Cell Stretch May Be Necessary for Normal Development

A review of: Kitano Y, Von Allmen D, Kanai M, et al. 2001 Fetal lung growth after short-term tracheal occlusion is linearly related to intratracheal pressure. J Appl Physiol 90:493–500; and Zheng W, Seftor EA, Meininger CJ, et al. 2001 Mechanisms of coronary angiogenesis in response to stretch: role of VEGF and TGF-beta. Am J Physiol Heart Circ Physiol 280: H909–917

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THE NATURE VS nurture issue bears on organ development. While organs grow and develop according to their gene driven programs, they also grow in an environment of variable atmospheric gas pressures, gene products and mechanical forces. Two recent papers have looked at the role of mechanical forces in the development of lung tissue and heart vasculature. Kitano et al. (1) have studied lung growth responses to augmented intratracheal pressure and Zheng et al. (2) have studied the role of stretch in angiogenesis.

Kitano, et al. (1) explored the relationship between tracheal pressure and fetal lung growth. Pulmonary hypoplasia is the most common single autopsy finding in the first week after birth (3) and congenital diaphragmatic hernia (CDH), which results in pulmonary hypoplasia, has a mortality which remains around 60% (1). Tracheal occlusion has been shown to increase lung growth but has deleterious effects on surfactant producing Type II pneumocytes. Kitano et al. (1) performed a tracheotomy on near term fetal sheep and controlled intratracheal pressure (P_{itr}) by fluid filling or draining to yield a high, moderate, or low (control) tracheal transmural pressure for 4 days. The authors argue that increased P_{itr} pressure applies force and stretch at the level of the parenchymal cell. Lung volume, lung to body weight ratio, and whole right lung dry weight were increased by even moderate pressure increases. Normalized lung DNA concentration and protein were linearly increased with increases in mean P_{itr}.

Zheng et al. (2) applied cyclic stretch to cultured cardiac myocytes and studied its effects on proliferation of coronary microvascular endothelial cells. Both cell types showed an increase in the release of vascular endothelial growth factor (VEGF) in response to cyclic stretch. In myocytes, the release was dependent on TGF-ß; stretch induced release of VEGF could be mimicked by the administration of exogenous TGF-ß or blocked by exposure to TGF-ß antibody. Conditioned media from the stretched myocytes induced cell proliferation of naïve endothelial cells and increased their migration and tube formation. These data support other studies showing that cyclic stretch induces a signaling/growth factor response by autocrine and paracrine actions.

Mechanical stress (force/area) that results in measurable strain (fractional change in dimension with stress) has been shown to be a growth stimulant in many different cell types. Osteocytes, fibroblasts, skeletal, cardiac, and smooth muscle, epithelial cells, endothelial cells, and mesangial cells all show increased proliferation in response to mechanical strain (4). The stress sensitive mechanisms that underlie the growth response include: ion channel activation, transmembrane protein deformation, integrin activation and a host of phosphorylation pathways (5).

The roles of nature and nurture are never wholly independent – even at the cellular level. Gene expression patterns of a developing individual occur in an environment of gravitational force and cyclic pressures and flows. It would not be surprising to find that many organs are dependent on the mechanical environment in which they develop – including organs distant from the heart and lungs. Such considerations may be important for the appropriate development of cells in culture and organs grown for use in transplantation. The interactions of mechanical and genetic "forces" in the determination of appropriate growth and development of human fetuses and neonates continues to be a vital field of research.

1. Kitano Y, Von Allmen D, Kanai M, Quinn TM, Davies P, Kitano Y, Flake AW 2001 Fetal lung growth after short-term tracheal occlusion is linearly related to intratracheal pressure. J Appl Physiol 90:493–500
2. Zheng W, Seftor EA, Meininger CJ, Hendrix MJ, Tomanek RJ 2001 Mechanisms of coronary angiogenesis in response to stretch: role of VEGF and TGF-beta. Am J Physiol Heart Circ Physiol 280:H909–H917
3. Liu M, Post M 2000 Invited review: mechanochemical signal transduction in the fetal lung. J Appl Physiol 89:2078–2084
4. Goldspink G 1999 Changes in muscle mass and phenotype and the expression of autocrine and systemic growth factors by muscle in response to stretch and overload. J Anat 194:323–334
5. Davies PF, Tripathi SC 1993 Mechanical stress mechanisms and the cell an endothelial paradigm. Circ Res 72:239–245

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