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Articles selected and commented on by:
Professor Nobuhiro Tanabe, Department of Advanced Medicine in Pulmonary Hypertension, Graduate School of Medicine, Chiba University, Japan

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Pro-Proliferative and Inflammatory Signaling Converge on FoxO1 Transcription Factor in Pulmonary Hypertension

Authors: Savai R, et al.
URL: [http://www.nature.com/nm/journal/v20/n11/full/nm.3695.html](http://www.nature.com/nm/journal/v20/n11/full/nm.3695.html)
Comments: Pulmonary hypertension (PH) is characterized by increased proliferation and resistance to apoptosis of pulmonary artery smooth muscle cells (PASMCs). Forkhead box O (FoxO) transcription factors are key regulators of cellular proliferation. This study shows that pharmacological inhibition and genetic ablation of FoxO1 in smooth muscle cells reproduce PH features both in vitro and in vivo. Reconstitution of the transcriptional activity of FoxO1 by gene therapy, restored the physiologically quiescent PASMC phenotype in vitro. Either intravenous or inhaled paclitaxel in vivo resulted in changes in cell cycle control and bone morphogenic protein receptor type 2 signaling, and reversed vascular remodeling and right-heart hypertrophy. The possible benefit of FoxO1 for PH refractory to current therapies should be elucidated.

Bottom line: PASMC FoxO1 is a critical integrator of multiple signaling pathways driving PH, and reconstitution of FoxO1 activity offers a potential therapeutic option for PH.

Mitomycin-Induced Pulmonary Veno-Occlusive Disease: Evidence From Human Disease and Animal Models

Authors: Perros, et al.
URL: [http://circ.ahajournals.org/content/early/2015/06/30/CIRCULATIONAHA.115.014207.long](http://circ.ahajournals.org/content/early/2015/06/30/CIRCULATIONAHA.115.014207.long)
Comments: Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension (PH) characterized by obstruction of small pulmonary veins and a dismal prognosis. PVOD may be sporadic or heritable due to mutations of the EIF2AK4 gene coding for GCN2. The authors reported 7 cases of PVOD from the French registry induced by mitomycin-C (MMC) therapy for squamous cell cancer of the anus. The estimated annual incidence of PVOD in anal cancer (3.9/1000) is much higher than the annual incidence of PVOD in the general French population (0.5/million). They also developed a rat PH model using intraperitoneal administration of MMC to produce PVOD. MMC administered to rats was associated with dose-dependent depletion of pulmonary GCN2 and decreased smad1/5/8 signaling. Amifostine prevented the development of MMC-induced PVOD in rats. These experiments have increased our understanding of the pathogenesis, treatment and prevention of PVOD.

Bottom line: MMC therapy is a potent inducer of PVOD in both humans and rats. The rat model could be useful to develop new strategies to prevent and treat PVOD.
Sex Affects Bone Morphogenetic Protein Type II Receptor Signaling in Pulmonary Artery Smooth Muscle Cells

Authors: Mair KM, et al.
URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201410-1802OC

Comments: Women develop pulmonary arterial hypertension (PAH) more frequently than men. However males with PAH have worse right ventricular function and prognosis, and females are protect-ed from PAH in an experimental model (the so called “estrogen paradox”). Decreased bone morphoge-netic protein type II receptor (BMPR-II) signaling is associated with PAH. In this study, estrogen-driven suppression of BMPR-II signaling in non-PAH human pulmonary artery smooth muscle cells (hPASMCs) derived from women contributed to a pro-proliferative phenotype in hPASMCs. Women without PAH had decreased BMPR-II signaling, and this may explain the increased frequency of PAH observed in women.

Bottom line: Estrogen-driven suppression of BMPR-II signaling in non-PAH hPASMCs derived from wom-en contributes to a pro-proliferative phenotype in hPASMCs, and this may predispose women to PAH.

Endothelial-to-Mesenchymal Transition in Pulmonary Hypertension

Authors: Ranchoux B, et al.
URL: http://circ.ahajournals.org/content/131/11/1006.long

Comments: In patients with pulmonary arterial hypertension (PAH), it is generally acknowledged that endothelial-to-mesenchymal transition (EndoMT) may have a role in the development of obstructive pulmonary vascular lesions, which are mainly composed of α-smooth muscle actin-expressing mesenchymal-like cells. However, it is not clear how EndoMT is involved in the development process of vascu-lar lesions. This is the first paper that has shown EndoMT-related processes in experimental and human PAH. EndoMT is linked to alterations in BPMR2 signaling and is involved in the occlusive vascular re-modeling of human PAH.

Bottom line: EndoMT is linked to alterations in BPMR2 signaling and is involved in the occlusive vas-cular remodeling of PAH.
Evaluation of the Microcirculation in Chronic Thromboembolic Pulmonary Hypertension Patients: The Impact of Pulmonary Arterial Remodeling on Postoperative and Follow-Up Pulmonary Arterial Pressure and Vascular Resistance.

Authors: Jujo T, et al.
URL: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0133167
Comments: Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension that is characterized by the presence of organized thrombi in the proximal pulmonary arteries. The development of pulmonary hypertension in this disease is caused not only by the occlusion of proximal pulmonary arteries, but distal pulmonary vascular remodeling can also contribute to elevated pulmonary arterial pressure or resistance. In this study, biopsied lung tissues from 17 CTEPH patients were pathologically analyzed. Both univariate and multivariate regression analysis showed that the extent of pulmonary arteriopathy was positively correlated with pulmonary vascular resistance evaluated at 1 month and 1 year after pulmonary endarterectomy. Interestingly, it was also suggested that pulmonary venopathy might not affect hemodynamics, although the pulmonary venopathy was recognized in most patients.

Bottom line: Residual pulmonary hypertension after PEA could be result from severe pulmonary arteriopathy.

Vascular Repair by Tissue-resident Endothelial Progenitor Cells in Endotoxin-induced Lung Injury

Authors: Kawasaki T, et al.
Comments: Acute respiratory distress syndrome (ARDS) is a severe intractable clinical condition with a high mortality rate in spite of intensive care; therefore, new therapeutic strategies for ARDS are needed. This research using experimental ARDS focused on the vascular repair mechanisms in ARDS, which might be able to ameliorate the disease. In previous reports, bone marrow (BM)-derived and lung tissue-resident endothelial progenitor cells (EPCs) were shown to exist and play a pivotal role in vascular endothelial repair; however, the type of EPCs that are predominant in the repair process is not clear. In this study, the authors demonstrated that lung tissue-resident EPCs rather than BM-derived EPCs play a major role in vascular endothelial repair in endotoxin-induced lung injury. This report strengthens our understanding of vascular biology and sheds light on the participation of EPC’s in the pathological mechanism of ARDS.

Bottom Line: The findings could lead to the development of a therapeutic strategy for ARDS based on the promotion of tissue repair.
Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism: A Randomized Clinical Trial

Authors: Mismetti P, et al.
URL: http://jama.jamanetwork.com/article.aspx?articleid=2279714
Comments: Retrievable inferior vena cava (IVC) filters are frequently used in addition to anticoagulation in patients with acute venous thromboembolism, but their benefit-risk ratio remains unknown. This is the first randomized study that compared anticoagulants alone versus placement of an IVC filter plus anticoagulants, focusing on a reduction of symptomatic recurrent pulmonary embolism in acute pulmonary embolism and a high risk of recurrences. The results of this study showed that, compared with anticoagulants alone, placement of a retrievable IVC filter for 3 months in addition to anticoagulants provided no benefit in terms of pulmonary embolism recurrence or mortality in acute symptomatic pulmonary embolism. These findings do not support the use of this type of filter in patients who are treated with anticoagulants. However, a possible benefit of filters in addition to anticoagulants in other subgroups of patients with massive pulmonary embolism should be elucidated.

Bottom line: This is the first study showing that the placement of a retrievable IVC filter in addition to treatment with anticoagulants provided no benefit in terms of pulmonary embolism recurrence or mortality in acute symptomatic pulmonary embolism.

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial

Authors: Couturaud F, et al.
URL: http://jama.jamanetwork.com/article.aspx?articleid=2382981
Comments: The optimal duration of anticoagulation after a first episode of unprovoked pulmonary embolism (PE) is uncertain. The recent ACCP guideline recommends that after 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy. In this study, patients who had a first episode of unprovoked PE and received 6 months of anticoagulant treatment were randomized to placebo or an additional 18 months of treatment with warfarin. Warfarin reduced the composite outcome of recurrent venous thrombosis and major bleeding compared with the placebo (HR, 0.22 (CI, 0.09-0.55) p<0.001). However, the benefit was not maintained after discontinuation of anticoagulation therapy, suggesting importance of the risk-benefit ratio of extended therapy even after 2 year treatment.

Bottom line: Among patients with a first episode of unprovoked PE who received 6 months of anticoagulant treatment, an additional 18 months of treatment with warfarin reduced the composite outcome compared with placebo.
Multi-Institutional Retrospective Cohort Study of Patients with Severe Pulmonary Hypertension Associated with Respiratory Diseases

Authors: Tanabe N, et al.
Comments: Previous studies have shown that a small number of patients develop severe pulmonary hypertension due to respiratory diseases (severe R-PH). In this multi-centre retrospective study of patients with severe R-PH, they found that the patients treated with phosphodiesterase-5 (PDE-5) inhibitors had a significantly better chance of survival from the date of diagnosis than those who did not receive PDE-5 inhibitors, although the overall prognosis was poor. Although this was a retrospective, observational, cohort study, these findings should form the basis for future prospective, randomized and placebo-controlled studies in this particular patient group.
Bottom line: This multi-institutional retrospective cohort study demonstrated potential survival benefits for those who received PDE-5 inhibitors in severe R-PH.

A New Era of Therapeutic Strategies for Chronic Thromboembolic Pulmonary Hypertension by Two Different Interventional Therapies: Pulmonary Endarterectomy and Percutaneous Transluminal Pulmonary Angioplasty

Authors: Inami T, et al.
URL: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0094587
Comments: Recently, percutaneous transluminal pulmonary angioplasty (PTPA) has resulted in remarkable hemodynamic improvement in inoperable chronic thromboembolic pulmonary hypertension (CTEPH). In this study, the use of interventional therapies (pulmonary endarterectomy or PTPA) resulted in a 98% 5-year survival from the time of diagnosis. This suggests that the use of PEA or PTPA in the current era has improved the prognosis of CTEPH patients compared with that in the previous era, where PEA was the only interventional therapy available. This is the first study to show the survival benefit for PTPA in CTEPH patients.
Bottom line: PTPA is a promising therapeutic strategy to improve the survival in CTPEH patients who are not suitable candidates for PEA.

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Articles selected and commented on by Nobuhiro Tanabe, Department of Advanced Medicine in Pulmonary Hypertension, Graduate School of Medicine, Chiba University, Japan
Editor: Dr David CL Lam, Department of Medicine, University of Hong Kong, Hong Kong, China
Compiled by Dr Christel Norman, Respirology Editorial Office, Perth, Australia

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