CALIFORNIA STATE SCIENCE FAIR
2015 PROJECT SUMMARY

Name(s)

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Project Number

S0507

Project Title

Mathematical Models of the Growth of Stem Cell Driven Cell Clusters

Abstract

Objectives/Goals

To investigate the effectiveness of controlling cell cluster growth using feedback in stochastic and spatially heterogeneous environments

Methods/Materials

I created a cell lineage model using the Cellular Potts Framework (CPM) to simulate the dynamics of cell clusters where stem cells undergo negative feedback regulation from non-stem cells. The results of this model were compared with those of Mean Field Models (MFM), which unlike the CPM do not consider spatial variation and stochastic effects and are governed by a system of coupled ordinary differential equations.

Results

In contrast to MFM predictions, I discovered that in the spatial and stochastic setting, negative feedback is not always sufficient to regulate the growth of cell clusters. Given any level of feedback regulation, MFM always predict growth of clusters to a predictable size and distribution. I do find that for a range of non-stem cell death rates, negative feedback is sufficient in growth control. However, when death rates are small or large, the effects of stochasticity and spatial heterogeneity become important, and negative feedback is unable to control cluster growth.

Conclusions/Discussion

I found that classical forms of negative feedback proposed as robust control for tissue growth may not work well in stochastic and spatially heterogeneous systems. Counterintuitively, agenesis occurs when death rates are small, while uncontrolled growth occurs for large death rates. Both these extremes are highly relevant biologically. During the early stages of the developing tissue growth, death rates are expected to be small--an expectation that is confirmed in experiments. Thus, our model predicts that development requires additional feedback to prevent agenesis. At the later stages of development where tissues reach homeostasis, cell birth should balance cell death. In highly renewing tissues, such as epithelial tissues (e.g., colon, breast, lung, etc), the birth and death rates are expected to be high, which is also confirmed in experiments. Thus, our model predicts that homeostasis requires additional feedback to prevent cancer formation. Further studies are needed to identify the mechanisms by which growth control of tissues in realistic environments can be achieved, such as positive feedback factors as well as feedback through tissue stress via mechanotransduction, both of which are known play a role in both development and homeostasis.

Summary Statement

I found that negative feedback regulation on stem cells is not sufficient to provide robust control of cell numbers, distributions and tissue sizes during tissue development and homeostasis in spatially heterogeneous and stochastic systems.

Help Received

Professor John Lowengrub supervised the development of this project and provided useful discussions. Professor Maciej Swat provided technical support with the CompuCell3D framework for the Cellular Potts Model.