Establishing a late gestational hypoxia model to study the effects of maternal hypoxia on offspring lung outcomes

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Maternal health during pregnancy is critical for proper newborn development. One example of maternal stress is being deprived of oxygen, termed as hypoxia. In human and animal models, substantial research has linked pregnancy at high altitude (<13% oxygen level) to organ development impairment of the fetus and newborn, including the lungs. Previous studies have focused on prenatal hypoxia affecting fetal development and perinatal hypoxia affecting adulthood. Prenatal hypoxia results in physiological stress to the body, resulting in oxidative damage and inflammation. Our lab is specifically interested in understanding the mechanisms responsible for abnormal lung and pulmonary vascular development and function across the age span. There are five stages involved in lung development: embryonic, pseudoglandular, canalicular, saccular, and alveolar. I am interested in the canalicular stage where the respiratory bronchioles and consequently, alveolar ducts are formed for gas exchange. Without normal development of this stage, alveoli, the air sacs in the lungs, will not efficiently take in oxygen and release CO_2. I that hypothesize that late gestational hypoxia, beginning at embryonic day 16.5, will impair lung and pulmonary vascular development in offspring.

I have developed a mouse model of late gestational hypoxia to study lung outcomes after birth and into early adulthood. Pregnant mice will be exposed to hypobaric hypoxic chambers (13% FiO2) at embryonic day 16.5 (E16.5), which is the time of gas exchange formation in the lungs, to birth. I will test the hypothesis on *14-day-* and *6-week-old offspring* in wildtype mice. To define the effects of late gestational hypoxia on pulmonary and pulmonary vascular development in the offspring, lungs will be agarose-inflated, and paraffin embedded for lung sections. Analysis of radial alveolar count quantification (RAC) and mean linear intercept (MLI) will be conducted in the distal lung to detect changes in the alveolar development. RAC measures the number of alveolar septae while MLI measures the distance between alveolar septae. To determine if the offspring exposed to prenatal hypoxia develop pulmonary hypertension, we will measure right ventricular systolic pressure via right heart puncture and right ventricle hypertrophy by weighing the right ventricle and left ventricle plus the septum.

We found a significant decrease in weight and length at postnatal day 4 (P4) of offspring exposed to prenatal hypoxia. However, by P14 both growth parameters have been recovered. In offspring exposed to prenatal hypoxia at P14 and P42, there is decreased RAC and conversely increased MLI suggesting impaired alveolar development. Importantly, though the offspring growth recovered, their lungs did not.

For future studies, I am interested in understanding the mechanisms responsible for abnormal lung and pulmonary vascular development and function due to prenatal hypoxia.