



Reduced Prenatal Pulmonary Lymphatic Function Is Observed in *Clp1^{K/K}* Embryos With Impaired Motor Functions Including Fetal Breathing Movements in Preparation of the Developing Lung for Inflation at Birth

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Embryonic lungs must be inflated immediately after birth to establish respiration. In addition to pulmonary surfactant, recently, we have revealed lymphatic function as a previously unknown regulator of prenatal lung compliance that prepares the embryonic lung for inflation at birth. It is well-documented that the late gestation embryo performs episodic breathing-like movements called as fetal breathing movements (FBMs), but the physiological importance of these events is not clear. Here we aimed to study the physiological role of FBMs in preparation for air inflation at birth. *Clp1^{K/K}* late gestation embryos develop a progressive loss of spinal motor neurons associated with axonal degeneration and denervation of neuromuscular junctions serving as an ideal genetic model to test the possible role of FBMs. We demonstrated that *Clp1^{K/K}* newborns show impaired motor function resulting in fatal respiratory failure after birth. Next, we showed that the alveolar septa are thicker, and the alveolar area is reduced in *Clp1^{K/K}* late gestation embryos, while the expression of molecular markers of lung development are not affected. Importantly, pulmonary lymphatic vessels are dilated and the prenatal pulmonary lymphatic function is reduced in *Clp1^{K/K}* late gestation embryos. Our results have revealed that *Clp1^{K/K}* mice show impaired motor functions including FBMs, and late gestation *Clp1^{K/K}* embryos display reduced prenatal lymphatic function and impaired lung expansion represented as thickened alveolar septa and reduced alveolar area in preparation of the developing lung for inflation at birth. These findings suggest a possible mechanism that FBMs, similarly to breathing movements after birth, stimulate prenatal lymphatic function in pulmonary collecting lymphatics lacking smooth