

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

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Jin-Hong Kim

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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.

Table of Contents

Acknowledgements.....	iii
Abstract.....	v
Table of Contents.....	vii
List of Figures.....	ix

Chapter I. Introduction.....	I-1
References.....	I-5

Chapter II. Tunable interplay between epidermal growth factor and cell-cell contact governs the spatial dynamics of epithelial growth.....	II-1
Abstract.....	II-1
Introduction.....	II-3
Results and Discussion.....	II-5
Materials and Methods.....	II-20
Acknowledgements.....	II-22
References.....	II-23
Supporting Information.....	II-26

Chapter III. Substratum stiffening promotes the quantitative, progressive loss of contact-inhibition of proliferation.....	III-1
Abstract.....	III-1
Introduction.....	III-3

Results.....	III-6
Discussion.....	III-20
Materials and Methods.....	III-24
Acknowledgements.....	III-26
References.....	III-27
Supporting Information.....	III-30

Chapter IV. Substratum compliance and EGF co-regulate spatial patterns in traction forces, cell shape, and proliferation within epithelial multicellular clusters.....IV-1

Abstract.....	IV-1
Introduction.....	IV-3
Results.....	IV-5
Discussion.....	IV-15
Conclusions.....	IV-17
Materials and Methods.....	IV-18
References.....	IV-21

Appendix I. Intercellular mechanotransduction during multicellular morphodynamics.....AI-1

Appendix II. Quantitative immunofluorescence for measuring spatial compartmentation of covalently-modified signaling proteins.....AII-1

List of Figures

Chapter II

- Fig. 1. E-cadherin-mediated contact-inhibition triggers spatial patterns in cell cycle activity only when EGF depletes to a threshold concentration.....II-7
- Fig. 2. Selective attenuation of Erk, but not Akt, among interior cells correlates with contact-inhibition.....II-11
- Fig. 3. A quantitative balance between GFs and cell-cell contacts dictates the spatial pattern in cell cycle activity in epithelial cell clusters.....II-15
- Fig. 4. Spatial dynamics of epithelial growth can be modulated by tuning the critical thresholds at which contact-inhibition is triggered.....II-17

Chapter III

- Fig. 1. State diagram for contact-inhibition of proliferation and the hypothesis of quantitative, progressive loss of contact-inhibition.....III-5
- Fig. 2. Substratum compliance affects spatial patterns in cell cycle activity and contact-inhibition of proliferation.....III-8
- Fig. 3. Substratum stiffening reduces the EGF threshold needed to transition from contact-inhibited to contact-independent proliferation.....III-13
- Fig. 4. Substratum compliance affects the molecular organization of adhesion structures at cell-cell contacts.....III-16
- Fig. 5. Substratum compliance affects subcellular localization of EGFR and selectively regulates EGFR and ERK, but not Akt, signaling.....III-19

Chapter IV

Fig. 1. The effect of substratum compliance on contact-maturation and spatial pattern in cell-matrix interactions.....IV-6

Fig. 2. The spatial patterns in cell adhesions correspond to spatial gradient in mechanical stresses within multicellular aggregates.....IV-10

Fig. 3. Treatment with supra-threshold levels of EGF induces rapid, short-lived traction forces and transient decondensation of clusters.....IV-14