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‘Take a deep breath in’: a new treatment for congenital lung disease

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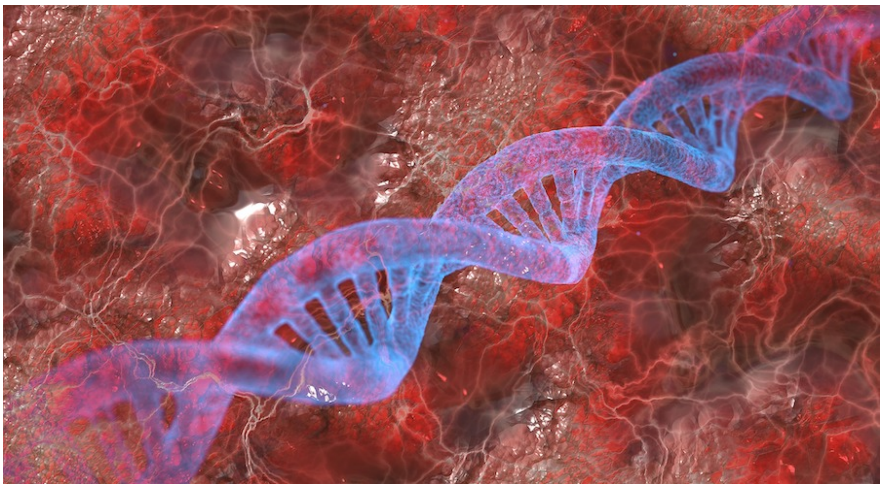
ABSTRACT

Scientists have developed a breakthrough method to genetically edit the genome of a developing mice fetus. This revolutionary treatment allows to treat a respiratory illness ahead of birth and it shows promise application for future treatment in humans.



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Diseases that affect young children and babies with no apparent cure are devastating to witness or even hear. One such group of diseases known as Children’s Interstitial and Diffuse Lung Disease (cHILD) has many symptoms associated with difficulty in breathing and a reduced ability of the air sacs in the lungs to absorb oxygen. This condition can lead to a lower life expectancy and in severe cases, can be life-threatening at an early age.

A mutation in a single gene is one of the leading causes of cHILD. The normal gene makes a protein that is a type of surfactant in the lungs. The lungs, like all machines, need to be 'well-oiled'. Surfactant proteins lubricate the air sacs of the lungs so that oxygen and carbon dioxide in the air we breathe can easily reach our blood. Therefore, just like the rusty gears on a bicycle that needs some 'WD-40', surfactant proteins are necessary for the vital intake of oxygen. Unfortunately, genetically inherited defects in surfactant proteins usually have limited treatment options, with researchers turning to gene editing as a possible solution.

The advancing field of gene editing with CRISPR-Cas9 technology allows scientists to make precise changes to DNA. It does this by using the protein, Cas9, to cut the DNA and introduce a specific 'edit' that will overwrite the original DNA sequence. CRISPR-Cas9 can change the DNA of almost any cell in an organism. Scientists have already successfully used this tool to change the DNA of a fertilized egg so that genetic mutations that are detected early on can be edited out. However, this is challenging for diseases of surfactant proteins as they are apparent only much later, usually nearer to a fetuses' birth. In the

case of cHILD, to attempt to cure it, the mutated gene would have to be edited in the older fetus instead while the lungs are still developing.

Researchers reasoned that they could cut out the entire defective gene in the mouse fetus so that it would be born with functioning lungs. To do this, they directly injected the editing machinery into the amniotic sac of the fetus, knowing that it would reach the lungs. Furthermore, the developing lungs of the fetus have lesser physical and immunological barriers for the editing protein to pass through. This straightforward method proved to be highly effective with cells in the lung, maintaining the genomic edit for up to 6 months after birth. Encouraged by the success of this method, they applied it to mice harboring the same gene mutation that leads to disease in humans. In mice, this mutation leads to deformities in adult lungs and certain conditions, no live births. This time, they used editing protein to delete out the entire defective gene, thereby eliminating the accumulation of the wrongly built protein that this mutation will produce. The results proved to be a success with a sizable percentage of the treated mice surviving birth with some up to a week, while none of the untreated mice survived beyond 6 hours of delivery. The mice that survived up to a week showed normal breathing, and when inspected, their lungs showed better development.

With this experiment, scientists demonstrated that the CRISPR-Cas9 technology could edit the genome of a fetus not only at a specific stage in its life, but it can target a particular organ. This result further leads to improvement and increased survival of a time-sensitive disease caused by a gene mutation in mice. However, for efficient therapies, it will be more complicated than deleting an entire gene and will need more targeted editing of the DNA.

For now, the safety and efficiency of editing the genome of a human fetus are unknown. Likewise, it is difficult to predict if the mother would be affected as well. However, this study opens up the possibility for future treatments of congenital disabilities that show themselves later in development. Like all parents that hope for a healthy child, the advancement of specific genetic congenital disabilities would provide them with more options for a better quality of life.