

Growth factors and fetal lung development mediated by mechanical forces

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Abstract

Incomplete development of the lung secondary to extreme prematurity or pulmonary hypoplasia causes significant morbidity and mortality during the neonatal period. Currently, the management is primarily supportive with no specific treatment to stimulate the growth and development of the lung. Mechanical forces generated inside the fetal lung by constant distention pressure and "breathing-like movements" are a major determinant of fetal lung development. However, the mechanisms by which lung cells sense these mechanical signals to promote lung development are not well-defined. Tracheal ligation has been used not only experimentally but also in human fetuses affected by severe congenital diaphragmatic hernia to stimulate lung growth and decrease the degree of pulmonary hypoplasia. Past investigations suggested that the increase of intratracheal pressure after tracheal ligation releases soluble factors that are critical for lung development. Studies from our laboratory have shown that mechanical strain of fetal type II epithelial cells, simulating mechanical forces in utero, promotes differentiation *via* release of epidermal growth factor receptor ligands heparin binding epidermal growth factor-like growth factor and transforming growth factor alpha. 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.

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Key words: Mechanical forces; Lung development; Tracheal ligation; Growth factors

Core tip: Identification of soluble factors released to the lumen of the lung after tracheal occlusion could lead to new therapeutic opportunities to accelerate lung development in newborns affected by extreme prematurity or pulmonary hypoplasia.

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INTRODUCTION

Pulmonary hypoplasia secondary to congenital diaphragmatic hernia, oligohydramnios, *etc.*, is an important cause of neonatal morbidity and mortality. Indeed, pulmonary hypoplasia is the most common finding (up to 26%) in neonatal autopsies^[1]. Furthermore, more than 20000 babies are born every year in the United States before 27 wk of gestation (canalicular stage of lung development). These disorders have in common an incomplete development of the lungs. In addition to the risk of death, these conditions can also cause severe respiratory distress at birth and serious long-term morbidities^[2]. Currently, the management is primarily supportive and there is not specific treatment to stimulate the growth/development of the lungs.

The lungs are unique in that their growth and development depends primarily on extrinsic factors and spe-

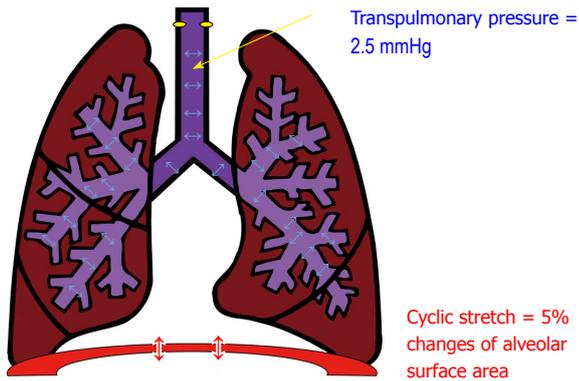


Figure 1 Mechanical forces generated by constant distension pressure (blue) and episodic breathing-like movements (red) are critical for normal fetal lung development.

cifically on mechanical forces^[3-7]. During gestation, the epithelium of the lung secretes fluid creating a constant distension pressure in the lumen of the lung of approximately 2.5 mmHg^[8]. Moreover, 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 to promote lung development are not well-defined.

Tracheal ligation has been used experimentally^[13] and in humans fetuses affected by congenital diaphragmatic hernia^[14] as a mechanism to increase the intraluminal pressure of the lung, accelerate development and minimize the degree of pulmonary hypoplasia. However, this approach has a high rate of complications such as pre-term labor, premature rupture of membranes and even death^[15] and limitations and inability to be used in other forms of pulmonary hypoplasia. Therefore, a different approach to 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]. These studies suggest that increased intratracheal pressure after tracheal ligation releases soluble factors that are important for lung development. This hypothesis is supported by previous *in vitro* studies from our laboratory in which fetal type II epithelial cells isolated during the canalicular stage of lung development were exposed to mechanical strain mimicking mechanical forces in lung development. Our data showed (Figure 2) that mechanical strain cleaves and releases the soluble, mature forms of epidermal growth factor receptor (EGFR) ligands heparin

binding epidermal growth factor-like growth factor and transforming growth factor alpha (TGF- α)^[18,19]. Release of these soluble factors bind and activate the EGFR *via* autocrine or paracrine signaling and promote differentiation of type II cells *via* the extracellular signal-regulated kinase signaling pathway (Figure 3).

The identification of soluble factors released by mechanical forces that are important for normal lung development could lead to novel avenues to accelerate lung development. Potential translational research applications would be prenatal administration to fetuses affected by pulmonary hypoplasia secondary to congenital diaphragmatic hernia or oligohydramnios or fetuses with borderline viability (22-24 wk) and at risk for delivery. Another theoretical application would be postnatal administration *via* the endotracheal tube. This is just an example on how the information obtained from these *in vitro* mechanistic studies could have the potential for clinical applicability. However, the therapeutic applicability of TGF- α in human neonatal and adult lung diseases is questionable since animal studies have demonstrated that transgenic overexpression of TGF- α disrupts neonatal lung development^[20] and induces adult lung fibrosis^[21]. In addition, increased epithelial EGF receptor signaling mediates airway hyperreactivity and remodeling in a mouse model of chronic asthma^[22]. Therefore, 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 untoward side effects.

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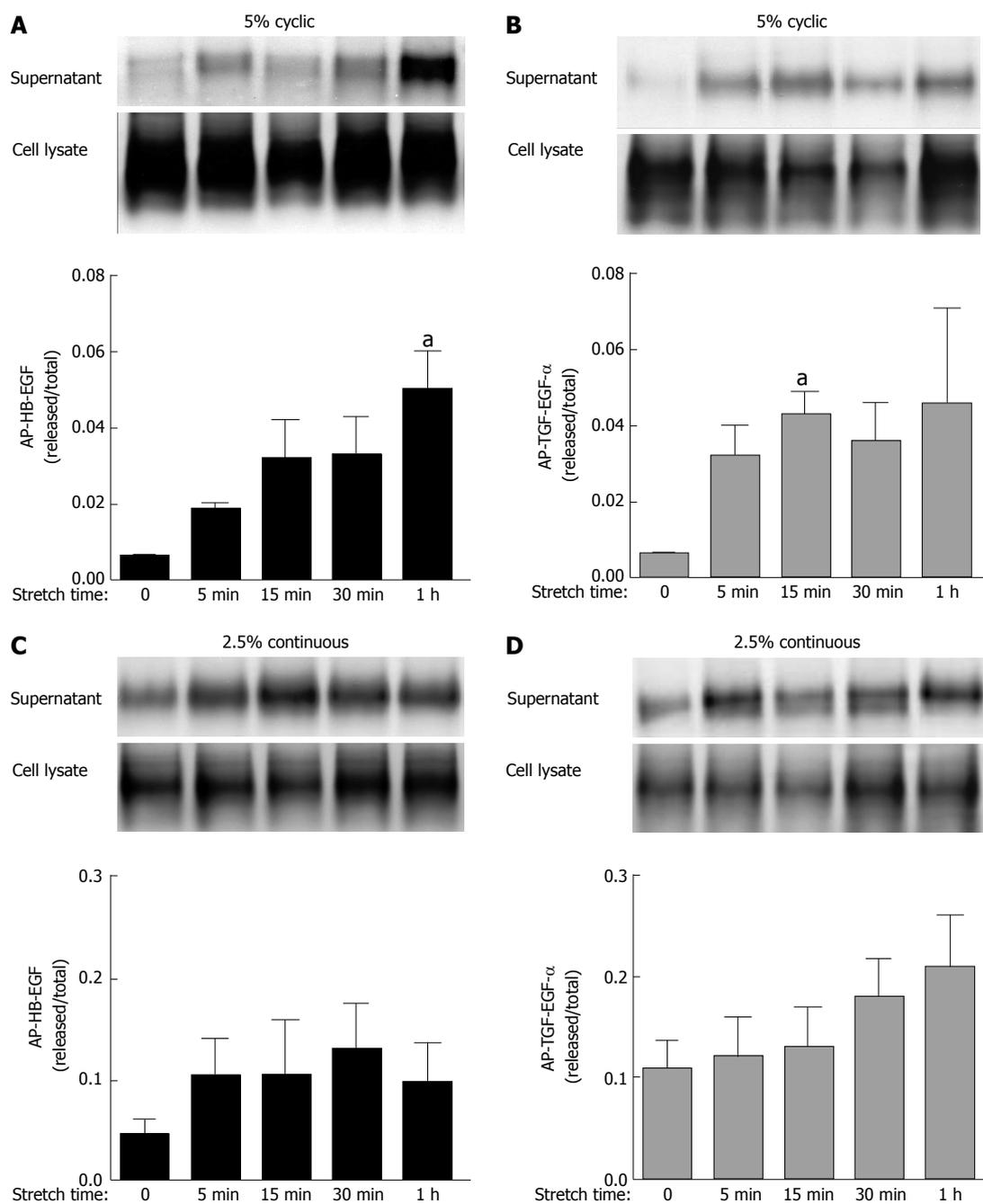


Figure 2 Cyclic mechanical strain releases heparin binding epidermal growth factor-like growth factor and transforming growth factor alpha ligands. Fetal type II cells were transfected by electroporation with cDNA constructs encoding alkaline phosphatase-tagged heparin binding epidermal growth factor-like growth factor (HB-EGF) and transforming growth factor alpha (TGF- α) ligands. 24 h later, cells were exposed to 5% cyclic strain or 2.5% continuous strain for the indicated periods of time. Samples were processed to assess ligand-release into the supernatant using the alkaline phosphatase shedding assay protocol. Data are expressed as the intensity of each alkaline phosphatase (AP) supernatant band divided by total AP (supernatant + cell lysate). Upper panels shown representative blots. Data in the lower panels are from three independent experiments. ^a $P < 0.05$ vs unstretched samples for 1 h.

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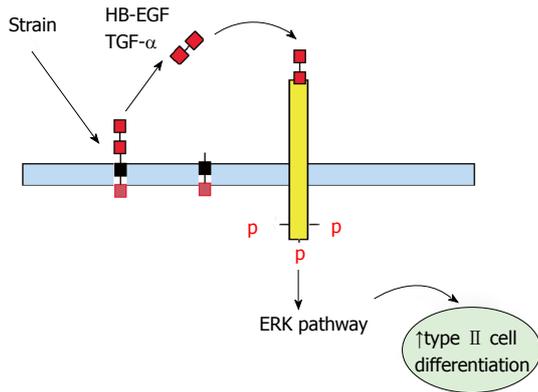


Figure 3 Mechanistic model. How mechanical forces promote differentiation of fetal type II epithelial cells via release of soluble growth factors heparin binding epidermal growth factor-like growth factor (HB-EGF) and transforming growth factor alpha (TGF- α) with subsequent binding and activation of the epidermal growth factor receptor and extracellular signal-regulated kinase (ERK) signaling pathway.

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