

Learning how Mechanical Forces Regulate Lung Development: Opportunities for Translational Research

Juan Sanchez-Esteban*

Associate Professor of Pediatrics, Alpert Medical School of Brown University, USA

Lung growth and development during fetal life are critical for extrauterine survival. Pulmonary hypoplasia secondary to congenital diaphragmatic hernia, oligohydramnios, etc, is an important cause of neonatal morbidity and mortality. In fact, pulmonary hypoplasia is the most common finding in neonatal autopsies [1]. In addition, more than 20,000 babies are born every year in the United States before 27 weeks of gestation (canalicular stage of lung development). These disorders have in common an incomplete development of the lungs. Despite the improvement in neonatal care, these conditions can cause serious short-term and long-term morbidities [2]. Currently, the management is primarily supportive and there is not specific treatment to stimulate the growth and development of the lungs.

Mechanical forces are a major determinant of fetal lung development [3-7]. Throughout gestation, the lung epithelium actively secretes fluid creating a constant distension pressure of around 2.5 mmHg in the potential airspaces [8]. In addition, the fetus makes Episodic Breathing Movements (FBM) starting in the first trimester and increasing in frequency up to 30% of the time by birth [9] (Figure 1). It is clear from experimental animals that drainage of lung fluid volume [10] or abolition of FBM [11,12] lead to lung hypoplasia. Therefore, both tonic hydrostatic distension and cyclic mechanical deformation provide physical signals necessary for normal fetal lung development. However, the mechanisms by which lung cells sense these mechanical signals and convert them into biochemical responses to promote lung development are not well-defined.

Tracheal ligation to stimulate lung growth and to correct pulmonary hypoplasia *in utero* has been used not only experimentally [13] but also in humans affected by congenital diaphragmatic hernia with some success [14]. However, and due to the high rate of complications [15], this treatment is only considered in severe cases of diaphragmatic hernia. Furthermore, this method has not been used in other forms of pulmonary hypoplasia, such as severe oligohydramnios secondary to prolonged rupture of membranes for example. *Therefore, a different way to approach this problem is to investigate how mechanical forces promote lung development and use that information to stimulate lung development.*

Past investigations in fetal lambs have shown that lung fluid composition after tracheal ligation was critical to promote lung development, since acceleration of growth and differentiation was not observed when lung fluids were replaced with normal saline [16,17]. The authors suggested that the increase of intra tracheal pressure after tracheal ligation releases soluble factors critical for lung maturation. This hypothesis is supported by previous *in vitro* studies from our laboratory in which fetal type II cells were isolated during the canalicular stage of lung development and exposed to stretch to mimic mechanical forces in lung development. Our data showed that differentiation of type II cells is mediated via release of Epidermal Growth Factor Receptor (EGFR) ligands. Specifically, mechanical stretch promotes cleavage and release of the soluble, mature forms of HB-EGF and TGF- α [18,19]. These growth factors induce differentiation by binding to the EGFR and subsequent phosphorylation of this receptor and activation of the ERK signaling pathway (Figure 2).

The identification of growth factors released by mechanical

forces that are important for normal lung development could lead to novel treatments to accelerate lung development. For instance, growth factors could be administered prenatally to fetuses affected by pulmonary hypoplasia secondary to congenital diaphragmatic hernia or oligohydramnios. Other potential candidates for this therapy are fetuses at borderline viability (22-24 weeks) and at risk for delivery. These growth factors could also be administered postnatally via endotracheal tube. This is just an example on how the information obtained from these *in vitro* mechanistic studies could have the

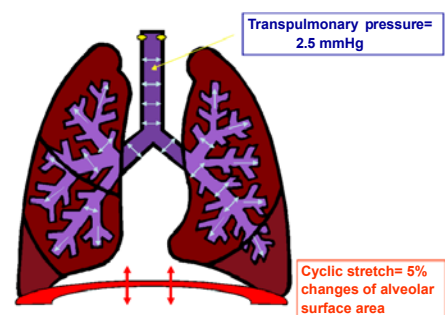


Figure 1: Mechanical forces are essential for normal lung development.

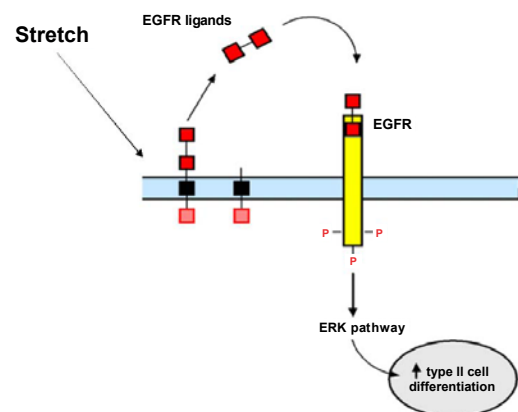


Figure 2: Mechanistic model to show how mechanical stretch promotes differentiation of type II epithelial cells via release of growth factors.

*Corresponding author: Juan Sanchez-Esteban, Associate Professor of Pediatrics, Alpert Medical School of Brown University, USA, E-mail: jsanchezesteban@wihri.org

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potential for clinical applicability. However, before considering their use in humans, rigorous experiments in animal models are required first to demonstrate the effectiveness of this therapy and the lack of side effects.

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