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Inside this issue: Interstitial Lung Diseases

Dear APSR colleagues:

Here you will find the following 10 important articles published in 2013, which I have selected from basic to clinic articles in association with interstitial lung disease (ILD). It is needless to say that the information obtained from "The ATS/ERS statement updated on idiopathic interstitial pneumonias", the importance of "serum VEGF-D as a biomarker of lymphangioleiomyomatosis (LAM)" , or the alveolar damage as a plausible cause of pleuroparenchymal fibroelastosis (PPFE) would directly support our daily clinics, and I also hope that the basic information on genetics, fibrocytes, or specific molecules, such as RAGE or Bach2, may also influence our clinical research in the future.

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An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias.

Authors: Travis WD, et al.

Reference: Am J Respir Crit Care Med. 2013 Sep 15;188(6):733-48.

URL: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201308-1483ST

Comments: This is an update of the American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonias (IIPs) published in 2002, as a supplement to the previous version. In this updated version, nonspecific interstitial pneumonia (NSIP) is now better defined, and respiratory bronchiolitis-interstitial lung disease is now commonly diagnosed without surgical biopsy. A group of rare entities, including pleuroparenchymal fibroelastosis (PPFE) and rare histologic patterns, are introduced. The update outlines advances in the past decade and potential areas for future investigation.

Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis.

Authors: Fingerlin TE, et al.

Reference: Nat. Genet. 45, 613-620, 2013.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3677861/

Comments: This is a genome-wide association study of non-Hispanic, white individuals with fibrotic idiopathic interstitial pneumonias (IIPs; n = 1,616) and controls (n = 4,683), with follow-up replication analyses in 876 cases and 1,890 controls. They confirmed association with TERT at 5p15, MUC5B at 11p15 and the 3q26 region near TERC, and identified seven newly associated loci, including FAM13A (4q22), DSP (6p24), OBFC1 (10q24), ATP11A (13q34), DPP9 (19p13) and chromosomal regions 7q22 and 15q14-15. Their results suggest that genes involved in host defense, cell-cell adhesion and DNA repair, all of which are supposed to contribute the pathogenesis of fibrotic IIPs.

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Identification of seven loci affecting mean telomere length and their association with disease.

Authors: Codd V, et al.

Reference: Nat. Genet. 45, 422-427, 2013.

URL: *http://www.nature.com/ng/journal/v45/n4/full/ng.2528.html*

Comments: There have been several studies suggesting the important pathogenic roles of aberrant biology in telomere. These authors reported a genome-wide meta-analysis of 37,684 individuals with replication of selected variants in an additional 10,739 individuals., and identified seven loci, including five new loci, containing candidate genes (TERC, TERT, NAF1, OBFC1 and RTEL1) that are known to be involved in telomere biology. Considering Lead SNPs at two loci (TERC and TERT) associate with idiopathic pulmonary fibrosis, these results are important for future study on IPF by supporting a causal role of telomere-length variation in age-related diseases.

MUC5B promoter polymorphism and interstitial lung abnormalities.

Authors: Hunninghake GM, et al.

Reference: N. Engl. J. Med. 368 (23), 2192-200, 2013

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747636/

Comments: The authors performed a blinded assessment of interstitial lung abnormalities (ILA) detected in 2633 participants in the Framingham Heart Study by means of volumetric chest CT, and found 177 cases (7%) presenting ILA, which is an amazingly high number. Then they evaluated the relationship between the abnormalities and a common promoter polymorphism (rs35705950) in MUC5B genotype to find out whether this polymorphism is associated with interstitial lung disease in the general population. After adjustment for covariates, for each copy of the minor rs35705950 allele, the odds of interstitial lung abnormalities were 2.8 times greater, and the odds of definite CT evidence of pulmonary fibrosis were 6.3 times greater. The evidence of an association between the MUC5B genotype and interstitial lung abnormalities was greater among participants who were older than 50 years of age. Interestingly, a history of cigarette smoking did not appear to influence the association.

Serum VEGF-D a concentration as a biomarker of lymphangioleiomyomatosis severity and treatment response: a prospective analysis of the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial.

Authors: Young L, et al.

Reference: Lancet Respir Med. 2013 Aug;1(6):445-52.

URL: *http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(13)70090-0/abstract*

Comments: To assess the usefulness of serum VEGF-D concentration as a marker of severity and therapeutic response to sirolimus in patients with lymphangioleiomyomatosis (LAM), the authors analyzed data from the Multicenter International LAM Efficacy of Sirolimus (MILES) trial. LAM patients with FEV1≤70% of predicted were randomly assigned (1:1) to 12 months masked treatment with sirolimus or placebo. As a result, baseline VEGF-D concentrations were higher in patients who needed supplemental oxygen than in those who did not need it and in those who had a bronchodilator response than in those who did not. Although median serum VEGF-D concentrations were similar at baseline in the sirolimus and placebo groups, the serum level of VEGF-D in the sirolimus group decreased at 6 and 12 months but not in the placebo group. In conclusion, serum VEGF-D is a biologically plausible and useful biomarker in LAM that correlates with disease severity and treatment response.

Detection of alveolar fibrocytes in idiopathic pulmonary fibrosis and systemic sclerosis.

Authors: Borie R, et al.

Reference: PLoS One. 2013;8(1):e53736.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547062/

Comments: Because the fibrocytes, circulating precursors for fibroblasts, are increased in patients with idiopathic pulmonary fibrosis (IPF), the authors examined the bronchoalveolar lavage (BAL) of patients with fibrotic lung diseases to assess whether alveolar fibrocytes are detected in them, to identify their prognostic value, and their potential association with culture of fibroblasts from BAL. They detected fibrocytes in BAL in 14/26 IPF (54%) and 5/9 SSc patients (55%), and never in controls. In IPF patients, the number of alveolar fibrocytes was correlated with the number of alveolar macrophages and was associated with a less severe disease but not with a better outcome. Fibroblasts were cultured from BAL in 12/26 IPF (46%), 5/9 SSc-ILD (65%) and never in controls. The detection of BAL fibrocytes did not predict a positive culture of fibroblasts.

Restrictive allograft syndrome post lung transplantation is characterized by pleuroparenchymal fibroelastosis.

Authors: Ofek E, et al.

Reference: Modern Pathology (2013) 26, 350–356.

URL: http://www.nature.com/modpathol/journal/v26/n3/full/modpathol2012171a.html

Comments: Restrictive allograft syndrome (RAS), characterized by restrictive physiology and peripheral lung fibrosis, is a novel form of chronic lung allograft dysfunction after lung transplantation. In their retrospective review of 493 patients, out of 47 patients with clinical features of RAS, 16 had lung specimens available for review, and the authors observed varying degrees of pleural fibrosis in all lungs examined. Fifteen of 16 showed pleuroparenchymal fibroelastosis (PPFE), characterized by hypocellular collagen deposition with preservation and thickening of the underlying alveolar septal elastic network. Interestingly, concurrent features of obliterative bronchiolitis (BO) were present in 14 cases and of diffuse alveolar damage in 13 cases. In conclusion, PPFE is a major histopathological correlate of RAS, and was often found concurrently with diffuse alveolar damage.

Transcription repressor Bach2 is required for pulmonary surfactant homeostasis and alveolar macrophage function.

Authors: Nakamura A, et al.

Reference: J Exp Med. 2013 Oct 21;210(11):2191-204.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3804940/

Comments: Most patients with pulmonary alveolar proteinosis (PAP) are known to have anti-GM-CSF antibody increased in their serum (autoimmune PAP), but secondary PAP is chiefly accompanied by myeodysplastic syndromes (MDS) without association with GM-CSF. This is the first basic study to show the lungs of mice deficient for the B lymphoid transcription repressor BTB and CNC homology 2 (Ba ch2) developed PAP-like accumulation of surfactant proteins in the lungs. The authors found Bach2-deficient AMs showed alterations in lipid handling in comparison with wild-type (WT) cells. Although Bach2-deficient AMs showed a normal expression of the genes involved in the GM-CSF signaling, they showed an altered expression of the genes involved in chemotaxis, lipid metabolism, and alternative M2 macrophage activation with increased expression of Ym1 and arginase-1, and the M2 regulator Irf4. Peritoneal Bach2-deficient macrophages showed increased Ym1 expression when stimulated with interleukin-4. They also improved the PAP-like lesions in Bach2-deficient mice by WT bone marrow transplantation, which may be applicable to clinics in future.

RAGE is a nucleic acid receptor that promotes inflammatory responses to DNA.

Authors: Sirois CM et al.

Reference: J. Exp. Med. 2013 Vol. 210 No. 11 2447-2463.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3804942/

Comments: Because high-mobility group box chromosomal protein 1 (HMGB1) is a key mediator in acute lung injury (AJRCCM 2008) and also in acute exacerbation of IPF (Pulm Med 2011), the mechanism of downstream of its receptor for glycation end-products (RAGE) is important. In this study, the authors showed that RAGE promoted DNA uptake into endosomes and lowered the immune recognition threshold for the activation of Toll-like receptor 9, the principal DNA-recognizing transmembrane signaling receptor. Structural analysis of RAGE–DNA complexes indicated that DNA interacted with dimers of the outermost RAGE extracellular domains, and could induce formation of higher-order receptor complexes. Furthermore, mice deficient in RAGE were unable to mount a typical inflammatory response to DNA in the lung, which is also interesting considering the observation that aged RAGE null mice spontaneously develop pulmonary fibrosis (Am J Pathol 2008).

A progression-free end-point for idiopathic pulmonary fibrosis trials: lessons from cancer.

Authors: Vancheri C, et al.

Reference: Eur Respir J 2013; 41: 262–269

URL: http://erj.ersjournals.com/content/41/2/262.long

Comments: This is a review article insisting on the importance of a progression-free endpoint for idiopathic pulmonary fibrosis clinical trials. Because many clinicians believe that an agent that impedes progression of the disease is more than acceptable, and because of the behavioural and biological similarities of cancer and IPF, the authors set out to argument that the similarities with cancer justify comparing the magnitude of therapeutic effects in clinical trials in nonsmall cell lung cancer with those in successful trials in IPF, and recommend that the demonstration of similar magnitudes of progression-free disease effect in IPF, using appropriate indices, should be considered as clinically meaningful benefit in future phase III clinical trials of novel therapies.

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