

Project title: Tensegrity as a main determinant of tissue morphogenesis

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DESCRIPTION: In the late 19th century, embryologists explained developmental events in terms of mechanics. This tradition was set aside with the emergence of biochemistry and molecular biology. However, these latter disciplines have not yet provided explanations of how the organism is built; hence there is a renewed interest in the role of physical force as determinants of biological structures. The integrity of tissues is maintained by a synergy between balanced tension and compression components (tensegrity). From the macro-scale to the nano-scale, the organism is shaped by tensional forces (balanced push and pull) [2]. Although considerable progress has been achieved in this field during the last two decades, a detailed analysis of these physical force-mediated processes is difficult to achieve in the embryo. Tissue engineering is providing experimental models to facilitate these studies [3]. For example, Engler et al have shown that the rigidity of the intercellular matrix can determine the commitment fate of stem cells [1].

We have developed a novel 3D tissue organogenesis model of the mammary gland that contains both epithelium and stroma (matrix and cells) [4]. We aim to use the model to identify the key physical processes that regulate epithelial organization into cylindrical structures (ducts and branching ducts) and spherical structures (acini). By altering the rigidity of the matrix and the degree of anisotropy of the matrix we have determined conditions that result in the preferential yield of ducts and conditions that yield alveoli. Our experimental results suggest that the elastic modulus of the matrix in which the epithelial cells are located is an important determinant, and that the orientation, density and arrangement of collagen fibers may play related roles (Figure 1). Based on these results, we propose to study the role of physical force (specifically, tension and compression), both globally at the tissue level, and locally, at the boundary of epithelial cells with the surrounding matrix including particular fiber arrangements.

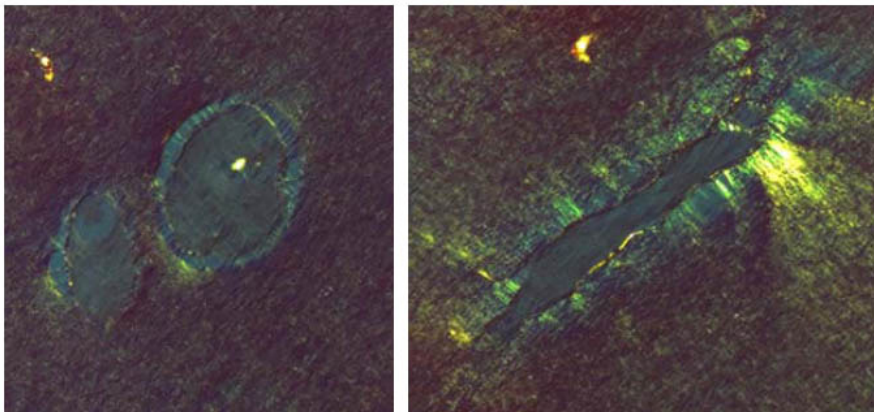


Figure 1: Picrosirius Red staining of collagen-I fibers in 3D cultures of breast epithelial cells growing within a 50% Matrigel-1 mg/ml collagen-I gels. The left panel shows a gel containing only epithelial cells. The epithelial cells formed exclusively acinar structures with thin fibers pointing radially outwards. The right panel shows a gel containing both epithelial cells and fibroblasts. The epithelial cells formed both ducts and acini. The micrograph shows a duct with thicker fibers organized perpendicular to duct axis. The left panel shows that in the areas where epithelial cells are absent the gel shows a fine grainy background staining due to the presence of thin fibers (small yellow dots), while the right panel shows a coarser grainy background due to the presence of more and thicker fibers. Source: Unpublished data (Eugen Dhimolea, Carlos Sonnenschein and Ana Soto, Tufts University).

Reference List

1. **Engler AJ, Sen S, Sweeney HL, Discher DE** 2006 Matrix elasticity directs stem cell lineage specification. *Cell* 126:677-689
2. **Ingber DE** 2003 Tensegrity II. How structural networks influence cellular information processing networks. *Journal of Cell Science* 116:1397-1408
3. **Ingber DE, Levin M** 2009 What lies at the interface of regenerative medicine and developmental biology? *Development* 134:2541-2547
4. **Krause S, Maffini MV, Soto AM, Sonnenschein C** 2008 A novel 3D *in vitro* culture model to study stromal-epithelial interactions in the mammary gland. *Tissue Engineering* 14:261-271