Critical period for alveologenesis and early determinants of adult pulmonary disease

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Abstract

The functional evidence of altered extracellular matrix in mice overexpressing TGF-α is a very low lung tissue elastic recoil (25). This and the less severely low recoil of lungs of rats treated with dexamethasone during the period of septation (34) indicate these manipulations alter development of extracellular matrix. Because collagen exerts its major effect on recoil at high lung volumes (22), the very large lungs of mice overexpressing TGF-α probably are due mainly to altered collagen (25). Defective lung elastin, as seems to exist in mice that overexpress TGF-α (25), would diminish recoil in the tidal volume range (22).

The functional evidence of altered extracellular matrix in mice overexpressing TGF-α (25) and in dexamethasone-treated rat pups (34), as well as the rapid thinning and altered composition of the alveolar wall in dexamethasone-treated rats, (32) raises the obvious possibility that abnormal extracellular matrix contributes, perhaps in a major way, to impaired alveologenesis. This notion is supported by finding that exposure to hypoxia shortly after birth results in adult rats that had failed to septate as pups (3, 39) and that have diminished lung elastic

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recoil (41). Interestingly, loss of lung recoil occurs during acclimatization of adults to high altitude (30).

The work by Le Cras et al. (25), importantly, also points to the impact early events have on the subsequent development of lung disease and adds to our meager understanding of the molecular basis of this effect. Others have provided clinical and experimental examples of late consequences of early events, including the very important observation that intrauterine and postnatal exposure to parental tobacco smoking is associated in adulthood with more respiratory symptoms, poorer lung function, and increased risk for obstructive lung disease than found in those not exposed (52). Similarly, viral bronchial and alveolar infections, common among infants, when produced in neonatal rats are associated with diminished alveolar surface area and bronchiolar hypoplasia in adult rats (9). One-quarter of children in a 24-block, very-low-income area of central Harlem in New York City, have asthma, which is generally attributed to allergens from insects (42). We wonder if early events aggravate or create a predisposition to the bronchial response to allergens. In particular, does a stressful environment during pregnancy mean maternal hypercorticism? If so, does it result in postnatal diminished airway growth and later low airway conductance in humans, as it does in ferrets (13)? Does early inadequate nutrition, which causes a later lower-than-normal number of ciliated cells in conducting airways of rats (38), also contribute to asthma in humans? The impact of early deleterious events on the later response to the environment is, in our opinion, a very understudied area of lung biology.

Late effects of early events may be relevant to the great variation of the number of alveoli among adults without lung disease, which exists even when the number of alveoli is corrected for body length and lung volume (2). These differences could result from early illnesses, generally considered harmless, e.g., febrile episodes, which, in fact, may elevate the blood’s corticosteroid concentration (51), and viral infections (9). Furthermore, differences in the number of alveoli per lung volume due to early events could influence the rate of progression of diseases associated with alveolar loss, e.g., could, at least partly, determine among individuals with chronic obstructive pulmonary disease, who is a rapid or a slow loser of forced expiratory volume (14). Because alveolar surface area is progressively lost beginning in the third decade (54) and because birth at altitude seems to result in impaired septation (8, 49), we wonder if the exodus of elderly from high altitude (45) is due, in some measure, to birth at altitude and the consequent presence of fewer alveoli (we recognize not all of the elderly who leave high altitude were born at high altitude). Equally interesting is the increased prevalence of chronic obstructive pulmonary disease at high altitude (12, 46), which could reflect early damage to the lung’s extracellular matrix.

Thus Le Cras et al. (25) have brought into view three underappreciated, understudied, but fascinating and important areas of lung biology and medicine: a critical period for septation, the role of stage of development has on the later impact of untoward events, and the effect of early events on the later development of disease. The challenge for all of us is to further understand the biology of these events and to develop means to prevent, or reverse, their untoward effects.

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DISCLOSURES

D. Massaro and G. D. Massaro hold a patent for the use of retinoids in lung diseases.

REFERENCES