

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

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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.

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