Critical period for alveologenesis and early determinants of adult pulmonary disease

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as the twig is bent

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LE CRAS ET AL., in one of the current articles in focus (Ref. 25, see p. L718 in this issue), synthesized divergent studies about transforming growth factor (TGF-α) pointing to its overexpression in important developmental and adult pulmonary diseases and performed an elegant, clinically and biologically important study (25). They show very brief overexpression of TGF-α by the lung, if produced when the gas-exchange sacs of the architecturally immature lung are being subdivided (septated) to form alveoli, permanently disrupts septation (25). More broadly, their results support the existence of a “critical” period for septation (3, 4, 19, 33, 34, 39, 43, 48) and for the formation of the pulmonary vasculature (26–29, 44, 53) and provide additional evidence early events can influence later lung anatomy (38), lung function (40, 41), and the development of lung disease (9, 52).

Precocial animals, e.g., guinea pigs and range animals, septate as fetuses (11, 24); altricial animals septate after birth (1, 7, and for additional references 33, 36). The usual laboratory mouse and rat septate from about postnatal day 4 to 14 but mainly from postnatal day 4 to 7 (7). Strikingly, in all species reported, septation, whether prenatal or postnatal, occurs during a period when the organism’s blood concentration of its major glucocorticoid hormone is low; septation ends (1, 4, 7, 11, 34, 37) as the glucocorticoid concentration rises (17, 18, 23). Administration of a glucocorticoid to rats (4, 34, 37) or mice (19) during the period of septation, when the concentration of corticosteroids in the blood is normally low, impairs spontaneous septation and the development of the pulmonary vasculature, resulting in pulmonary hypertension (28). There is neither spontaneous post hoc septation (4, 19, 34, 37) nor spontaneous post hoc vasculogenesis (28), thereby demonstrating a critical period for these developmental events. Put differently, once the molecular processes responsible for these architectural processes are disrupted, they are not spontaneously reconstructed. Microarray analysis of lung gene expression identified downregulation of VEGF receptor-2 with the inhibition of septation by dexamethasone (10). Now Le Cras et al. (25) report another molecule (TGF-α), one whose overexpression in lung, when its concentration is normally low, permanently impairs spontaneous septation.

The paper by Le Cras et al. (25) also brings to mind additional aspects of critical periods. Treatments, or altered signaling, applied at the same chronological age may, based on sexual differences in the timing of development, have an effect in one sex but not the other. For example, the responsiveness of rats to prenatal treatment with dexamethasone, which given prenatally depresses the postnatal increase of alveolar surface area, appears earlier in females than in male fetuses (35). In a similar vein, inhibition of signaling by FGF in the fetal, but not postnatal, lung results in altered alveolar architecture in adult lungs (20). Clearly, timing is key.

Exposure to other than a sea-level PO₂, either experimentally, as part of medical treatment, or by virtue of place of birth, diminishes septation (3, 6, 8, 16, 39, 49). A “high” oxygen tension need only be relative to the organism’s stage of development. Thus premature birth into room air at sea level results in entry, before the lung’s antioxidant defenses are fully developed (15), into relative hypoxia, which causes, or contributes to, arrested alveologenesis (31, 49, 50). Exposure to absolute hypoxia (6), or to a low PO₂ (3, 39), impairs septation and is not followed by post hoc spontaneous septation when the organism is placed in 20% O₂ and allowed to develop further (3, 39). The molecular deficits responsible for these impairments are largely unknown.

It is especially interesting, and may be clinically important, that Fawn-Hooded rats raised at high altitude (e.g., Denver, 5,000 ft) septate less than those of the same strain raised at sea level (16, 26, 27). Although those native to high altitude for centuries have adapted extraordinarily well (21), the meager anatomical data available suggest even they have large alveoli and hence may have impaired septation (8, 49). If the latter is the case, it would result in a diminished number of alveolar attachments to small conducting airways (3), which could explain (47) the lower upstream conductance and higher residual volume (21) in highlanders compared with lowlanders (5). One of the most impressive effects of 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 very 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 the 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


