Update in Pulmonary Vascular Disease 2016 and 2017

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Since the last update in this series was published in 2015, pulmonary vascular medicine has seen important advances from the molecular to population levels (1). Basic, translational, and epidemiologic science have rapidly advanced the understanding of how genetic, endocrine, immune, and metabolic factors contribute to pulmonary vascular disease. Preclinical and early-stage clinical efforts highlight promising treatments addressing emerging targets in the pathophysiology of pulmonary arterial hypertension (PAH).

Mechanisms of Sex Bias

Prior work exploring the molecular basis of sex bias in PAH, namely increased female susceptibility and survival in PAH, has been focused on the regulation and activity of estrogen in women. The importance of sex hormone activity was recently extended to men with PAH, in whom worse hemodynamic and functional parameters correlate with higher concentrations of estradiol and lower concentrations of dehydroepiandrosterone sulfate (2). Indeed, the observed low concentrations of dehydroepiandrosterone sulfate associated with pulmonary hypertension (PH) risk have been reproduced (3). In mice carrying a pathogenic *BMPR2* (bone morphogenetic protein receptor type 2) mutant gene, inhibition of estrogen activity mitigated experimental PH and normalized critical metabolic signaling axes (4). The aryl hydrocarbon receptor regulates downstream estrogen production in pulmonary vascular cells via both CYP1A1 (cytochrome P450 family 1 subfamily A member 1) and aromatase. The aryl hydrocarbon receptor can be targeted in BMPR2-overexpressing mice (5), increasing microRNA (miR)-29, which recapitulates elevated miR-29 found in heritable pulmonary arterial hypertension (HPAH) lung tissue. By contrast, anti–miR-29 attenuates experimental PH and restores PPAR-γ (peroxisome proliferator-activated receptor-γ) (6). Finally, the Y chromosome appears to protect against experimental PH (7), offering a novel genetic explanation for sex bias in PAH.

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Signaling

Genetic, experimental, and pharmacologic lines of evidence continue to reveal mechanisms by which BMPR2 mutations and dysregulated BMP (bone morphogenetic protein) and TGF-β (transforming growth factor-β) receptor family signaling drive PAH. TNF-α (tumor necrosis factor-α) inhibits BMPR2 expression and promotes post-translational cleavage via ADAM (a disintegrin and metalloproteinase domain-containing protein)-10 and ADAM17 in pulmonary arterial smooth muscle cells (PASMCs), favoring BMP-mediated proliferation via ACVR2 (activin receptor type 2), whereas anti–TNF-α treatment restores BMP signaling and reverses disease progression in experimental PH (8). Linking metabolic dysfunction and idiopathic pulmonary arterial hypertension (IPAH), exposure of PASMCs to high glucose concentrations increases expression of SMURF1, an E3 ubiquitin–protein ligase that dampens BMP signaling and decreases phospho-SMAD1/5/8 (fusion of Caenorhabditis elegans Sma genes and the Drosophila Mad, Mothers against decapentaplegic), mimicking signaling patterns in mutation-negative IPAH-derived PASMCs that are normalized by blocking glucose uptake (9). As a potential regulator of the balance between protective BMPR2 and deleterious TGF-β signaling, elevated miR-130a/301b, previously found in PAH tissues (10), acts downstream of TGF-β1 in PASMCs to downregulate protective BMPR2 and PPAR-γ signaling, consistent with amelioration of experimental PH in TGF-β1–transgenic mice by the PPAR-γ agonist pioglitazone (11, 12). Consistent with the pathogenic role of TGF-β, a selective TGF-β1/3 trap dampened TGF-β–Smad2–plasminogen activator inhibitor 1 signaling and inhibited pulmonary vascular remodeling in experimental PH without cardiotoxicity previously associated with anaplastic lymphoma kinase (ALK) 4/5/7 inhibitors, suggesting a translatable approach (13). SMAD3, typically considered an effector of TGF-β signaling and fibrosis, was paradoxically decreased in PAH lungs and pulmonary arteries (PAs) derived from experimental PH, whereas SMAD3 depletion caused proliferation and migration of PASMCs and pulmonary artery endothelial cells (PAECs) and increased expression of smooth muscle actin in PASMCs mediated by myocardin-related transcriptional factor (14). Expression of HMGA1 (high mobility group AT hook 1) is elevated in PAH versus control PAECs and is coexpressed with smooth muscle markers in obstructive and plexiform lesions, suggesting endothelial-to-mesenchymal transition (15). VEGF3 (vascular endothelial growth factor 3) and hypermethylation of BMPR2 emerged as potential penetrance factors in HPAH. BMP-mediated receptor endocytosis and SMAD signaling are impaired in VEGFR3-deficient zebrafish and mice, the latter of which develop exaggerated experimental PH (16). Hypermethylation of the BMPR2 promoter was more frequent in affected versus unaffected mutation carriers from 11 families (17). The notion that BMPR2 mutations influence vascular structure and development was supported by the observation of dilated and thickened bronchial arteries in BMPR2 mutation–positive (HPAH) versus BMPR2 mutation–negative (IPAH) lungs (18).

MicroRNA Biology

Noncoding RNAs including miRNAs continue to emerge as critical regulators of PAH pathogenesis (19), and an endocrine function of active extracellular miRNAs packaged in microvesicles as a means of cell-to-cell communication in experimental PH was recently supported (20). Specific miRNAs are regulatory factors in metabolic dysregulation, BMP signaling, and cellular plasticity in PAH. A miR-124/PTBP1 (polypyrimidine tract binding protein 1)/PKM (pyruvate kinase muscle isozyme) axis regulates glycolysis in endothelial cells (21) and adventitial fibroblasts (22) to promote cellular proliferation and PH. miR-138– and miR-25–dependent signaling contributes to PH in monocrotaline-exposed rats through impairment of the mitochondrial calcium uniporter complex (23). BMP signaling in PAH appears to be regulated by miR-140-5p via its effects on SMURF1 (24), and miR-204 induces transdifferentiation of smooth muscle to osteoblast-like cells, potentially enhancing calcification of diseased PAs (25).

Stem Cell Technology

Inducible pluripotent stem cells (iPSCs) are stem cells that can be reprogrammed directly from adult cells and subsequently can be differentiated *in vitro* into a variety of mature cell types, including cardiopulmonary vascular cells. iPSCs retain their original genomic sequences from their individual donors and thus have been used advantageously to model the role of BMPR2 in HPAH (26, 27). iPSCs hold promise for future strategies for "retuning" BMP signaling that are difficult to test in traditional cellular or animal models, thus potentially facilitating high-throughput drug screening in PAH.

Vascular Stiffness

Vascular stiffness has emerged as a key pathogenetic driver in PAH (28, 29), with evidence that vascular matrix stiffness is an early, pervasive driver of many types of PAH (30, 31) that is regulated via mechanoactivation by two related transcriptional coactivators, YAP (Yes-associated protein) and TAZ (transcriptional co-activator with PDZ-binding motif), members of the Hippo signaling pathway. Their activation initiates vascular cell proliferation in PAH (32), in part via anaplerosis, a metabolic pathway that replenishes tricarboxylic acid cycle intermediates, providing cellular biomass for hyperproliferative vascular phenotypes in PAH (33).

Vascular Tone

Identification of loss-of-function mutations in the *KCNK3* (potassium two-pore domain channel subfamily K member 3) gene in HPAH led to the elucidation of its impact in plasma membrane depolarization and regulation of pulmonary arterial tone, vascular remodeling, and consequent PH *in vivo* (34). Omega-3 fatty acids such as docosahexaenoic acid regulate pulmonary vascular tone in PH (35) via activation of the calcium-activated potassium (KCa) currents in PASMCs and pulmonary vasodilation. Hemoglobin-α, an avid scavenger of nitric oxide in diseased vascular endothelium, also contributes to altered pulmonary vasomotor tone in PAH (36).

Other Signaling Pathways

Emerging targets in PAH include Notch signaling, a system of ligands and transmembrane receptors that regulate embryonic development and vascular homeostasis. Whereas Notch3 is known to control proliferation and differentiation in PAH (37), Notch1 is a crucial regulator of endothelial proliferation and survival (38), and Notch2 is a key effector bridging

BMPR2 and TNF signaling in PAH (8). The important role of osteoprotegerin in PAH continues to be further elucidated (39). The therapeutic potential of rescuing expression of SERCA2A (sarcoplasmic reticulum Ca^{2+}-ATPase 2a) in pulmonary vascular remodeling and right ventricular (RV) dysfunction has been reported (40).

The effect of pulmonary vascular tone on RV energy use is increasingly recognized. Among treatment-naive patients with PAH, the administration of prostacyclin improved RV stroke volume through a reduction in end-systolic volume that was modulated predominantly via improved RV contractility and decreased diastolic stiffness (41). These data and findings derived from other similar studies (42) imply an opportunity to enhance RV energy use efficiency, and thus performance, by normalized pulmonary vascular stiffness and tone (reviewed in detail in [43]). In summary, new insights into the molecular and cellular regulation of pulmonary vascular tone and vascular cell fate, as well as the diverse contributions of sex hormones, glucose metabolism, and inflammatory cytokines, reveal a remarkable degree of convergence of these influences on common effectors of the BMP/TGF-β, PPAR-γ, and other pivotal axes of PAH (Figure 1).

Immunity and Inflammation in PAH

The long-standing notion that inflammation and immunity contribute to remodeling of the pulmonary vascular bed in PAH

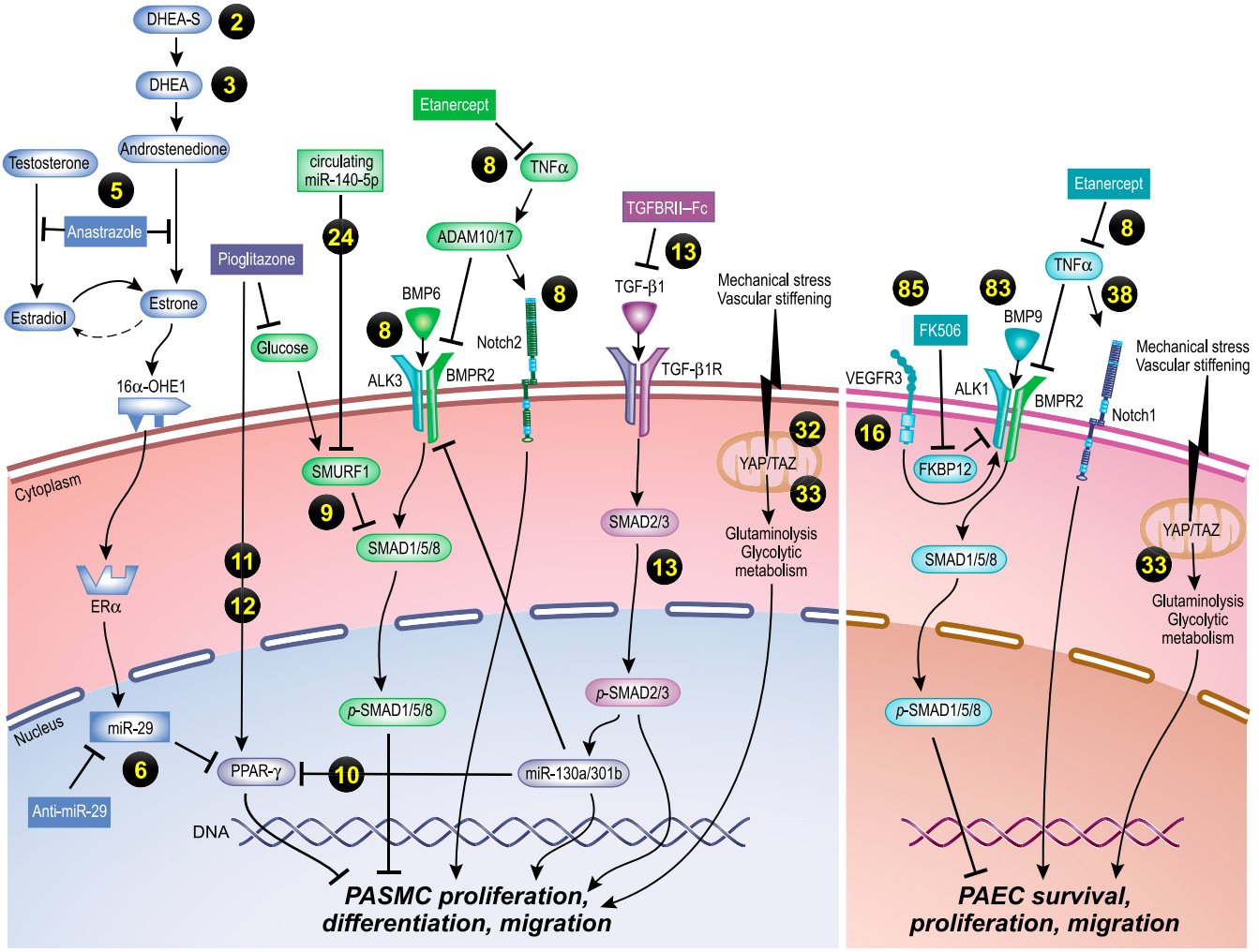

Figure 1. Novel molecular and cellular insights into pulmonary arterial hypertension signaling reveals convergence of sex hormone, glucose metabolism, and inflammatory signaling on common effectors of the BMP (bone morphogenetic protein)/TGF-β (transforming growth factor) and PPAR-γ (peroxisome proliferator-activated receptor-γ) axes and other signaling axes. The yellow numbers indicate references. Illustration by Jacqueline Schaffer. 16α-OHE1 = 16α hydroxyestrone 1; ADAM = a disintegrin and metalloprotease; ALK = activin-like kinase; BMPR2 = BMP receptor type 2; DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate; ERα = estrogen receptor α; Fc = fragment crystallizable region; FK506 = tacrolimus; FKBP12 = FK506 binding protein; miR = microRNA; PAEC = pulmonary artery endothelial cell; PASMC = pulmonary artery smooth muscle cell; p-SMAD = phosphorylated SMAD; SMAD = fusion of Caenorhabditis elegans Sma genes and the Drosophila Mad, Mothers against decapentaplegic; SMURF1 = E3 ubiquitin-protein ligase SMURF1; TAZ = transcriptional co-activator with PDZ-binding motif; TGF-β1 = transforming growth factor β-1; TGF-β1R = TGF-β1 receptor; TNFα = tumor necrosis factor α; VEGFR3 = vascular endothelial growth factor receptor 3; YAP = Yes-8 associated protein.

(44–47) has been extended by observations that pulmonary vascular lesions in patients with PAH and animal models include perivascular inflammatory infiltrates comprised of T and B lymphocytes, macrophages, dendritic cells, and mast cells (48–51). In addition, PAH is newly associated with IL-1R1/MyD88 signaling, CCL2 (CC chemokine ligand 2), CXCL-1 (chemokine [C-X-C motif] ligand 1), and PHD (prolyl 4-hydroxylase) deficiency; and regulatory T-cell dysfunction (52–55). Macrophages, bone marrow–derived cells, and myeloid-derived suppressor cells may represent important local sources of factors that regulate pulmonary vascular remodeling (49, 56, 57) which may initiate maladaptive immune and inflammatory responses through immune cell recruitment and feedback regulation. Factors further contributing to the activation of an immune response are aging of the pulmonary circulation, chronic exposure to hypoxia, dysregulation in BMPR2-mediated signaling, shear stress, metabolic derangements, and circulating autoantibodies and immune complexes (58–61).

Genetics and Genomics

Mutations in the gene encoding BMPR2 account for over 80% of HPAH and approximately 10 to 20% of sporadic IPAH (62). Mutations in other genes have recently been identified in PAH and overlap syndromes, including *ACVRL1* (ALK-1), *BMPR1B* (ALK-6), *GDF2* (growth differentiation factor 2) (BMP-9), *TBX4* (T-box 4), *ENG* (endoglin), *SMAD9* (Smad-8), *CAV* (caveolin), and KCNK3 (34, 61–66). A recent, large case–control analysis revealed overrepresentation of several novel rare variants, including *ATP13A3* (ATPase 13A3), *AQP1* (aquaporin 1), and *SOX17* (transcription factor SOX-17), and independently validated *GDF2* in PAH (67).

The potential for rare variant analyses to add precision to the characterization of patients with PAH was demonstrated in the prediction of acute vasodilator responses (68). Likewise, biallelic *EIF2AK4* (eukaryotic translation initiation factor 2 α kinase 4) mutations, shown to associate with pulmonary venoocclusive disease/pulmonary capillary hemangiomatosis spectrum disease (69, 70), were discovered in 1% of patients diagnosed with IPAH or HPAH, suggesting that genetic testing could reclassify these patients and facilitate early referral for lung transplant (71). Although such patients frequently had abnormal imaging, a substantial portion of these patients' diagnoses would not be confirmed by computed tomography alone. The understanding of the complex genetic and genomic factors involved in PAH continues to expand as genomic medicine plays a rapidly growing role in guiding PAH diagnosis and therapy.

Metabolism/Mitochondrial Function

In human and experimental PAH, metabolic dysregulation resembling the Warburg effect (described in cancer cells) has been observed in pulmonary arterial cells, RV cardiomyocytes, skeletal myocytes, and immune cells (72). Increased glycolysis is found in platelets isolated from patients with PAH, extending metabolic dysregulation to the hematologic compartment (73). Abnormalities in fatty acid metabolism in blood and steatosis in the RV myocardium are observed in human and experimental PH (74, 75), attributed to interplay between glucose and fatty acid metabolism via the Randle cycle.

As a potential driver of these adaptations, miR-124 was shown to regulate polypyrimidine tract binding protein and promote an increase in the PKM2/PKM1 ratio associated with increased glycolysis in adventitial fibroblasts (22) and PAECs (21) in PH, suggesting therapeutic potential of PKM2 inhibition. Severe obliterative vascular remodeling and severe PH were described in PHD2-deficient mice *in vivo*, which was due to PASMC proliferation in PHD2-deficient endothelial cells through a mechanism involving hypoxia-inducible factor (HIF)-2α–dependent CXCL12 release (55). The HIPPO central component, large tumor suppressor 1, is inactivated in PAH, resulting in upregulation of its effector YAP associated with coordinated shifts in cell metabolism favoring cell growth and proliferation (32). YAP and TAZ are also mechanoactivated by vascular extracellular matrix stiffness: By modulating the expression of glutaminase, pyruvate carboxylase, and lactate dehydrogenase A, YAP-TAZ stimulates a glutaminolytic metabolic phenotype as well as glycolytic metabolism in PAECs and PASMCs exposed to vascular stiffness in PAH (33).

Providing novel insight into the pathobiological basis of stimulant-associated PAH, *in vitro* exposure to amphetamine under hypoxia induces HIF-1α deacetylation and degradation through the protein phosphatase 2A/AKT/Sirtuin 1 axis, limiting adaptive cellular responses to oxidative stress, whereas administration of amphetamine to mice under hypoxia suppresses Hif-1α to exacerbate DNA damage and pulmonary vascular remodeling (76). Glycolytic reprogramming is associated with an increase in the reduced coenzyme NAD^+ reduced (NADH). Accompanying increases in NADH production, NADH sensor CtBP (C-terminal binding protein) was activated in PAH, resulting in suppressed expression of the cyclin-dependent genes *p15* and *p21*, the proapoptotic genes *NOXA* (phorbol-12-myristate-13-acetate-induced protein 1) and *PERP* (TP53 apoptosis effector), and the antiinflammatory gene *HMOX1* (heme oxygenase 1) in lung fibroblasts (77). These findings suggest 4-methylthio-2-oxobutyric acid (a pharmacologic agent decreasing NADH) and CtBP1 inhibitors as potential therapeutic strategies in PAH. NAMPT (nicotinamide phosphoribosyltransferase), which regulates intracellular NAD concentrations, is expressed at higher concentrations in the plasma and lungs of patients with PAH (78). Consistent with an important pathophysiologic role, $NAMPT^{+/-}$ mice are protected from hypoxia-mediated PH, and inhibition of NAMPT activity prevented and partially reversed experimental PH.

These findings highlight the potential of mitochondria- and metabolism-targeting therapies, which have now been explored in human studies. Dichloroacetate, a pyruvate dehydrogenase kinase inhibitor, was assessed in a 4-month, open-label clinical trial in patients with IPAH, with improved hemodynamics reported in a subset of them (79). Dichloroacetate responses were associated with genetic variation in Sirtuin 3 and/or uncoupling protein 2, highlighting a potential precision medicine approach to metabolic therapy in PAH.

Clinical Trials and Repurposing Existing Drugs for the Treatment of PAH

Interventions and outcomes of key clinical trials are summarized in Table 1. Inhibition of aromatase, the key enzyme in estrogen

Table 1. Summary of Key Clinical Trials in 2016 and 2017

Study	Population	Characteristics	Intervention	Key Findings
AIPH (81)	PAH ($n = 18$)	12-wk multicenter double-blind RCT	1 mg of anastrozole vs. placebo (2:1)	• 29-m improvement in 6MWD • No change in functional class, quality of life, or serum NT-proBNP levels
TransformPAH (86)	PAH ($n = 23$)	16-wk double-blind RCT	Tacrolimus at three target serum levels vs. placebo	• No improvement in 6MWD, NT-proBNP, RV function, or time to clinical worsening
PAHTCH (88)	PAH ($n = 24$)	24-wk double-blind RCT	Low fixed dose, dose-escalating carvedilol, or placebo (1:1:1)	• Carvedilol well tolerated • No improvement in 6MWD, RV function, or quality of life
RESPITE (89)	PAH with inadequate response to PDE5I ($n = 61$)	24-wk multicenter open-label uncontrolled trial	Replacing PDE5I with riociguat	• Improved functional class, 6MWD, and NT-proBNP
GRIPHON-CTD (90)	CTD-associated PAH ($n = 334$)	*Post hoc* analysis of multicenter RCT	Selexipag vs. placebo	• Selexipag reduced the combined morbidity and mortality endpoint by 41% in patients with CTD-PAH • Selexipag was well tolerated
SIOVAC (91)	Patients with mPAP $\geqslant$30 mm Hg $\geqslant$1 yr after valve surgery ($n = 200$)	Multicenter parallel-group double-blind RCT	Sildenafil 40 mg three times daily vs. placebo	• Sildenafil was associated with increased risk of composite endpoint of death, heart failure–related hospitalization, functional class, and patient global self-assessment • No change in 6MWD, NT-proBNP, or Doppler estimated pulmonary artery pressures

Definition of abbreviations: 6MWD = 6-minute-walk distance; AIPH = Anastrozole in Pulmonary Arterial Hypertension trial; CTD = connective tissue disease; GRIPHON = Selexipag for the Treatment of Pulmonary Arterial Hypertension; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro–brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAHTCH = PAH Treatment with Carvedilol for Heart Failure trial; PDE5I = phosphodiesterase 5 inhibitor; RCT = randomized controlled trial; RESPITE = Riociguat Clinical Effects Studies in Patients with Insufficient Treatment Response to Phosphodiesterase-5-Inhibitors; RV = right ventricular; SIOVAC = Sildenafil for Improving Outcomes after Valvular Correction; TransformPAH = FK506 (Tacrolimus) in Pulmonary Arterial Hypertension.

synthesis, with anastrozole improves experimental PH in multiple models (80). The researchers in the AIPH (Anastrozole in Pulmonary Arterial Hypertension) study randomized 18 postmenopausal women or men with PAH to 1 mg of anastrozole or placebo (2:1 ratio) (81). Anastrozole significantly reduced 17β-estradiol concentrations compared with placebo (-40% vs. -4%; $P = 0.003$) and was well tolerated without deleterious effects on RV function. Anastrozole modestly increased 6-minute-walk distance (6MWD) compared with placebo ($+26$ vs. -12 m; $P = 0.023$) without altering functional class, quality of life, or serum NT-proBNP (N-terminal pro–brain natriuretic peptide) concentration. The mechanism for improvement in 6MWD is unclear because another study suggested that 17β-estradiol improves skeletal muscle mitochondrial function (82).

BMPR2 is reduced in experimental and human PAH (83, 84), whereas activation of BMPR2 using tacrolimus reverses PH in multiple experimental models (85). To translate this approach, the researchers in the double-blind TransformPAH (FK506 [Tacrolimus] in Pulmonary Arterial Hypertension) trial examined the safety and tolerability of tacrolimus in 23 patients with stable PAH and good functional capacity (median 6MWD, 526 m) on baseline therapy who were randomized to three target serum tacrolimus trough concentrations or placebo for 16 weeks (86). Tacrolimus did not improve 6MWD, NT-proBNP, echocardiographic markers of RV function, or time to clinical worsening. Some patients receiving high-dose tacrolimus had a significant increase in peripheral blood mononuclear BMPR2 expression and improvement in 6MWD, supporting further studies to identify potential responders.

On the basis of beneficial effects of β-blockade on RV function in experimental PH (87), the researchers in the PAHTCH (PAH Treatment with Carvedilol for Heart Failure) trial randomized 30 patients in a 1:1:1 ratio to placebo, low fixed dose, or dose-escalating carvedilol for 24 weeks (88). Carvedilol was well tolerated, with promising effects of decreased heart rate and RV fluorodeoxyglucose–positron emission tomography uptake and increased β-adrenergic receptor expression in peripheral leukocytes. However, it did not change 6MWD, RV function, or quality of life. This study suggests that carvedilol may be safe in PAH, but further studies are needed to determine its efficacy.

The researchers in the RESPITE (Riociguat Clinical Effects Studies in Patients with Insufficient Treatment Response to Phosphodiesterase-5-Inhibitors) study evaluated the safety and efficacy of replacing phosphodiesterase 5 inhibitors (PDE5Is) with sGC (soluble guanylate cyclase) activator riociguat in patients with PAH

with inadequate responses to PDE5Is in a 24-week, multicenter, open-label, uncontrolled study of 61 patients (89). Switching to riociguat significantly improved functional class in 52%, increased 6MWD by 31 m, and reduced NT-proBNP. However, adverse events (52%) and serious adverse effects (16%) were common. The superiority of switching versus adding nitric oxide/sGC–targeted therapies will require confirmation in randomized controlled trials.

In a *post hoc* analysis of the GRIPHON (Selexipag for the Treatment of Pulmonary Arterial Hypertension) trial, the effects of the oral prostacyclin analog selexipag were examined in 334 patients with connective tissue disease (CTD)–associated PAH (90). There was no difference in maximum tolerated selexipag dose between CTD-PAH patients and the overall GRIPHON study cohort, with a similar side effect profile and frequency in patients with CTD versus other PAH etiologies. Selexipag reduced the combined morbidity and mortality endpoint by 41% in patients with CTD-PAH, with similar risk reduction regardless of underlying CTD ($P = 0.89$) and independent of background PAH-specific therapies ($P = 0.87$), and this was driven by a reduction in hospitalization and disease progression.

The researchers in the SIOVAC (Sildenafil for Improving Outcomes after Valvular Correction) trial examined the effect of sildenafil versus placebo on clinical outcomes in subjects with residual PH after valve surgery (91). There was no difference between groups in clinical outcomes, 6MWD, or BNP. These results argue against the use of sildenafil in patients with this PH phenotype.

Epidemiology and Clinical Outcomes

The putative classification of borderline PH was considered at the 2013 World Symposium on Pulmonary Hypertension, but its recognition as a clinical entity was deferred owing to lack of robust epidemiologic data. Recently, three reports involving more than 26,000 individuals have shown that borderline PH is present in 18 to 36% of patients referred for right heart catheterization (RHC) (92–94). Mean pulmonary pressure values between 19 and 24 mm Hg were consistently associated with increased adjusted mortality in these studies, and retrospective data suggest that many patients with borderline PH subsequently develop overt PH (93). Although it is unknown if interventions against PH risk factors can forestall or prevent disease (95), these observations suggest that the current diagnostic framework and hemodynamic criteria for PH do not capture a subset of vulnerable patients.

Advances in group I PAH have included data on medical use and associated PAH phenotypes. An analysis of the Medicare National Inpatient Sample showed that PAH-related hospitalizations declined between 2001 and 2012, whereas hospital charges and length of stay have increased, with no change in in-hospital mortality (96). In the largest prospective cohort of patients with presumed methamphetamine-associated PAH, patients with methamphetamine-associated PAH had worse hemodynamics and a twofold increase in adjusted mortality compared with IPAH, were less adherent to medications, and were less likely to receive parental therapy, highlighting several challenges in this population while strengthening the epidemiologic link between methamphetamine exposure and PAH (97).

Advances in group 2 PH include two reports focused on combined pre- and postcapillary pulmonary hypertension (pre- and post-CPH). First, patients with typical PAH, "atypical" PAH (PAH hemodynamics with multiple risk factors for left heart disease), or CPH from the COMPERA registry (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) were found to have similar survival; however, PAH therapies were less effective in improving 6MWD and NT-proBNP among patients with CPH (98). This study suggested the existence of a disease spectrum spanning typical PAH and CPH and showed that cardiometabolic comorbidities influence the response to PAH therapies among patients with atypical PAH or CPH. Second, patients with CPH develop pulmonary vascular disease similar to that of patients with PAH despite a severity and chronicity of left heart disease similar to that of patients with isolated post-CPH. Authors of an exploratory genetic analysis in patients with CPH found overrepresentation of genes and biologic pathways known to be perturbed in PAH (99). Thus, some patients with CPH may harbor a predisposition for pulmonary vascular disease, suggesting the potential to identify patients who might respond to PAH therapies and highlighting the need for further investigation into CPH pathobiology.

In a study analyzing the burden of echocardiographic PH among individuals with HIV infection, the combination of HIV and PH was associated with high mortality after adjusting for cardiovascular risk factors and left ventricular function and after excluding individuals with any chronic disease (100). When examined as a continuous variable, adjusted mortality risk in HIV began at PA pressure values currently considered to be normal, suggesting that current screening thresholds may not adequately capture risk related to rising pulmonary pressure in patients with HIV.

Two large prospective studies in subjects with chronic thromboembolic pulmonary hypertension (CTEPH) demonstrated excellent short- and long-term outcomes among patients who underwent pulmonary endarterectomy (3-yr survival, 84 to 91%) (101, 102). Persistent severe PH and elevated pulmonary vascular resistance (PVR) were associated with worse long-term survival.

Biomarkers

Agnostic "omics" approaches to biomarker identification allow insight into disease diagnosis and prognosis that is unconstrained by current knowledge of disease pathology. Metabolomic profiling ($n = 1{,}416$ metabolites) of patients with PAH versus healthy control subjects revealed that constituents of nucleoside, lipid, and amino acid pathways distinguished patients with PAH from healthy control subjects, independent of previously identified prognostic biomarkers (NT-proBNP, red cell distribution width) (3). The same group performed proteomic profiling ($n = 1{,}129$ proteins) in discovery and validation cohorts with IPAH or HPAH, identifying nine proteins involved in myocardial stress, inflammation, iron metabolism, and coagulation that improved the prognostic ability of NT-proBNP and the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) score (103). In a targeted analysis, hepatoma-derived growth factor, an angiogenic factor expressed by PAECs, was associated with worse clinical status and reduced survival in two independent

PAH cohorts (104, 105). Relating metabolomic profiling to RV-PA function, indoleamine 2,3-dioxygenase–dependent tryptophan metabolites were associated with RV–pulmonary vascular dysfunction (resting increases in right-sided pressure/resistance, and abnormal pressure–flow relationship during exercise) in subjects undergoing rest/exercise RHC and RV radionuclide ventriculography (106). Finally, increased endothelin 1 was associated with elevated echocardiographic RV systolic pressure in African American individuals in the Jackson Heart Study (107). These studies identified exciting new biomarkers of prognostic and mechanistic significance, highlighting biologic pathways with therapeutic potential in PAH.

Two studies examined the role of TAFI (thrombin-activatable fibrinolysis inhibitor) in patients with CTEPH. TAFI is increased in the plasma and is highly expressed in PAs and thrombus from patients with CTEPH. TAFI inhibition reduces 4-hour clotting in the whole-blood clot lysis assay and improves experimental PH, suggesting a potential new therapeutic target in CTEPH (108, 109).

Imaging

An important step in the diagnostic algorithm for PH is the performance of $\dot{V}/\dot{Q}$ scintigraphy. It was recently shown that a considerable number of patients with an abnormal $\dot{V}/\dot{Q}$ single-photon emission computed tomographic scan are ultimately diagnosed with nonthromboembolic PAH after undergoing pulmonary angiography (110). In these patients, global perfusion abnormalities in the $\dot{V}/\dot{Q}$ single-photon emission computed tomographic scan were associated with poor outcome. It is possible that occult thromboembolic lesions could be revealed by using specialized methods such as optical frequency domain imaging or pulmonary angioscopy (111).

The feasibility of echocardiography for assessment and monitoring of RV function during exercise continues to be debated. Exercise stress echocardiography was shown to be feasible and identified RV pathology with reasonable accuracy (112). In patients with systemic sclerosis (SSc), speckle-derived strain determinations revealed a heterogeneous pattern of regional heart strain independent of RV systolic pressure not detected by conventional echocardiographic measures (113). Using cardiac magnetic resonance, the therapeutic superiority of combination therapy over monotherapy in PAH was related to a greater improvement in RV ejection fraction (114). In large derivation and validation cohorts, stiffness of the proximal PA and RV end-systolic volume index were the strongest independent predictors of mortality in PAH (115). A machine learning approach predicted outcomes in PAH on the basis of three-dimensional RV motion via cardiac magnetic resonance imaging (116).

Physiology

Age was found to be associated with different hemodynamic responses to exercise, with subjects older than 50 years of age exhibiting higher PVR and lower pulmonary vascular compliance at peak exercise than subjects 50 years old or younger (117). Another study showed that 7 ml/kg saline fluid challenge at RHC reclassified 6% and 8% of non-PH and pre-CPH, respectively, to a post-procedural diagnosis of post-CPH (118). These data suggest that an integrated approach including provocative maneuvers (e.g., exercise or fluid challenge) is useful for diagnosing abnormal pulmonary vascular responses (119). Abnormal RV function has emerged as a central part of the HPAH phenotype, although the underlying mechanisms for this effect could not be explained fully by the germline mutation (120). In preclinical physiologic studies, neurohormonal overactivation (121), myocardial stiffness (122), abnormal shear responses (60), and genetic modifiers (123) were identified as key contributors to PAH and right heart failure pathophysiology.

In PAH, the right ventricle may be affected differentially across different disease subtypes and independent of RV afterload. For example, RV–PA uncoupling occurs in SSc-PAH but not IPAH, despite similar levels of pulmonary hypertension and PVR between these cohorts (124). This suggests a primary defect in the SSc-PAH right ventricle, such as impaired sarcomere function (125). The disease-specific mechanisms regulating sarcomere dysfunction in SSc-PAH (or IPAH) remain unknown, but they may involve SERCA2A, phospholamban, or other calcium-regulating proteins (40, 126).

Pediatric Pulmonary Vascular Disease

The diagnosis and clinical management of patients with pediatric PH was advanced by parallel efforts in North America and Europe to create comprehensive care guidelines (127–129). These guidelines *1*) highlight the varied nature of pediatric PH subtypes, including the prevalence of developmental lung disease and complex syndromic conditions; *2*) emphasize the potential utility of genetic counseling and testing, as well as screening of relatives at specialized PH centers; and *3*) provide algorithms for management of PH-specific therapies. In September 2017, the U.S. Food and Drug Administration approved bosentan as the first chronic therapeutic for PAH care in children in the United States.

The guidelines also emphasized the importance of specialty centers for PH diagnosis and care, including the performance of cardiac catheterization with acute vasodilator testing (AVT). In a multinational registry study, the conduct and interpretation of AVT was found to be tremendously variable, even among experienced pediatric centers (130). Only 70% of centers employed inhaled nitric oxide in the AVT protocol, and only 23% of patients with PAH determined to "respond" were trialed on a calcium channel blocker single-therapy regimen, contrary to international guidelines. In addition, evaluation of different criteria for response showed that the Sitbon criteria were most predictive of a successful long-term response to calcium channel blocker monotherapy (131).

Improving precision in treatment will require improved endpoints for clinical trials and observational studies. The utility of accelerometry for measurement of physical activity and its correlation with clinical severity markers was demonstrated in pediatric PAH, with affected children exhibiting dramatically decreased physical activity compared with their healthy peers (132). Accelerometry was associated with functional class, 6MWD, and adverse PAH-related events, supporting potential utility in future studies. Comprehensive clinical guidelines, multicenter and multinational collaborations, and novel approaches to monitoring response to therapy are among the advances driving continued progress in treatment of children with PH.

Conclusions

These recent studies demonstrate accelerated progress in basic and clinical PAH science, heralding expanded treatment options in coming years. Future directions will include enhanced understanding of the genetic and molecular bases of pulmonary vascular remodeling (133, 134), molecular classification of PH phenotypes (135, 136), leveraging of underlying biology to personalize therapy (137, 138), and understanding the determinants of RV compensation versus failure. ■

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