Developmental alveologenesis: longer, differential regulation and perhaps more danger

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BY DEVELOPMENTAL ALVEOLOGENESIS, we mean the formation of mature pulmonary gas-exchange units (alveoli) that occurs during the overall maturation of the organism. Morphometric estimates of the total number of alveoli in humans who died of nonpulmonary causes led to the conclusion that developmental alveologenesis ends at about the eighth postnatal year (6, 8, 26). In this issue of AJP-Lung, Hyde et al. (12) show developmental alveologenesis continues until early adulthood in a nonhuman Old World primate. This finding, we think, favors an interpretation of morphometric data in humans (6, 8, 26) to indicate developmental alveologenesis continues until about the time longitudinal growth ends. Why is this important? Because impaired developmental alveologenesis may not be followed by spontaneous “catch-up” alveologenesis (17), and extending the duration of developmental alveologenesis lengthens the period of its vulnerability to impairment and thereby may increase the likelihood growing children will experience events that impair alveologenesis, leaving them at a functional disadvantage as they lose alveoli to aging or to lung disease. More specifically, the number of alveoli, and hence size of the gas-exchange surface area at the onset of aging or disease, would contribute to the time of onset of symptoms and disability because of loss of gas-exchange function and to premature closure of conducting airways because of insufficient alveolar attachments to them and therefore decreased radial traction.

Developmental alveologenesis takes place in part by subdivision (septation) of the large, thick-walled saccules, present throughout the lung, that constitute the gas-exchange units of the anatomically immature lung (1, 5, 29). In rats and mice, septation of these saccules is a postnatal event occurring from about postnatal day 4 to 14 (1, 5). However, Randell et al. (24), based on their morphometric observations, calculated septation of the alveolar saccules present at birth accounts for only about one-third of the alveoli formed in rats by the seventh postnatal day. This was confirmed and extended by finding in rats studied between postnatal day 2 and 14 that only ~26% of alveoli present at age 14 days were formed by septation of alveolar saccules present at age 2 days (2). Thus only about a third of alveoli formed during the first 2 postnatal wk are, in fact, formed by septation of the gas-exchange saccules present at birth. The majority, at least two-third, are generated by forming septa at sites other than within saccules present at birth.

We proposed that most alveoli formed during the first 2 postnatal wk in rats and those formed thereafter are formed by septation (subdivision) of enlarging subpleural alveoli (18). This formulation requires that alveoli formed by septation of the gas-exchange saccules present at birth, those formed by other means during the first 2 postnatal wk, and those that continue to be formed after the first 2 postnatal wk be regulated differently. The following indicates the presence of differential regulation during developmental alveologenesis: 1) the rate of alveolus formation in rats exposed to a 13.5% O₂ environment is slower during the first 2 postnatal wk than the rate in rats breathing 20.9% O₂, but after the first 2 wk, the rate of alveolus formation in rats breathing 20.9% O₂ falls to the unchanged slower rate, present since birth, in those that continue to breathe 13.5% O₂ (2); 2) retinoic acid receptor (RAR)-β knockout mice form alveoli twice as fast as wild-type mice during the first 2 postnatal wk but at the same rate as wild-type mice thereafter (20); and 3) RAR-α knockout mice form alveoli at the same rate as wild-type mice during the first 2 postnatal wk but at a slower rate than wild-type mice thereafter (19). Thus it seems clear that developmental alveologenesis is differently regulated within as well as after the first 2 postnatal wk.

Is there reason to think that, in addition to possible genetic variability of developmental alveologenesis, impaired developmental alveologenesis occurs in children delivered at term who grow into adulthood having experienced only the usual childhood illnesses and febrile episodes? We think the answer is yes. Green et al. (10), based on wide differences in expiratory flow rates in “normal” individuals, introduced the concept of dysanapsis of lung growth resulting in a mismatch between the size of the alveolar region and the conducting airways. With this insight in mind, analysis of measurements by Turlbeck (26) on lungs of individuals who died of nonpulmonary causes revealed the presence of a twofold or greater difference in the number of alveoli in individuals with approximately the same lung volume. Brody et al. (4) found lower upstream conductance in lungs of healthy Peruvian natives of high altitude compared with lowlander Peruvian natives. This was attributed to pulmonary dysanapsis (4) based on the knowledge that conducting airways are formed in utero and hence protected from the full brunt of the hypoxia of high altitude by adaptations of the supporting placenta, whereas alveolus formation occurs postnatally under the presumed stimulatory effect of hypoxia (4). But rodents born into and maintained at a low inspiratory O₂ concentration, whose dams were acclimatized to hypoxia, although certainly not native highland rodents, had impaired, not stimulated, alveologenesis and, as a consequence, fewer alveolar attachments to small conducting airways (2). The latter would result in premature closure of small conducting airways and decreased upstream conductance as found in natives of high altitude in Peru (4). Supporting this interpretation of the data is the demonstration that normal Peruvian highlanders have a high residual lung volume, a sign...
of air trapping (11), and the reported morphometrically determined presence of large alveoli, i.e., impaired septation, in high altitude Peruvian natives (25).

As is often the case, an important new finding raises the call for more information. In this case, for example, do the trials and tribulations of passage through childhood, worse in some than others, adversely affect developmental alveologenesis? The use of corticosteroids, potent inhibitors of developmental alveologenesis (17), to treat asthma and various rheumatic diseases easily come to mind. However, what about febrile episodes that increase production of corticosteroid hormones (13)? Also, consider that ibuprofen, an inhibitor of cyclooxygenases (3), is now available as a nonprescription analgesic and antipyretic for children and that indomethacin, another inhibitor of cyclooxygenases, is an inhibitor of developmental alveologenesis in rats (22). Probably more important, little is known about the effect of environmental pollution (9, 23), including cigarette smoke, on alveologenesis.

Impaired developmental alveologenesis in humans, recognized or not, would result in a smaller reserve of alveoli to sustain gas exchange and patency of small conducting airways, whether alveoli are lost to disease (14), normal aging, or both. Fortunately, rodent models of developmental alveologenesis are relevant to primates (1, 5, 16), as are rodent models of developmental alveologenesis in rats (22). Probably more important, little is known about the effect of environmental pollution (9, 23), including cigarette smoke, on alveologenesis.

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