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BMP9 Morphs into a Potential Player in Portopulmonary Hypertension

The last 30 years of pulmonary hypertension research is a qualified translational success story. Patients with portopulmonary hypertension (PoPH) have benefitted from inclusion in the licensed indications for novel therapies, despite small numbers of patients enrolled in studies (1). There has, however, been very little movement in our parallel understanding of the pathophysiology. Perhaps as a consequence of this gap between evolving treatments aimed primarily at other disease causes, as well as our lack of mechanistic insight in PoPH, outcomes for patients remain poor. Modern registry data demonstrate 5-year survival stuck around 40% for patients with PoPH, in contrast to the improving survival in other disease forms (2). With a paucity of funded research, limited preclinical modeling, and no real external drivers for industry to engage in this question rather than focus resources on subsets of patients in phase 3 trials, there has been little in the way of new hypotheses to consider. An added complication is that patients have two disease processes, pulmonary hypertension and liver disease, and the relationship between the degree and nature of liver disease and splanchnic and pulmonary pressures has not been clearly resolved (3).

In this edition of the *Journal* (pp. 891–902), Nikolic and colleagues report a potentially fundamental advance in our understanding of disease (4). BMP9 (bone morphogenetic protein 9), a ligand of the TGF-β (transforming growth factor-β) superfamily that has a selective binding affinity to the BMPR2 (bone morphogenetic protein receptor type 2)/ALK1 (activin receptor-like kinase 1) complex, is significantly reduced in PoPH but not in other forms of pulmonary arterial hypertension (PAH). BMP9 is emerging as an important and novel regulator of vascular homeostasis (5). The concept that BMP signaling may be important in the liver vasculature has clear precedent. Hereditary hemorrhagic telangiectasia (HHT) is characterized by arteriovenous malformations that affect organs heterogeneously. They are found commonly in the liver, and HHT is associated in around 80% of individuals with mutations in ALK1 and the circulating coreceptor endoglin (6). In addition to the established link between HHT, BMP signaling, and PAH, the genetics of PAH have been pointing for some time to the critical importance of this specific ligand and its receptor complex. Completing the tertiary receptor/ligand complex, mutations in BMPR2 and BMP9 cause PAH (7). Fitting beautifully with the human genetics, the BMPR2/ALK1/endoglin tertiary complex is highly expressed in the pulmonary endothelium, and BMP9 circulates at physiological levels (8). To complete the background story, BMP9 is produced predominantly by the liver (9).

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We therefore have a ligand that is highly pulmonary endothelial specific and regulates vascular homeostasis, and PAH develops when there is a reduction in signaling downstream of BMP9 related to rare mutations in all of the ligand receptors and, moreover, the BMP9 ligand itself. We now know that in liver disease, the development of PAH is associated with reduced levels of BMP9, and this was not clearly demonstrated in the context of all patients with liver disease and no PoPH. Critically, BMP9 is not reduced in other forms of PAH, and therefore the reduction in BMP9 is unlikely to be simply a consequence of pulmonary vascular remodeling and secondary to dysregulated homeostasis. Though the number of patients in Nikolic and colleagues' study (4) with PoPH was modest ($n = 28$), this was repeatable in two separate cohorts. The underlying causes of the liver disease were heterogeneous, though with a predominance for hepatitis C virus, and were reasonably matched with the liver disease without PoPH group. This seems likely to be a consequence of liver disease itself and therefore relevant to the spectrum of underlying diseases, though further work will be needed to confirm this. There is the tantalizing suggestion that the liver disease with no PH group, though not significantly reduced overall, may have a biphasic or nonnormal distribution, with a small number of patients with low BMP9 (significantly below the 99th percentile in the control group). Future work will have to clarify if the reduction of BMP9 precedes the development of PH and BMP9 is reduced on a spectrum related to extent of liver disease. The authors conclude that this is not the case on the basis of a lack of association with fibrosis scores and the utility of BMP9 in predicting PoPH, particularly in multivariate models over and above classical factors. As they acknowledge in their article, their numbers are small, and as such, these analyses need to be treated with caution.

One interesting area not commented on in the report by Nikolic and colleagues (4) is hepatopulmonary syndrome (HPS). HPS is characterized by liver disease, intrapulmonary vasodilation, and hypoxemia. There were only two patients with HPS in this cohort, but further work can clarify if BMP9 is also altered in these patients, who may sit on a spectrum with PoPH. PoPH and HPS share similarities but with wildly different phenotypes. Both syndromes are thought to relate to an imbalance in vasoactive regulators, though in PoPH we see pulmonary vasoconstriction, and in HPS we see the opening up of intrapulmonary shunts. HPS will usually regress with liver transplant, but PoPH classically does not (10). It is not currently clear why patients with liver disease, portal hypertension, and hyperdynamic states can have two apparently diametrically opposed pathologies. Cirrhosis and liver disease are known not just to profoundly affect liver and splanchnic vascular beds but also to have significant systemic vascular effects (11). We know that the effects of mutations downstream of BMP9, notably ALK1 and endoglin in HHT, are not restricted to the pulmonary vasculature. The liver features prominently in arteriovenous malformation, and vascular dysplasia phenotypes, though heterogeneous, are partially influenced by mutation status (6). Hervé and colleagues suggested 20 years ago that a "hepatic factor contained in normal hepatic venous blood plays a role in the control of pulmonary angiogenesis" (12). BMP9 now looks like a strong candidate for this vascular homeostatic role. Looking from the perspective of PAH, if there was any doubt about the centrality of BMPR2 signaling across multiple forms of PAH, this work surely adds another significant brick in the wall.

The recent demonstration of a role for BMP10 in zebrafish vascular homeostasis and arteriovenous malformations (13) means that alternative BMP signaling may need to be reevaluated in the context of liver disease. In addition to clarifying an association between PoPH and BMP9 in human disease, Nikolic and colleagues (4) confirm previous work on an orphan model of liver disease–associated pulmonary hypertension: the carbon tetrachloride–induced cirrhotic murine model (14). This underused model will give the field an animal model for mechanistic and therapeutic studies focused on modulating the pathway in the future. The net result of this work is to open up a rich vein of possible research looking at the role of BMPs in pulmonary and systemic vascular homeostasis in liver disease and cementing a model for preclinical animal work to compliment patient studies. The recent demonstrations of efficacy in animal models of PAH using BMP9 therapy and ligand traps for transforming growth factor-β (15, 16) mean that the roadmap to experimental studies in liver disease is both plausible and possible. The authors are to be highly commended for reinvigorating preclinical studies in PoPH. ■

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Mark Toshner, M.D.
Royal Papworth Hospital NHS Foundation Trust
Cambridge, United Kingdom
and
Department of Medicine
University of Cambridge
Cambridge, United Kingdom

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Arousability in Obstructive Sleep Apnea: Friend or Foe?

Obstructive sleep apnea (OSA) afflicts 3–9% of women and 10–17% of men in the United States (1) and is associated with a host of comorbid cardiovascular and metabolic conditions, including hypertension, diabetes, coronary artery disease, and stroke. Despite decades of research, it remains unclear which, if any, patients with OSA are at greatest risk for developing these possible complications and which might be safely left untreated. A number of previous epidemiologic and case–control studies identified the greatest risk to be in the group with "severe OSA," which is to say the group with an apnea–hypopnea index (AHI) $>$ 30 events/h (2, 3). However, recent randomized controlled trials that enrolled patients based on their AHI have not confirmed these findings, leaving investigators and clinicians wondering whether there might not be better ways to stratify risk in patients with OSA (4, 5).

OSA is characterized by repeated episodes of upper-airway occlusion during sleep, which can be complete (apnea) or incomplete (hypopnea) and of varying duration. Obstructive episodes trigger a number of ensuing pathophysiologic disturbances, including hypoxemia, hypercapnia, sympathoexcitation, and intrathoracic pressure swings. Although there has been some debate on this point, the traditional model of OSA posits that airway occlusion is terminated when the subject experiences an arousal from sleep, thereby restoring pharyngeal dilator muscle tone and opening the airway. Viewed from this perspective, longer apneas or hypopneas must therefore be characterized by some relative failure of the arousal's normal protective function, either due to inadequate chemostimulation leading to arousal or due to some defect of the arousal response itself. When obstructive episodes last longer, downstream effects such as hypoxemia and sympathoexcitation will be worse, not only because the subject is exposed to them for a longer period of time but also because of their increasing magnitude. Stated plainly, it seems that longer apneas must be physiologically worse than shorter apneas.

In this issue of the *Journal*, Butler and colleagues (pp. 903–912) analyze data from the Sleep Heart Health Study and show us that things are not so simple (6). Among 5,712 subjects, almost a quarter of whom died during the 11 years of follow-up, individuals with the shortest-duration obstructive events had a significantly increased risk of death (1.31; 95% confidence interval, 1.11–1.54) after adjusting for the AHI, demographic factors, and prevalent cardiovascular and metabolic disease. The relationship was observed in both men and women, and was strongest in those with moderate OSA.

How can we reconcile this observation with our established knowledge of OSA pathophysiology? First, we should recognize that perhaps we have paid too much attention to the presence and morphology of OSA during polysomnography as it relates to downstream effects, and not enough to *upstream* effects. That is to say, OSA manifests uniquely in a given subject based on a large number of underlying factors, which are only incompletely understood. Obesity and anatomical crowding of the upper airway are obvious predispositions. Chemical control instability and loop gain are less obvious, but are supremely important in the pathogenesis of Cheyne-Stokes respiration and central sleep apnea, and increasingly recognized as contributing to OSA as well (7, 8). Cheyne-Stokes respiration may be a particularly instructive example: although its presence surely predicts a worse prognosis, its treatment does not seem to improve that prognosis (9), possibly because the upstream disturbances that *cause* the sleep apnea are the relevant ones, not the downstream disturbances that are *caused by* the sleep apnea.

Similarly, although it is difficult to imagine why a shorter apnea should be more harmful than a longer one when viewed in the light of its lesser downstream effects, it is easy to envision some upstream predisposing host factor that prematurely causes apnea termination (the authors call it "arousability"). It is possible that the mortality risk demonstrated in this study stems not from the shorter apneas *per se*, but rather from this predisposing factor. If this is the case, then treatment of OSA in these individuals would not be expected to confer a mortality benefit, as treatment would decrease the frequency of apneas and apnea-related arousals, but would not be expected to improve arousability itself. On the other hand, it is possible that increased arousability exerts its effects through sleep fragmentation. However, that explanation is not borne out by the data, as sleep efficiency was not different between the groups. Why

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