

Role of the physico-chemical environment in lung development

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During lung development, which extends beyond birth in most species, the lung is exposed to numerous mechanical stimuli, which are critical determinants of cellular proliferation and differentiation (of alveolar epithelial cells; AEC) as well as 3-dimensional tissue structure within the lung. These stimuli include sustained stretch, phasic stretch associated with breathing activity as well as tissue compression and expansion. Before birth, the future airways of the lungs are liquid-filled and this liquid maintains the lungs in a distended state which is essential for lung growth and development. However, at birth this liquid must be cleared to allow the entry of air, but a thin film must remain to protect the epithelium from desiccation. This creates an air/liquid interface which increases lung recoil, despite the presence of surfactant, and leads to the formation of a sub-atmospheric intra-pleural pressure. Phasic expansion of the lung, associated with breathing, also markedly increases after birth as before birth breathing movements are essentially iso-volumetric due to the high viscosity of lung liquid relative to air. Thus, the mechanical stimuli applied to the lungs vary markedly before and after birth and, therefore, the timing of birth can have a major impact on the type of mechanical stimuli experienced by lung tissue at specific developmental stages.

The mechanisms by which sustained stretch stimulates growth, AEC differentiation and structural maturation of the lung are largely unknown, although they are highly significant to later lung function. Increases in lung expansion cause a time dependent acceleration in lung growth and a large increase in type-II to type-I AEC trans-differentiation. However, attempts to identify specific growth factors and intracellular pathways mediating these processes have been surprisingly unsuccessful. We have used a unique animal model and differential gene analysis techniques (eg. subtraction hybridization) to identify genes that are activated or suppressed in response to a sustained increase in lung expansion. Numerous differentially expressed genes (both activated and suppressed) have been identified, which will allow the identification of potential pathways whereby a mechanical stimulus, such as tissue stretch, is translated into a lung cellular proliferation/differentiation response.