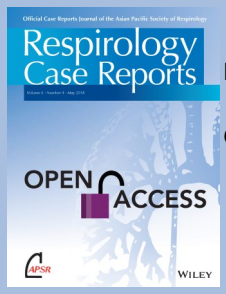

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Articles selected and commented on by Dr. Hirotaka Matsuzaki, Naoya Miyashita, Kosuke Makita, Yasuhiro Yamauchi, and Takahide Nagase. Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, TOKYO, JAPAN.

Editor in chief: Dr David CL Lam, Department of Medicine, University of Hong Kong, Hong Kong, China

Compiled by Dr Christel Norman, Respirology Editorial Office, Perth, Australia