Bone growth protein might help more newborns survive severe lung disorders

April 19 2022

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When babies are born with alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV), their skin starts to turn blue from the under-oxygenated blood in their systems. But unlike most other breathing problems a newborn might experience, there's little to nothing that can be done to save these children unless they get a lung

transplant.

That's because their lungs lack the ability to grow enough alveolar capillaries to support healthy gas exchange, which in most cases leads to death within a month after birth. Now, after conducting a cell-by-cell analysis of genetic activity occurring among many different cell types within the lung, scientists at Cincinnati Children's are shedding new light on how ACDMPV develops—and a possible way to treat it.

Detailed findings were published online April 19, 2022, in *Nature Communications*. The study was led by first author Guolun Wang, Ph.D., corresponding author Vladimir Kalinichenko, MD, Ph.D., and seven other experts collaborating with the Center for Lung Regenerative Medicine at Cincinnati Children's Perinatal Institute.

"Treatment with BMP9 effectively restored capillary density, improved alveolarization, increased arterial oxygenation, increased expression of BMP9 receptor on the surface of capillary endothelial cells called Acvrl1, and improved survival in the ACDMPV mouse model," Kalinichenko says. "The improvements are striking. However, several more research steps are needed before BMP9 therapy could be ready for human clinical trials."

Intricate detective work isolates key molecular signaling pathway

The study in *Nature Communications* describes how the research team sifted through a mountain of single-cell RNA sequencing data collected from more than 7,000 lung cells from mice carrying a gene mutation linked to ACDMPV (a loss-of-function for the gene FOXF1 in humans) and another nearly 6,000 normal lung cells to find the one cell type where the disease creates its devastating results.

The work began by isolating a dozen cell clusters of potential interest. These clusters included alveolar epithelial cells, fibroblasts, club cells, endothelial cells, pericytes, ciliated cells, and myofibroblasts. The initial results prompted the team to focus more closely on activity involving pulmonary endothelial progenitor cells (EPCs) that reside in the inner linings of the lung's microvascular blood vessels.

Using data from about 800 of these cells, the team found 93 downregulated and 43 upregulated genes in the Foxf1 mutation group compared to the normal group. From this data, the team further reduced the suspects to a critical signaling pathway involving the proteins BMP9, ACVRL1 and SMAD1.

When the FOXF1 protein goes missing or contains one of detrimental mutations, the expression of Acvrl1 is reduced, which in turn reduces expression of downstream target genes. This pathway proves necessary for healthy blood vessel formation in the lungs.

Assessing the importance of this pathway required using a nanoparticle "delivery platform" developed by the Kalinichenko lab to "silence" the ACVRL1 protein–but only in the endothelial cells in the lungs of the mice.

Confirming a pathway leads to a potential treatment

The good news: the team found that adding synthetic bone morphogenetic protein BMP9 to cells that were deficient for functional FOXF1 genes helped re-create the signaling pathway, stimulating Acvrl1 activity and instructing the lungs to keep making capillaries. The researchers confirmed this through tests in lab cell cultures and in mice.

BMP9 is one of about 20 different such proteins found in humans. Originally discovered to play major roles in bone growth, more recently

this class of molecules has been shown to play a variety of roles in development.

Two other related proteins—BMP7 and BMP2—have been approved by the US Food and Drug Administration for treating bone growth disorders. But so far, no drug that stimulates BMP9 activity has been approved for human use.

ACDMPV is an extremely rare condition. It has been identified globally in just a few hundred births, ever, while in the United States more than 3.6 million births occurred in 2020 alone.

If a safe BMP9 "agonist" or synthetic BMP9 molecule suitable for human use can be developed, it could become more than a treatment strictly for ACDMPV, Kalinichenko says. It might also stimulate blood vessel growth that gets hampered by bronchopulmonary dysplasia (BPD)–a complication of premature birth that occurs in about 10,000 to 15,000 babies a year. While most infants survive this condition, early interventions that could spur lung damage repair could help prevent increased risks of asthma and lung infections later in life.

The treatment eventually might also benefit infants with congenital diaphragmatic hernia (CDH), a birth defect that strikes about 1,000 newborns a year in the US. In these children, gaps in the diaphragm allow other internal organs to crowd into space needed by the lungs. While surgery can repair the hernia, in many cases the lungs struggle to return to a normal pattern of growth.

More information: Guolun Wang et al, Endothelial progenitor cells stimulate neonatal lung angiogenesis through FOXF1-mediated activation of BMP9/ACVRL1 signaling, *Nature Communications* (2022). DOI: 10.1038/s41467-022-29746-y

Provided by Cincinnati Children's Hospital Medical Center