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Christina Scheel – 20th September 12.15

Dynamic collagen deformation drives branching morphogenesis in mammary organoids derived from human breast tissue

Branching morphogenesis in murine mammary gland organoids embedded in matrigel or collagen has been shown to be driven by localized proliferation processes. However, the resulting organoids differ geometrically from the structures generated by epithelial cells from human mammary glands embedded in collagen. In contrast to the murine mammary gland, tissue adjacent to the human mammary epithelium mainly consists of a collagen enriched matrix, whereas the murine gland is directly embedded in the surrounding fat pad. To date, little is known whether these differences in tissue architecture are instructive for species-specific differences in development and growth of the mammary gland.

Based on these considerations, we studied the interaction of primary human mammary epithelial cells with the surrounding collagen matrix during branching morphogenesis in an organoid assay. In this assay, single, primary mammary epithelial cells of the basal lineage isolated from normal human breast tissue are embedded in collagen gels that freely float in liquid growth medium, thereby promoting mechanical feedback between cells and matrix.

Using this assay, we observed that branching morphogenesis relies on an intricate tension feedback mechanism based on the nonlinear mechanical response of the surrounding collagen network. Specifically, the collective motion of basal cells within organoid branches resulted in tension generation, which was strong enough to induce a plastic reorganisation of the surrounding collagen network. This mechanical plasticity of the matrix ultimately led to the formation of a mechanically stable collagen-cage surrounding the branches of organoids to guide further tension generation and branch outgrowth. We propose that this mechanical feedback loop is the basis for the observed self-organization of the evolving organoid structures, including cellular differentiation and the formation of luminal cells.

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The research of the Scheel group focuses on mechanisms of epithelial plasticity in the context of normal regeneration and metastatic progression. For this purpose, the group has developed an organoid assay for primary epithelial cells harvested from human breast tissue and milk. Epithelial plasticity, defined as the ability of cells to dynamically change cell state, for example from epithelial to mesenchymal, is crucial for many processes during epithelial morphogenesis and homeostasis. The Scheel lab is interested in identifying mechanisms of epithelial plasticity that promote tumor progression and therapeutic resistance in breast cancer by studying cell state transitions at the single-cell level. In the context of normal regeneration, they study how dynamic physical interactions with the extracellular matrix impinge on morphogenesis and plasticity during mammary organoid formation.”