

Sponsor: National Institute of Dental and Craniofacial Research

Dates: August 1, 2008 - July 31, 2013

Amount: \$1,514,276

Modeling Dynamics of Salivary Gland Branching Morphogenesis

This application is a collaborative project between an experimental biologist and a theoretical mathematician in order to develop a simulation framework to model the early stages of salivary gland branching morphogenesis and create an interactive tool that can be used to predict cell behavior within this context. Existing strategies for engineering salivary glands have been unable to create a complex branched structure or successfully produce saliva-secreting acinar cells, which may relate to the lack of appropriate 3D structure in these models. Although there is currently a clinical need for artificial salivary glands to replace the damaged saliva-producing tissue in patients suffering from Sjogren's Syndrome or from side effects of radiation therapy for head and neck tumors, few predictive tools are available to model cell behavior. To engineer branched tissues, we need to understand how the branching occurs during development and how signaling pathways translate into physical changes. While many signaling pathways and structural components have been identified that play a role in branching, they so far have not been incorporated into a comprehensive integrated model that explains branching morphogenesis. This highly dynamic structural process can hardly be understood using conventional molecular biology methods alone. Only a close association between experiments and mathematical modeling will allow an integrated, systems level understanding of the process of branching morphogenesis. We previously generated a simulation framework to model lung branching based on localized proliferation. This model is limited since basement membrane dynamics are critical for branching. Our hypothesis is that basement membrane dynamics controlled by Rho kinase (ROCK)-mediated signaling is a critical component of salivary gland branching morphogenesis. To address this hypothesis and to create a framework for understanding the role of basement membrane dynamics during branching morphogenesis, we propose five specific aims: Aim 1 Develop a simulation framework for salivary gland branching morphogenesis based on Level Set Methods, Aim 2 Develop the experimental model system and compare experimental results with predictions of the new mathematical model and simulation framework, Aim 3 Investigate the function of cytoskeletal inhibitors on branching morphogenesis and use this data to train the model, Aim 4 Determine if ROCK inhibitors affect cytoskeletal tension during branching morphogenesis, and Aim 5 Identify the cellular mechanism by which ROCK affects branching morphogenesis. The robust simulation framework and the mathematical models developed as a result of this project will constitute the first crucial step towards development of a comprehensive model of salivary gland branching morphogenesis. Significantly, it will guide experimentalists by revealing missing links and suggesting directions for future research. Further, the mathematical model and simulation framework can be modified as more data is obtained and will provide us with a tool to predict, and eventually, control cell behavior on different matrix substrates for intelligent engineering of a functional salivary gland.

Sponsor: National Institute of Dental and Craniofacial Research
Dates: August 1, 2008 - July 31, 2010
Amount: \$402,317

Engineering Functioning Salivary Glands Using Micropatterned Scaffolds

The goal of this application is to engineer a complex 3D artificial salivary gland using an innovative strategy combining adult salivary gland cells with a micropatterned artificial scaffold. The long-range goal of my research program is to facilitate translational research by engineering of an artificial salivary gland for use in human patients suffering from salivary hypofunction. Head and neck radiation therapy and Sjogren's syndrome both lead to decreased saliva production following irreversible salivary gland tissue damage. In these patients, lack of saliva production causes significant morbidity due to dry mouth that results in dysphasia, dental caries, oropharyngeal infections, mucositis, and loss of taste. A novel strategy for restoring salivary flow is to replace damaged salivary tissue with engineered tissue that is composed of self-organized cells attached to a scaffold. The hypothesis tested in this application is that self-organized salivary gland functional units that are attached to a micropatterned artificial scaffold can create a functioning artificial gland. This hypothesis is based on our previous demonstration that embryonic salivary gland cells have an inherent capacity to self-organize into functional salivary gland tissue. In Aim 1, conditions will be established for growing primary adult mouse salivary gland cells, a functionalized micropatterned scaffold will be created, and conditions whereby the salivary gland cells can attach to the scaffold will be established. In the second Aim, we will assemble an engineered gland by first facilitating self-organization of the adult salivary gland cells into functional units and then attach these units to the scaffold through functionalized nucleation sites, and form a 3D artificial gland structure. The function of this artificial gland will be tested in vivo in a future RO1 application. The methods used for this approach will facilitate engineering of a human artificial salivary gland and also serve as a prototype for engineering other complex branched organs such as pancreas, kidney, and lung.