Cellular Responses to Mechanical Stress
Invited Review: Mechanochemical signal transduction in the fetal lung

MINGYAO LIU$^1$ AND MARTIN POST$^2$
$^1$Thoracic Surgery Research Laboratory, University Health Network, Toronto General Hospital, Toronto M5G 2C4; and $^2$Lung Biology Program, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada M5G 1X8

Liu, Mingyao, and Martin Post. Invited Review: Mechanochemical signal transduction in the fetal lung. J Appl Physiol 89: 2078–2084, 2000.—Growth and maturation of fetal lungs are regulated by both humoral and physical factors. Mechanical stretch stimulates fetal lung cell proliferation and affects fetal lung maturation by influencing the production of extracellular matrix molecules and the expression of specific genes of fetal lung cells. These effects are mediated through special signal transduction pathways in fetal lung cells. Various in vivo and in vitro model systems have been developed to investigate the mechano-transduction process. The diversity and discrepancy of these studies have raised many questions. We will briefly summarize mechanical force-induced signals in fetal lung cell proliferation and differentiation and then discuss several important issues related to these studies.

mechanotransduction; proliferation; differentiation; maturation; intracellular signaling

PHYSICAL FORCES AND FETAL LUNGS

Based on clinical observations and physiological studies, it has been realized for a long time that physical factors play important roles in regulating fetal lung growth and maturation (12, 13, 18, 19). Physical force-related lung disorders during the perinatal period could be very severe or lethal. Pulmonary hypoplasia is the most common single autopsy finding in the first week after birth (20, 35). It is associated with a variety of congenital disorders and malformations, which have in common a reduction in lung volume and/or fetal breathing movements (20, 35). For example, lesions such as congenital diaphragmatic hernia (8) and thoracic abnormalities (6) limit the amplitude of fetal breathing movements and reduce the liquid volume and pressure in the potential airway and alveolar space. In utero tracheal occlusion is one of the most potent stimuli of fetal lung growth (4). Clinical trials have been conducted to test whether this approach could be used to treat severe pulmonary hypoplasia (7, 15). However, it has been found from animals that prolonged tracheal occlusion causes qualitative and quantitative deficiencies of the lung alveolar type II epithelial cells, resulting in significant reduction of lung surfactant and surfactant proteins (SPs) (17). To properly overcome pulmonary hypoplasia, mechanisms regulating mechanical stretch-induced cell proliferation and differentiation need to be elucidated.

Bronchopulmonary dysplasia is the most common cause of chronic lung disease in infants (36). Mechanical ventilation-induced lung injury, as well as pulmonary immaturity, oxygen toxicity, and secondary infection, are the major etiologic factors for this disease. Many clinical studies and animal models have been developed to investigate the effects of physical forces on fetal and neonatal lung growth, maturation, and injury (3). However, it is difficult to ascribe the effects of mechanical perturbation to individual components, because of the cellular and spatial complexity of lung tissue. Models at the cellular and molecular levels have been developed over the last decade. The effects of
physical forces on the functions of lung cells have drawn increasing attention (27). In this paper, we will focus on mechanical stretch-induced fetal lung cell proliferation, differentiation, and cellular injury, and related signal transduction events.

**PHYSICAL FORCES AND FETAL LUNG CELL PROLIFERATION**

In a fetal sheep model, it was found that, after tracheal obstruction, fetal lung DNA synthesis rates increased to a maximum at day 4, and returned to control levels by day 10 (16). However, the relative contributions of fetal breathing movements vs. lung volume cannot be easily resolved by using experimental animal models, because these two mechanisms are interdependent, i.e., breathing movements influence regional lung volume and the effectiveness of breathing movements depends on an adequate lung volume. Most experimental approaches in animal models cannot discriminate between the effects of the static stretch of lung liquid in the potential airways and the effects of cyclic stretch derived from fetal breathing movements (13). For example, spinal cord transection has been used to abolish fetal breathing movements, but it also reduces fluid production from the potential airway (14). In vitro studies, therefore, are very helpful in determining the role of stretch in fetal lung cell proliferation.

Different from regular breathing, the bursts of fetal breathing movements are separated by resting periods (12). Using a three-dimensional (3D) culture model (24, 45), it has been shown that an intermittent mechanical stretch regimen (5% elongation, 60 cycles/min, 15 min/h) stimulated DNA synthesis and cell division of mixed fetal rat lung cells (26). A continuous cyclic stretch (1 cycle/min) has been shown to increase DNA synthesis of primary cultured fetal rabbit pneumocytes cultured as a monolayer (43). Continuous stretch (60 cycles/min) also stimulated proliferation of a human embryonic fibroblast cell line (IMR-90) (1). In addition, the 3D cell-stretch model increased proliferation of primary cultured fetal rat lung fibroblasts as well as epithelial cells (29, 54) in a gestational-dependent manner (54). Therefore, cyclic mechanical stretch appears to stimulate fetal lung cell growth directly.

Mechanical stretch-induced fetal lung cell proliferation is mediated by growth factors. It has been found that conditioned medium collected from stretched fetal rat lung cells contained proliferating activities for static cultured fetal rat lung epithelial cells (31). Similarly, conditioned medium from the human embryonic fibroblasts (IMR-90 cell line) enhanced proliferation of static cultured cells (1). Further studies with fetal rat lung cells demonstrated that mechanical stretch stimulated gene expression and protein synthesis of platelet-derived growth factor B (PDGF-B) and its β-receptor (23). These in vitro results are in agreement with observations from animal models. Either lung liquid drainage (16) or spinal cord transection (14) decreased mRNA levels of insulin-like growth factor II, whereas tracheal occlusion increased insulin-like growth factor II mRNA expression (16). Therefore, mechanical stretch could effectively and inversely regulate the production of growth factors and enhance the responsiveness of cells to growth factors by upregulating the expression of related receptors, which can further mediate cell proliferation through autocrine and/or paracrine mechanism(s) (27).

Mechanical stretch-induced cell-proliferating activities are mediated through intracellular signal transduction pathways (27). It appears that mechanical stretch-induced activation of protein kinase C (PKC) is critical for the mediation of stretch-induced proliferation of fetal rat lung cells (28). PKC activation requires increased diacylglycerol (DAG) and Ca\(^{2+}\) mobilization from its intracellular storage with inositol 1,4,5-trisphosphate \([\text{Ins}(1,4,5)\text{P}_3]\) as the second messenger (28). Mechanical stretch activates protein tyrosine kinases (PTK), such as pp60\(^{src}\), which consequently activates phospholipase C\(\gamma\) (PLC\(\gamma\)) by increasing its tyrosine phosphorylation (25). Activated PLC\(\gamma\) resulted in hydrolysis of phosphatidylinositol 4,5-diphosphate to generate DAG and \([\text{Ins}(1,4,5)\text{P}_3]\) (28). In addition, phospholipase D is also activated by mechanical stretch, which maintains the prolonged elevation of DAG levels after the onset of mechanical stretch (28). The entry of extracellular Ca\(^{2+}\) through stretch-activated ion channels is also involved in stretch-induced PKC activation and cell proliferation. Blocking these steps on the signal pathway inhibited or attenuated stretch-induced fetal lung cell growth (23, 25, 28–30). Therefore, the PTK-PLC\(\gamma\)-PKC axis appears to be a major pathway for stretch-induced proliferation of fetal rat lung cells (Fig. 1).

How PKC mediates stretch-induced fetal cell proliferation is still unknown. One possible mechanism is to activate transcriptional factors, which can bind to the regulatory elements of the promoter region of the target gene. A shear stress-response element has been characterized for the PDGF-B chain promoter (39) and has also been found in several other genes that could be induced by shear stress (39). A stretch response element (42) and several other similar elements, which could mediate physical force-initiated gene expression in various cell types, have also been found from different genes (summarized in Ref. 27). Whether similar mechanisms are present in fetal lung cells needs to be elucidated. Once the expression of growth factors is upregulated, newly synthesized growth factors may activate their specific receptors and further stimulate cell proliferation (Fig. 1). It is likely that the interaction between mechanotransduction pathways and growth factor-related signal transduction pathways is overlapping, which requires further investigation.

In addition to the PTK-PLC\(\gamma\)-PKC axis, several other signal transduction pathways are also activated by mechanical stretch in fetal or adult lung cells (27). For example, cAMP is increased by stretch in fetal lung cells (43, 46). The p125\(^{FAK}\) pathway is activated by stretch in airway smooth muscle cells (47) and so is mitogen-activating protein kinase in type II pneumo-
cytes (38). However, the downstream cellular functions mediated by these pathways still need to be elucidated.

**PHYSICAL FORCES AND LUNG CELL DIFFERENTIATION**

Maturation of the fetal lung is a complicated process that requires proper coordination of cell growth and differentiation at each stage of lung development. Mechanical force-initiated signals have been found to affect the gene expression, protein synthesis, and secretion of many differentiation-related molecules. The effects and signals vary, depending on the molecules of interest, gestational stages, experimental conditions, and many confounding factors. Thus in contrast to the stretch-induced cell proliferation, mechanical forces likely affect these molecules through many different mechanisms and signaling pathways.

**Effects of mechanical forces on extracellular matrix molecule production from fetal lung cells.** Synthesis and secretion of extracellular matrix (ECM) molecules is one of the important signs of lung maturation. ECM plays important roles in holding different cell types together and mediating cell proliferation and differentiation via cell-ECM interactions. The components of ECM can be divided into four broad categories: collagens, noncollagenous glycoproteins (such as fibronectin and laminin), glycosaminoglycans (GAGs) and proteoglycans, and elastic fibers (11).

Mechanical force has significant impact on the synthesis and secretion of several of these ECM molecules. Applying intermittent cyclic stretch to mixed fetal rat lung cells in 3D culture inhibited the accumulation of fibronectin mRNA but stimulated synthesis and secretion of fibronectin protein (33), suggesting that stretch-mediated fibronectin production is mainly a posttranscriptional event. Mechanical stretch also stimulated secretion of proteoglycans and GAGs from fetal rat lung cells via both the constitutive and regulatory secretory pathways (52). Fetal lung cells secreted GAGs mainly through the constitutive pathway that was further stimulated by mechanical stretch. Stretch-induced constitutive secretion could be partially blocked by the cytoskeletal disrupting agents, colchicine or cytochalasin B, but not by the small G-protein inhibitors. Mechanical stretch also triggered the regulatory secretion of GAGs. The stretch-induced regulatory pathway depended on a rapid Ca²⁺ influx via stretch-activated ion channels (52). As mentioned in **PHYSICAL FORCES AND FETAL LUNG CELL PROLIFERATION**, activation of stretch-activated ion channels is also an important component of stretch-induced activation of PKC and cell proliferation (28, 29). This is a good example of how a single signaling mechanism, initiated by mechanical stretch, can participate in different cellular processes. With the use of the same 3D culture and stretch regimen, mechanical stretch reduced mRNAs for procollagen-α(I) but increased the levels of mRNA for collagen-α(I) and α(II) (53). Regardless of mRNA changes, mechanical stretch increased the protein content of type I and type IV collagens in the cell culture medium (53). In this model, mechanical stretch did not affect gene expression of several matrix metalloproteinases (MMPs), such as MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), and MMP-3 (stromelysin 1). Neither collagenase nor gelatinase (A and B) activities in conditioned medium were affected by mechanical stretch. Tissue inhibitor of metalloproteinase activities in conditioned medium also remained unchanged during mechanical stretching (53). Therefore, the increase in ECM molecules appears to be mainly a result of an increased synthesis of these molecules and not of decreasing activity of degrading enzymes (53).

Fig. 1. Mechanical stretch-activated intracellular signal transduction pathways. Putative mechanisms of mechanical stretch-induced fetal lung cell proliferation are used as an example to demonstrate the complexity of mechanotransduction in fetal lung cells. Mechanical stretch activates protein tyrosine kinases (PTK) and consequently activates phospholipase C (PLC) via its tyrosine phosphorylation. PLC mediates the hydrolysis of phosphatidylinositol 4,5-biphosphate (PIP₂) to produce inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG). DAG activates protein kinase C (PKC), which requires Ca²⁺ mobilized by IP₃ from intracellular storage and the entry of extracellular Ca²⁺ via stretch-activated ion channels. Phosphotidylcholine (PC) is another source of DAG through stretch-induced activation of phospholipase D (PLD). PKC and other signals may activate transcriptional factors that bind to special response elements, such as stretch response element (SRE) and shear stress response element (SSRE). Increased gene expression and production of growth factors and their receptors may further regulate cell proliferation via related signal pathways.
A continuous cyclic stretch regimen applied to a monolayer culture of the human fetal lung fibroblast cell line (IMR-90) increased procollagen protein synthesis when the cells were cultured on a laminin or elastin, but not fibronectin, substrate. It was concluded that this response is signaled by cell-ECM interactions (2). However, in contrast to the results from fetal rat lung organotypic cultures (53), the increased procollagen production was associated with increased α1(I) procollagen mRNA (2). Thus, although collagen synthesis increased in both studies, the regulatory mechanisms appear not to be the same. This difference may be due to primary culture vs. cell line, or two-dimensional (2D) monolayer vs. 3D cultures.

Mechanical stretch can also activate gene transcription of ECM proteins. For example, mechanical stretch-induced tropoelastin gene expression of fetal rat lung cells has been found to be associated with increased transcriptional activation of the gene (34).

**Effects of mechanical stretch on fetal lung epithelial cells.** It has long been thought that hormonal factors control fetal lung differentiation, whereas mechanical factors control growth (9, 17). However, mechanical stretch also affects fetal lung epithelial cell differentiation. The pulmonary alveolar epithelium of the mature lung is composed of two types of cells. Type I cells, which cover most of the alveolar wall for gas exchange, are extremely large and very thin. Type II cells are cuboidal-shaped cells containing morphologically distinct lamellar bodies, the storage organelles of pulmonary surfactant. Type II cells are likely progenitors of type I cells. The morphology, function, and phenotype of alveolar epithelial cells continuously change during development. During early lung development, undifferentiated alveolar epithelial cells have a cuboidal appearance but contain few lamellar bodies. They further differentiate into type II cells, and some of them then turn to type I cells.

Specific genes and proteins have been used as markers to determine the effects of mechanical forces on alveolar epithelial cell differentiation. Although prolonged tracheal obliteration in fetal sheep stimulated lung cell growth, it also reduced the mRNA levels of SP-C, a specific marker for type II cells (37). In addition, tracheal ligation in sheep reduced SP-A mRNA (21), as well as protein (17). It has been suggested that this decrease in SP expression is due to a reduction in the number of differentiated type II cells, which is associated with an increase in the number of differentiated type I cells (37). To further determine the effects of mechanical stretch on SP gene expression, a time course study was conducted. It was found that, after 2 or 4 days of tracheal obliteration, time points before the conversion of type II cell into type I cells (as identified by the presence of lamellar bodies with electron microscopy), the mRNA levels of SP-B and SP-C were already decreased (21). Furthermore, lung liquid drainage, an experimental approach to reduce the mechanical distention on lung cells in vivo, significantly increased SP-C but not SP-A mRNA levels (21). These results suggest that SP-C gene expression is closely and inversely regulated by the degree of lung expansion. In the time course study, a time delay was observed between the drop of SP-A mRNA and that of SP-A protein, but both drops occurred before the conversion of type II cells into type I cells (21).

To further study the molecular mechanisms of stretch on alveolar epithelial cell gene expression, Gutierrez et al. (9) used a lung explant culture model to apply static mechanical distension to small pieces of fetal rat lung parenchymal tissues. Stretch increased rTI40 mRNA, a specific marker for type I cells after 18 h, as well as rTI40 protein, as determined by immunofluorescent staining. Meanwhile, the expression of SP-B and SP-C, specific markers of type II cells, decreased (9). These effects were at least partially regulated at the transcriptional level, as determined by nuclear run-on assay (9). Similar results were obtained when primary cultured adult type II pneumocytes were statically stretched with the same apparatus (10). In contrast, intermittent stretch resulted in an increase in SP-C gene expression because of an increase in transcription in fetal rat lung cells (34). Furthermore, contrary to the in vivo observation (21), the mRNA levels of SP-A were not altered by mechanical distension either in the fetal lung explant model (9) or the primary cultured adult type II pneumocytes (10). SP-A gene expression was also not affected in organotypic cultures of fetal lung cells subjected to intermittent cyclic stretch (34).

Regardless of the effects on SP gene expression, mechanical stretch stimulates the secretion of lung surfactant lipids from either adult rat lung type II cells (40, 41, 51) or fetal rabbit pneumocytes (43).

These results are important in the context of clinical application of tracheal obliteration as a therapeutic modality. Ideally, we should stimulate the fetal lung growth as well as maturation. A timely control of tracheal obliteration, combined with other methods, such as administration of hormones, surfactant, and proper mechanical ventilation, should be considered.

**IMPORTANT ISSUES FOR MECHOTRANSDUCTION STUDIES**

Above, we described that mechanical stretch has different effects on gene expression and other cellular functions when applied under different experimental models (in vivo vs. in vitro), on different cells (primary culture vs. cell line), and with different cell culture conditions (static vs. cyclic stretch, 2D vs. 3D culture, single cell types vs. mixed cells, etc.). These discrepancies of experimental results from mechanotransduction studies raise many questions that need to be addressed in future investigations.

**In vivo vs. in vitro.** The complexity and chronic nature of in vivo experimental systems make mechanical force-induced intracellular or intercellular signal transduction studies difficult or impossible. Cell stretch and lung explant stretch models in vitro could provide invaluable information if they are used properly. In tissue culture studies, lung tissues or cells are sub-
involved in augmenting glucocorticoid binding, in-
has been postulated that this paracrine mechanism is
blasts, stimulating cAMP as the second messenger, to
blasts to PTHRP (49). PTHRP released by type II cells
of a differentiation factor, parathyroid hormone-re-
on the same cells may activate different signal trans-
epithelial cells. These different types of physical forces
various developmental stages, and with different me-
face area-lung volume relationship in other species, at
fetal lungs because the potential airway is filled with
folding-unfolding phenomenon may not exist in the
lung volume in isolated adult rat lungs using electron mi-
scope followed by morphometric analysis. They
also established a mathematical model to correlate the
stretch applied to cells cultured on flexible membrane
to lung volume changes in vivo (50). It is worthwhile to
note that the cellular surface area-lung volume relation-
ship may vary among different species, and the
folding-unfolding phenomenon may not exist in the
fetal lungs because the potential airway is filled with
liquid. Further studies to define and compare the sur-
face area-lung volume relationship in other species, at
various developmental stages, and with different me-
chanical ventilation strategies will provide essential
information for mechanotransduction studies in vitro.

In addition, on different sites of cells, the types of
physical forces are also different. For example, liquid
in the potential airway of fetal lungs applies pressure
and fluid shear stress on the apical surface of epithel-
ium, whereas the distension from the basement mem-
brane applies stretch to the basolateral surface of the
epithelial cells. These different types of physical forces
on the same cells may activate different signal trans-
duction pathways to mediate different biological func-
tions.

Cell-cell interaction. Interactions between different
cell types or the interactions among the same type of
cells via autocrine and paracrine mechanisms are
likely important for mechanical force-initiated signal-
ing. It has been found that mechanical stretch in mono-
layer culture stimulated the expression and production
of a differentiation factor, parathyroid hormone-re-
lated peptide (PTHRP), from fetal lung epithelial cells
and increased the responsiveness of fetal lung fibro-
blasts to PTHRP (49). PTHRP released by type II cells
can specifically bind to its receptor on contiguous fibro-
blasts, stimulating cAMP as the second messenger, to
induce specific functions of fetal lung fibroblasts (49). It
has been postulated that this paracrine mechanism is
involved in augmenting glucocorticoid binding, in-
creasing metabolic activities (such as lipoprotein lipase
elaboration and triglyceride uptake), and stimulating
production of cytokines (such as interleukin-6 and -11).
These cytokine molecules may act as intercellular me-
diators and, thereby, increase the synthesis of surfac-
tant phospholipids and SPs from alveolar epithelial
cells (49). Mechanical stretch-induced upregulation of
PDGF-B and its β-receptor is another example of aut-
crine and/or paracrine communication (23). Thus, on
one hand, stretch increases the production of growth
factors, and, on the other hand, stretch enhances the
responsiveness of target cells toward these proliferat-
factors.

In addition to these soluble mediators, direct cell-cell
contact and cell-ECM interactions are also very im-
portant. To elucidate the interactions between different
cell types, isolated fetal rat lung epithelial cells and
fibroblasts have been recombined in various ratios (54).
To further elucidate the gestational-specific interac-
tions between these two cell types, epithelial cells iso-
lated from one gestational stage have been mixed with
fibroblasts isolated from another stage, and the result-
ning recombinants have been subjected to mechanical
stretch (54). These results showed that the mechanical
stretch-induced fetal rat lung cell proliferation was
mainly determined by the responsiveness of mesenchy-
mal cells (54). The importance of cell-ECM interactions
has been demonstrated by stretching cells cultured on
different ECM substratum (2, 29).

3D vs. 2D culture: maintaining cell phenotypes. An
important issue in studying lung-specific functions and
gene regulations is to maintain the phenotypes of lung
cells. For this reason, primary cultured cells are com-
monly used, even though it is very expensive, time
consuming, and technically demanding with greater
interexperimental variations. To prevent the loss of
cell phenotype, rat alveolar epithelial cells, for exam-
ple, were stretched 1 day after being inoculated on
fibronectin-coated membranes (10). Fetal lung ex-
plants have been used to maintain the 3D property of
lung tissues (10). Mixed fetal rat lung cells in organo-
typic culture is another method to create miniature
“alveolar-like structures” in vitro (26, 29, 44). Cultur-
ing lung cells in a 3D environment has been considered
an important issue (22), specifically for mechanotrans-
duction studies (27). However, data from mixed cell
cultures are usually difficult to interpret, and the 3D
structure of tissues makes the observation of cell mor-
phology and other microscopic studies less possible.
Therefore, mechanotransduction studies using mono-
layer cell culture are needed, but some important cel-
lar responses have only been observed when different
cell types were coexisting (22, 29).

Cofactors of mechanotransduction pathways. The
presence of costimuli is also very important to simulate
in vivo conditions for mechanotransduction studies. At
different gestational stages, the endocrine system pro-
vides a different hormonal environment for the fetal
lung cells. These environmental conditions need to be
considered carefully when planning related studies in
vitro. Mechanical stretch and oxygen toxicity are the
two major components of ventilation-induced acute lung injury, especially in infants (36). The combined effects of stretch and oxygen need to be studied. The transmission of signals initiated by mechanical stretch could depend on the activation of other pathways. For example, PGI₄ and its stable chemical analog iloprost enhanced mechanical stretch-induced surfactant secretion in alveolar epithelial type II cells by increasing cAMP content, whereas the increase in cGMP content, induced by a nitric oxide donor, spermine NONOate, has no such effect (41). Prostacyclin could bind to its cellular membrane receptor through G protein to activate the cAMP-protein kinase A pathway and to facilitate mechanical stretch-activated signals for surfactant secretion (41). Similar mechanisms may exist for other factors when they are applied to cells together with mechanical forces.

Static vs. cyclic stretch. A major debate over the past three decades has been the importance of fluid-derived airway expansion vs. fetal breathing movements in fetal lung development (17, 18), because both are interdependent in animal models. With the use of cell or tissue culture models, it has been shown that both static (tonic) (9, 10, 51) and cyclic stretches (1, 2, 26, 45) have profound effects on cellular functions. Mechanical stretch is applied to the substratum on which cells or lung explants are cultured. Detachment and reattachment of cells through cell-ECM interaction continuously change the adhesion of cells to the surface of culture substratum. Thus, when prolonged static stretch is applied to the substratum, the tension applied to the cells could be released by the rearrangement of cells. Similarly, it has been found that the alignment of cells can be changed by cyclic stretch. Randomly distributed fetal lung cells on culture surface could be rearranged perpendicularly to the direction of the stretch (1, 2).

Intermittent cyclic stretch has been used to simulate fetal breathing movements (26, 45). The response of cells to this type of stretch pattern could be very different from either continuous static or cyclic stretch. It has been noted that an intermittent stretch stimulated cell proliferation (26, 29, 54) and ECM production (33, 52, 53) of fetal rat lung cells without cellular injury (26), whereas a continuous cyclic stretch induced cytokine production (32) and cell injury (32, 48). With primary cultures of adult type II cells, it has been found that mechanical stretch not only increased lung surfactant secretion, but also induced apoptosis (5). Therefore, the type of stretch regimen is crucial for mechanotransduction studies.

In summary, mechanical force-initiated intracellular signaling is an important regulatory mechanism for proper fetal lung cell proliferation and differentiation. Understanding this mechanism at the cellular and molecular level will help us to elucidate how fetal lung growth and maturation are regulated by mechanical forces, to design therapeutic strategies to overcome pulmonary hypoplasia during fetal lung development, and to prevent the development of bronchopulmonary dysplasia after birth.

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