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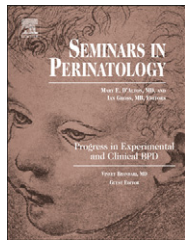

Regular article

The role of hyperoxia in the pathogenesis of experimental BPD ☆

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ABSTRACT

Supplemental oxygen is often used as a life-saving therapy in the treatment of preterm infants. However, its protracted use can lead to the development of bronchopulmonary dysplasia (BPD), and more recently, has been associated with adversely affecting the general health of children and adolescents who were born preterm. Efforts to understand how exposure to excess oxygen can disrupt lung development have historically focused on the interplay between oxidative stress and antioxidant defense mechanisms. However, there has been a growing appreciation for how changes in gene–environment interactions occurring during critically important periods of organ development can profoundly affect human health and disease later in life. Here, we review the concept that oxygen is an environmental stressor that may play an important role at birth to control normal lung development via its interactions with genes and cells. Understanding how changes in the oxygen environment have the potential to alter the developmental programing of the lung, such that it now proceeds along a different developmental trajectory, could lead to novel therapies in the prevention and treatment of respiratory diseases, such as BPD.

Preterm birth (defined as live birth prior to 37 weeks of completed gestation) affects an estimated 15 million infants worldwide every year, with over 1 million of these infants dying due to complications of being born too soon.[1] Although there has been a marked reduction in mortality associated with respiratory disease in this vulnerable population of infants due to improvements in perinatal care, the prevalence of respiratory morbidity has unfortunately not changed.[2,3] Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease that develops as a result of neonatal lung injury and is one of the most common complications of preterm birth.[4,5] Although BPD is a multi-causal disease, its etiology is largely attributed to premature exposure to oxygen and the production of cytotoxic reactive oxygen species (ROS) that injure or reprogram the development of the lungs.[6,7] In fact, children who develop BPD are often re-hospitalized following respiratory infection and are at an increased risk for reduced lung function as they age.[3,8,9] Moreover, these children are also at a higher risk for retinopathy of prematurity, impaired learning, and high blood pressure.[10–12] Nevertheless, as the number of surviving infants near the lower limit of viability continues to rise, the number of children with respiratory diseases is also likely to increase. Therefore, there is an urgent need to understand how prematurity and early-life exposure to oxygen contribute to the pathogenesis of BPD and general health later in life.

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Although the introduction of mechanical ventilation with high concentrations of oxygen (hyperoxia) to the neonatal intensive care unit (NICU) improved the survival of preterm infants with respiratory distress syndrome (RDS), it resulted in a new form of lung injury and disease, later termed BPD by Northway et al.[13] BPD was initially described in a cohort of moderately preterm infants (mean gestational age of 34 weeks) in the late saccular stage of lung development who were treated with aggressive mechanical ventilation and high fractions of inspired oxygen due to severe respiratory distress.[13] Pathologic findings in the lung tissues of infants that died with BPD revealed extensive inflammatory and fibrotic changes in the airways and lung parenchyma. The availability of new therapies, such as exogenous surfactant, milder ventilation strategies, and antenatal steroids, has increased the survival of infants of younger gestational age, thus changing the "classic" description of the BPD phenotype. The "new" BPD described today typically occurs in very preterm infants (mean gestational age of less than 28 weeks) in the early saccular stage of lung development and is characterized pathologically by alveolar hypoplasia and abnormal vascular organization.[14,15] BPD is now considered to be a developmental disease resulting from interference, or an interruption, in the growth of the lung.[14] The disease is characterized by many as an "arrest" in lung development, which is misleading because it implies that the lung has stopped growing, when in fact the developmental programing of the lung has been altered in such a way that lung growth now proceeds along a different developmental trajectory. Putting semantics aside, the incidence of BPD remains high amongst preterm infants with extremely low birth weight and continues to be one of the most common morbidities associated with preterm birth.[16] As the number of surviving preterm infants continues to increase, it is critical that we advance our understanding of the developmental sensitivity of the lung and how disruption of the developmental programing of the lung increases the risk for BPD.

Although there are many risk factors that contribute to the pathogenesis of BPD, exposure to hyperoxia remains one of the principal factors, or conditions, responsible for its development.[6,7] Regardless of gestational age, transitioning at birth from a relative hypoxic environment *in utero* into room air will always be a hyperoxic event and is likely the greatest environmental exposure we will ever encounter in our life. Fortunately, evolutionary-dependent mechanisms, particularly those relating to the development of the respiratory system, have made this extreme environmental transition manageable. Unfortunately, the premature interruption of *in utero* lung development, such as that relating to preterm birth, may lead to unfavorable consequences affecting respiratory health postnatally. For example, the structurally and functionally immature lungs of preterm infants are often inadequately prepared to breathe oxygen, usually requiring the administration of therapeutically elevated levels of oxygen to prevent tissue hypoxia and respiratory distress (Fig. 1). Hence, the lung is exposed to hyperoxia regardless of when it transitions to air at birth and the magnitude of the hyperoxic exposure can be enhanced in preterm infants who are treated with supplemental oxygen. Although the use of supplemental oxygen in the neonatal period is often necessary to support life, we have learned from newborn animal models that exposure to hyperoxia alone acutely injures the lung during a period of rapid growth and development, resulting in pathologic findings which are similar to those observed in human BPD.[17,18]

Since the "fetal origins" hypothesis was first conceptualized by Barker et al., there has been an increased appreciation for how the environment can alter organ development, and thus the occurrence of disease later in life.[19] In order to fully appreciate a discussion on the developmental impact of early-life exposure to oxygen and its contribution to oxidant-mediated diseases, such as BPD, a brief review of the evolutionary origins of the mammalian lung is essential. Lung development and the undefined use of oxygen in neonatal care are then reviewed, followed by the vulnerability of the lung to oxygen toxicity and the development of suitable animal models to study oxidant-mediated lung disease. Lastly, the interplay between genes, cells, and the environment (principally exposure to oxygen) is discussed, as well as the contribution of such interactions to the pathogenesis of BPD. These insights may help refine our view of how the premature exposure to oxygen in the neonatal period disrupts lung development, ultimately giving rise to disease later in life.

Evolution of the lung in response to changing atmospheric levels of oxygen

The geological record indicates that until the present atmospheric level of oxygen was reached, specifically 21%, there were cyclical episodes of low and high oxygen, ranging from as low as 15% to as high as 35%.[20] These fluctuating oxygen conditions have been suggested to play a substantial role in the development and evolution of cellular and organismal respiration.[20,21] In fact, the transition from aquatic to terrestrial habitation by vertebrates likely occurred during a time when atmospheric levels of oxygen were high.[22] The cutaneous respiration and inadequate removal of carbon dioxide by aquatic species was incompatible with life on land, leading to the evolution of a more sophisticated circulatory and respiratory system.[22] As organismal size and complexity increased over time, these two systems became critical for the efficient uptake and transport of oxygen to tissues and organs, thus increasing chances for survival.[23] Generational studies in fruit flies (*Drosophila melanogaster*) have demonstrated that under hyperoxic breeding conditions, defined as oxygen in excess of 21%, body weight and wing size are increased, whereas breeding under hypoxic conditions, defined as oxygen less than 21%, gives rise to the opposite.[20] Furthermore, oxygen concentration has been shown to negatively correlate with tracheal diameter and cell size in these insects.[20,24]

In light of the fluctuating oxygen conditions throughout evolution and the increasing dependency of many organisms on a constant supply of oxygen in order to effectively function, molecular pathways concurrently evolved to respond to conditions where oxygen demand exceeded supply (hypoxia).[25] Physiological hypoxia plays an important role in the differentiation of cell types and the signaling of multiple cascades, including angiogenesis, for example. It is also associated with a range of pathophysiological