STATE DIAGRAM FOR CONTACT-INHIBITION OF PROLIFERATION: A QUANTITATIVE FRAMEWORK FOR MODULATING GROWTH PATTERNS IN EPITHELIAL CELL CLUSTERS

Thesis by

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In Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

2010

(Defended May 7, 2010)

Acknowledgements

First, and most importantly, I would like to thank my advisor, Prof. Anand Asthagiri, for his guidance, inspiration, and encouragement throughout my graduate study. His breadth of knowledge and dedicated enthusiasm to science have guided me to conduct this project with interest and motivation. All that he taught me during these years will be invaluable assets throughout my career as a scientist.

I am grateful to Prof. David Tirrell, Prof. Elliot Meyerowitz, and Prof. Chin-Lin Guo for allowing their valuable time to serve on the committee. Their critical comments and insights were tremendous help to the improvements and completion of this study.

Thank you to the past and current members of the Asthagiri group, Claudiu Giurumescu, Nicholas Graham, Niki Galownia, Stephen Chapman, Ehsan Jabbarzadeh, Melissa Pope, Keiichiro Kushiro, Paul Minor, and Larry Dooling. I am thankful to their technical assistances for helping me with many aspects of my research, and more importantly to their friendships that made my time in Pasadena very memorable one.

I also want to acknowledge my collaborator, Jacob Notbohm, for working with me on the mechanics-related work. It was a great working and learning experience for me to venture a new field. I want to thank to Prof. Guruswami Ravichandran and Prof. Anand Asthagiri for setting up such opportunity.

All my love and thanks to my parents, my two sisters, Hye-Yeon and Hye-Jeen, and my grandmother. It was their unfailing love and trust that enabled me to accomplish this journey at ten-thousand miles away from home. To my father, you always have been my best mentor and my life-long role model. To my mother, none of this would have been possible without your unconditional love and sacrifice for me.

Abstract

Cell-cell contacts play a key role in the assembly and integrity of epithelial tissues. Cell-cell contact is not only a mere physical link between neighboring cells, but also a critical regulator of many cell behaviors including proliferation. Contact-inhibition of proliferation is a hallmark of normal epithelial tissues. Cancer development involves the loss of this key constraint. Both biochemical and physical mechanisms mediating contact-inhibition are emerging. A current, principal challenge is elucidating how the integrated performance of these mechanisms enforce or modulate contact-inhibition in a rich microenvironment that includes multiple, potentially conflicting cues such as soluble growth factors (GFs) and extracellular matrix (ECM).

Here, we propose a quantitative paradigm for contact-inhibition of proliferation. Our quantitative analysis of single cells within multicellular aggregates reveals that epithelial cells transition from a contact-inhibited to contact-independent mode of proliferation at a critical threshold EGF level. This transition point is a tunable property and can be modulated by varying the level of cell-cell contact. Furthermore, the proximity to this transition point is a quantitative gauge of “degree” of contact-inhibition. Using this metric, we demonstrate that stiffening the adhesive matrix, a widely observed phenomenon during cancer development, leads to the quantitative, progressive reduction in the EGF threshold needed to induce contact-independent proliferation. Thus, stiffening the ECM moves an epithelial cell system closer to the transition to contact-independence, thereby quantitatively reducing the amount of EGF amplification needed

to induce population-wide proliferation. Our results reveal that the potent effect of substratum compliance on contact-inhibition involves changes in contact-maturation and multicellular mechanics. The proposed quantitative model of contact-inhibition provides fundamental insights into our understanding of tissue morphogenesis and cancer progression in multicellular organisms. Furthermore, our findings provide design principles for engineering multicellular growth in applications such as tissue engineering.

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