

and host defense functions in human diseases with an excessive inflammatory response. ■

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## Ⓜ BMP9 in Acute Respiratory Distress Syndrome: Decades of BMP Studies in Vascular Biology Paying Off?

Roughly 20 years ago, BMPR2 was found to be the causative mutation for most heritable pulmonary arterial hypertension (PAH) (1). This was surprising because until then, the BMP pathway was thought to be extremely important in embryonic development, but it did not yet have a known role in adults. The paradigm of reactivation of developmental pathways in injury repair was not common. The discovery of BMPR2 as the PAH gene thus drove two decades of fascinating science about the role of BMP—and other developmental pathways—in the injury repair process. These findings are now starting to make their way to the clinic.

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The original BMPR2 mutations were primarily haploinsufficiency, which means there was still a functional pathway, but there just wasn't enough signaling through it. Why not just add more ligand? Unfortunately, the answer to that was the BMP pathway does too many things in too many places. Add ligand, and you might cause heterotopic ossification; in blast injuries, and in fibrodysplasia ossificans progressiva, the problem is too much BMP signaling (2). Therefore, off-target effects made the approach of just adding ligand apparently too dangerous to try.

For the last decade or so, the Morrell group out of Cambridge has been working on a clever workaround to this—BMP9 (3, 4). Although there are many ligands for BMPR2, BMP9 has two singular properties that make it more suitable—and safer—for this purpose. First, most BMP ligands are relatively short range; they are meant to impact cells within a few dozen microns, not halfway across the body. BMP9, in contrast, is primarily made in the liver and circulates (5); in fact, it is the predominant circulating form of BMP ligand (6). Second, BMP9 does not signal through BMPRIa or BMPRIb, the more common type

I receptor heterodimers for BMPR2, but rather Alk1 (7). Their work in pulmonary hypertension preclinical rodent models supports the idea that the exogenous BMP9 ligand might be useful for treating human disease (4), supported by the discovery of causal BMP9 mutations in patients with heritable PAH (8).

In this issue of *Journal*, Li and colleagues (pp. 1419–1430) show the power of this approach, adapting findings originally produced for pulmonary hypertension to acute respiratory distress syndrome (ARDS), a much more common problem than PAH, with an estimated 190,000 cases per year in the United States (9, 10). They show in mice that blocking BMP9 leads to pulmonary vascular leak comparable to adding LPS, that BMP9 regulates genes involved in endothelial cell integrity, and that giving BMP9 to mice prevents vascular injury with inhaled LPS in mice. Human relevance was supported by data showing that BMP9 is reduced in patients with sepsis, likely driven by an increase in neutrophil elastase, which cleaves BMP9 and is increased in sepsis. Although the paper is brief, it is worth diving into the details in the supplemental tables and figures, with lists of BMP9-regulated genes in Tables E1 and E2 in the online supplement, and some absolutely beautiful intravital confocal microscopy showing dextran leak in blood vessels with and without anti-Bmp9 in Figure E1.

On the one hand, then, this article is important because it represents the culmination of the promise of 20 years of basic research. A genetic pathway once only of interest to developmental biologists, and examined because of a rare disease, uncovers basic biology potentially critical and therapeutically targetable in one of the most important remaining problems in pulmonary clinical care, ARDS. On the other hand, this article is important because this isn't purely theoretical; 5 years ago, Cambridge spun out development of BMP9 as a clinical target to a biotech company, Morphogen-IX, which has developed a form of it, MGX292, which it expects to have in clinical trials soon (11). Recent trials in ARDS have been disappointing, to say the least; proteins and small molecules that showed great promise in preclinical models have largely failed to bear out that promise in trials (12). Statins,  $\beta_2$ -adrenergic agents, keratinocyte growth factor, and aspirin have all failed in the past decade. The power of this finding is that it may hit a central control node, so far untargeted in ARDS, which is direct control of pulmonary vascular endothelial homeostasis and barrier.

There are, of course, many reasons why this could yet fail. Lack of BMP9, in actual patients, could be only one of many pathways controlling endothelial barrier function and so fail to translate. There is still some risk around BMP9 having off-target effects; for instance, it apparently does still have tremendously high osteogenic activity (13), which may manifest slowly enough that it has not yet become apparent in the animal models. With activities as diverse as stem cell differentiation, osteogenesis, metabolism, neurogenesis, and regeneration of joints, the potential for harmful off target effects is real. Even if there are off-target effects when systemically delivered, there may be work-arounds involving targeting methodologies or delivery mechanisms.

In all, the findings here lay the groundwork for the use of BMP9 regulation to regulate barrier function in ARDS. This may be directly translatable via MGX292, in which case translation will likely be rapid, but if not, a better understanding of the molecular biology

regarding barrier function in inflammation is bound to have significance in treating ARDS. ■

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