Mechanisms of Lung Injury in a Mouse Model of Bronchopulmonary Dysplasia

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av

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I. Beta6 integrin subunit deficiency alleviates lung injury in a mouse model of bronchopulmonary dysplasia.
Hogmalm A, Sheppard D, Lappalainen U, Bry K.
Am J Respir Cell Mol Biol In press. E-publ. Aug 28, 2009.

II. Matrix metalloproteinase-9 deficiency worsens lung injury in a model of bronchopulmonary dysplasia.
Lukkarinen H, Hogmalm A, Lappalainen U, Bry K.
Am J Respir Cell Mol Biol 2009;41(1):59-68.

III. Expression of IL-1β in the distal lung epithelium disrupts lung development in fetal mice.
Hogmalm A, Lappalainen U, Bry K.
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Mechanisms of Lung Injury in a Mouse Model of Bronchopulmonary dysplasia

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects preterm infants. Increased levels of inflammatory mediators in the amniotic fluid and in the lungs of preterm infants are associated with the development of BPD. It has been shown that infant transgenic mice that express interleukin (IL)-1β in the lung epithelium from approximately embryonal day 14 (pseudoglandular stage of lung development) develop a pulmonary injury that resembles BPD, supporting the idea that inflammation plays an important role in the pathogenesis of BPD. The mechanisms by which inflammation causes lung injury have not been identified.

The aim of this thesis was to define mechanisms by which perinatal inflammatory lung injury develops by using transgenic mice that express IL-1β in the lung epithelium in an inducible manner.

The β6 integrin subunit has previously been shown to be involved in the progression of pulmonary diseases in adult mice. To investigate the involvement of the β6 integrin subunit in IL-1β-induced lung disease in the neonate, lung development of IL-1β-expressing mice lacking the β6 integrin subunit were compared with that of IL-1β-expressing mice with wild-type β6 loci. Absence of the β6 integrin subunit alleviated the IL-1β-induced lung injury, as demonstrated by smaller alveoli, thinner alveolar walls, and a milder lung inflammation than IL-1β-expressing mice with wild-type β6 integrin loci. The results suggest that the β6 integrin subunit plays a role in the development of neonatal lung disease.

Increased levels of matrix metalloproteinase (MMP)-9 and an imbalance between proteases and antiproteases in the lungs of infants and animals developing BPD have led to the hypothesis that MMP-9 may be involved in the pathogenesis of the disease. No differences in lung histology were detected between mice with wild-type MMP-9 loci and mice with null MMP-9 loci, implying a non-essential role of MMP-9 during lung development. However, IL-1β caused a more severe alveolar hypoplasia in mice deficient in MMP-9 than in MMP-9 wild-type mice, suggesting that MMP-9 may have a protective role during inflammatory lung injury.

A short-term exposure of IL-1 has been shown to accelerate development of the surfactant system in fetal rabbits and lambs. Using transgenic mice where the expression of IL-1β is restricted to the distal lung epithelium, the effects on lung development and function of chronic prenatal IL-1β production were studied. Distal lung expression of IL-1β disrupted acinar bud formation prior to birth and decreased the expression of the important surfactant proteins SP-B and SP-C. The 100% mortality observed among the IL-1β-expressing mice was probably due to the inflammation-induced structural changes and to deficient surfactant function. The results suggest that an early and continuous inflammatory stimulus in the distal lung epithelium causes severe lung injury and disrupts surfactant production.

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