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Effects of Mechanical Properties on Tumor Invasion: Insights from a Cellular Model

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Abstract

Understanding the regulating mechanism of tumor invasion is of crucial importance for both fundamental cancer research and clinical applications. Previous *in vivo* experiments have shown that invasive cancer cells dissociate from the primary tumor and invade into the stroma, forming an irregular invasive morphology. Although cell movements involved in tumor invasion are ultimately driven by mechanical forces of cell-cell interactions and tumor-host interactions, how these mechanical properties affect tumor invasion is still poorly understood. In this study, we use a recently developed two-dimensional cellular model to study the effects of mechanical properties on tumor invasion. We study the effects of cell-cell adhesions as well as the degree of degradation and stiffness of extracellular matrix (ECM). Our simulation results show that cell-cell adhesion relationship must be satisfied for tumor invasion. Increased adhesion to ECM and decreased adhesion among tumor cells result in invasive tumor behaviors. When this invasive behavior occurs, ECM plays an important role for both tumor morphology and the shape of invasive cancer cells. Increased stiffness and stronger degree of degradation of ECM promote tumor invasion, generating more aggressive tumor invasive morphologies. It can also generate irregular shape of invasive cancer cells, protruding towards ECM. The capability of our model suggests it a useful tool to study tumor invasion and might be used to propose optimal treatment in clinical applications.

I. INTRODUCTION

Tumor invasion is of crucial importance for both fundamental cancer research and clinical applications. During tumor progression, cells invade into the surrounding host tissues, adapt to the environment, and develop resistance to therapies. Invasive cells are also left behind after resection and are responsible for tumor recurrence, ultimately resulting in human deaths [1]. Therefore, significant efforts have been made to understand the mechanism of regulating tumor invasion.

During tumor invasion, it is obvious that cell movements are ultimately driven by mechanical forces. Although significant efforts have been made to study the genetic and biochemical aspects of tumor invasion [2], how mechanical properties affect tumor invasion is still poorly understood.

The goal of this study is to use a mechanical cellular model to study the effects of mechanical properties on tumor invasion. We study the effects of cell-cell adhesions as well as the degree of degradation and stiffness of extracellular matrix (ECM). Our simulation results show that increased adhesion to ECM and decreased adhesion among tumor cells must be satisfied for tumor invasion. When tumor invasion occurs, ECM plays an important role for both promoting tumor morphology and generating the irregular shape of invasive cancer cells. This study also aims to suggest novel pharmaceutical targets for anticancer therapy by blocking these essential mechanical changes.

II. METHODS

A. Cellular Model

We use a previously developed cellular model to describe interacting cells [3]. This model represents accurately the geometric properties of a single cell as well as the topological properties of cells in a tissue in two dimensions (Fig. 1A–C). It can approximately model epithelial tumors that are largely two-dimensional in nature.

In our model, cell movement depends on the mechanical forces a cell experiences. There are two types of forces in our model: tension and pressure. *Tension* models the compressional forces acting within a cell. These forces arise from cytoskeletal microfilaments, intermediate filaments, and cell membrane. For an edge between cell a and b , the direction of tension is tangential to edge ab (Fig. 1D):

$$\mathbf{F}_{ab}^t = \eta_{ab} \mathbf{e}_{ab},$$

where η_{ab} is the tension coefficient, which may depend on the cell types of both cells, and \mathbf{e}_{ab} is the edge vector. *Pressure* represents the forces resisting compression. These forces arise mainly from microtubules and extracellular matrix. The direction of pressure is normal to edge ab (Fig. 1D). The net force at a vertex is obtained by summing all the forces due to tension and pressure acting on the vertex (Fig. 1D) (more details can be found in ref. [4–8]).

B. Cell Types

Cells in our model correspond to real tumor cells, cells in stroma or extracellular matrix (ECM). To study the effect of mechanical properties on tumor invasion, we model four types of cells involved in tumor and its microenvironment: non-invasive tumor cells, invasive cancer cells, degraded ECM treated as cells, and normal ECM treated as cells.

- *Non-invasive tumor cells (T)* are inside the primary tumor, surrounded by invasive cancer cells. These cells cannot invade into the tumor stroma, thus cannot interact with the ECM.
- *Invasive cancer cells (C)* are at the tumor-host interface. These cells can directly degrade the ECM, thus can invade into the tumor stroma.
- *Degraded ECM (D)* are at the tumor-host interface. They can be degraded by invasive cancer cells directly.
- *Normal ECM (N)* are at the outer region of tumor stroma, which cannot interact with tumor cells.

C. Mechanical Properties

Tumor exists in a constantly evolving microenvironment of diverse cell types and ECM structures [9]. ECM is a complex mixture of molecules that provide mechanical support for the tumor, and it also plays an important role for cell adhesion and motility [10, 11]. Our model represents ECM structures virtually as cells. Thus our model can explicitly take into account the mechanical interactions between tumor cells and ECM structures. In our current work, we focus on two types of mechanical properties:

- *Cell-cell adhesions:* During tumor invasion, invasive cancer cells lose the adhesion to neighboring tumor cells and tend to adhere to ECM cells [12, 13]. In our model, tension coefficient η_{CD} reflects the difference in adhesion ability between cells. We set tension co-efficient $\eta = 1$ as default value for all edges. Larger $\eta_{CD} (> 1)$ indicates invasive cancer cells have stronger adhesion to tumor cells and less adhesion to ECM cells. Smaller $\eta_{CD} (< 1)$ indicates invasive cancer cells have less adhesion to tumor cells and stronger adhesion to ECM cells.
- *Degree of degradation and stiffness of ECM:* During tumor invasion, invasive cancer cells can degrade ECM cells using matrix metalloproteinases (MMPs) in order to migrate [14, 15]. Previous studies have also shown that the stiffness of ECM promotes tumor invasion [9]. In this study, we model degree of degradation and stiffness of ECM by tension coefficient η_{DD} . Larger $\eta_{DD} (> 1)$ indicates more tension on the edge between degraded ECM cells, thus ECM cells experience more compressional forces to degrade and become more stiff. Smaller $\eta_{DD} (< 1)$ indicates less tension on the edge between degraded ECM cells, thus ECM cells experience less compressional forces to degrade and become less stiff.

D. Quantitative Measurement of Invasive Pattern

To quantitatively characterize the invasive pattern of simulations, we define *Invasive Index* I_T to describe the degree of tumor invasiveness:

$$I_T = \frac{N_C}{N_C + N_T},$$

where N_C and N_T are the number of invasive cancer cells and non-invasive tumor cells, respectively. A larger invasive index I_T value indicates more aggressively invasive pattern.

E. Simulation Methodology

For a typical simulation, an initial tissue (Fig. 3A) consisting around 500 cells is constructed. This tissue is composed of two types of cells: non-invasive tumor cells in the center and normal ECM cells at the outside. Tension coefficients η are set to 1 on all edges at this point. When primary tumor intends to invade into ECM, non-invasive tumor cells at the tumor-host interface change to invasive cancer cells, and normal ECM cells connecting the invasive cancer cells change to degraded ECM cells. At the same time, cells begin to grow and divide. During cell growth, we increase cell volumes with random amounts. We explore the effects of cell-cell adhesions and degree of degradation and stiffness of ECM on tumor invasion with different value of tension coefficients η_{CD} and η_{DD} . We measure the invasive index I_T , and check the tissue morphology and cell shape for visualization. For each set of parameters, we run simulations for 5 times, and take the average as our results.

III. RESULTS AND DISCUSSIONS

A. Effect of cell-cell adhesions

We first studied the effect of cell-cell adhesions on tumor invasion. Tension coefficient η_{CD} is simply set to three values: 0.5, 1.0, and 1.5, explicitly indicating invasive cancer cells with stronger adhesion to ECM (decreased adhesion to tumor cells), equal adhesion to ECM cells and tumor cells, and decreased adhesion to ECM (stronger adhesion to tumor cells), respectively.

We found that invasive index I_T decreases when η_{CD} increases despite of the value of η_{DD} (Fig. 4). Invasive index I_T are 0.43, 0.20, and 0.18 when η_{CD} are set to 0.5, 1.0, and 1.5, respectively ($\eta_{DD} = 1.0$). When $\eta_{CD} = 0.5$, tumor experiences most invasive behaviors. Invasive cancer cells invade into the ECM, forming an irregular and loose tumor-host interface (Fig. 3B). When $\eta_{CD} = 1.0$, tumor experiences slightly invasive behaviors. Invasive cancer cells do not invade into the ECM, but the shape of tumor-host interface is slightly irregular and loose (Fig. 3C). When $\eta_{CD} = 1.5$, tumor does not show any invasive behaviors. Invasive cancer cells do not invade into the ECM, restricted in the primary tumor and forming a stiff tumor-host interface (Fig. 3D). These simulation results demonstrate that stronger adhesion to ECM cells and decreased adhesion to tumor cells can result in invasive tumor behaviors.

B. Effect of extracellular matrix

We then studied the effect of extracellular matrix on tumor invasion. Tension coefficient η_{DD} is simply set to three values: 0.5, 1.0, and 1.5, explicitly indicating decreased stiffness with

less degree of degradation of ECM, control group, and increased stiffness with stronger degree of degradation of ECM, respectively.

1) Tumor invasive morphology—We found that invasive index I_T responds to η_{DD} differently dependent on tumor invasive behaviors (the value of η_{CD}) (Fig. 4). When aggressively invasive behaviors occur ($\eta_{CD} = 0.5$), invasive index I_T increases with η_{DD} significantly. Invasive index I_T are 0.29, 0.43, and 0.48 when η_{DD} are 0.5, 1.0, and 1.5, respectively (Fig. 4). Larger value of η_{DD} generate more aggressively invasive pattern (Fig. 5A). When slightly invasive behaviors occur ($\eta_{CD} = 1.0$), invasive index I_T increases with η_{DD} slightly. Invasive index I_T are 0.18, 0.19, and 0.27 when η_{DD} are 0.5, 1.0, and 1.5, respectively (Fig. 4). When invasive behaviors do not occur ($\eta_{CD} = 1.5$), invasive index I_T is not influenced by η_{DD} (Fig. 4). These simulation results show that ECM affects the tumor invasive morphology only if the invasive behaviors occur. That is, cell-cell adhesion relationship needs to be satisfied to enable the invasive cancer cells to invade into ECM. Thus cancer invasive cells can be influenced by ECM in return, consequently affecting the tumor invasive pattern.

2) Shape of cancer invasive cells—When aggressively invasive behavior occurs ($\eta_{CD} = 0.5$), we found that the shape of cancer invasive cells change with different values of tension coefficient η_{DD} . When $\eta_{DD} = 1.5$, invasive cancer cells form stretched, irregular cell shapes, protruding towards ECM (Fig. 5B). When $\eta_{DD} = 0.5$, invasive cancer cells does not deform, forming regular cell shapes (Fig. 5D). These simulation result is consistent with experimental observations that the deformability of cancer invasive cell (MCF-7) was significantly higher than that of normal tumor cells (MCF-10) [16]. We note that, to our knowledge, our model is the first to generate this stretched, irregular cell shapes during tumor invasion. This suggests our model a valid tool to study both the tissue morphology and cell shapes in tumor invasion.

IV. CONCLUSIONS

We present a cellular model to study the effects of mechanical properties on tumor invasion. Our simulation results show that decreased adhesion between tumor cells and increased adhesion to ECM is the prerequisite for tumor invasion. Following the change of cell-cell adhesion, the change of ECM may further promote tumor invasion, generating more aggressive tumor invasive morphologies and deformable cell shapes. These results may suggest novel pharmaceutical targets for cancer therapy by blocking these essential mechanical changes. Furthermore, the capability of our model suggests it a valid tool to study tumor invasion and might be used to propose optimal treatment in clinical applications.

Acknowledgments

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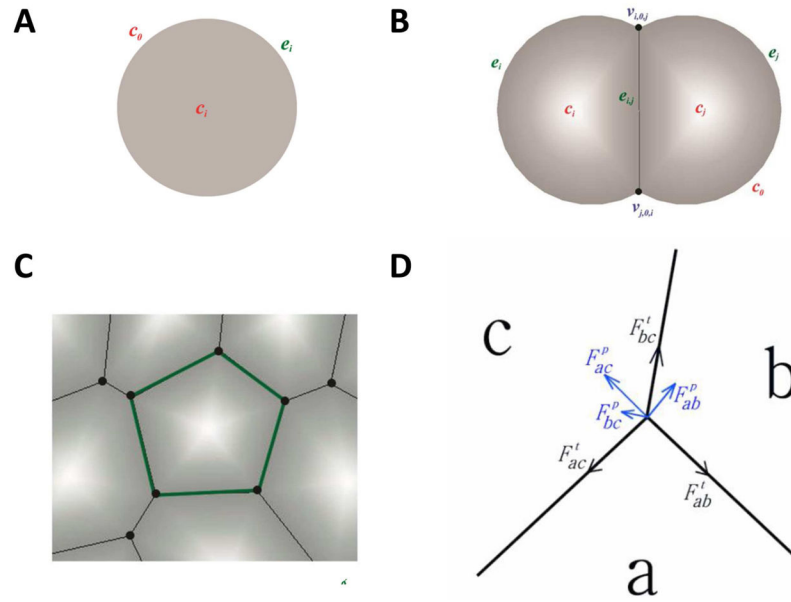


Fig. 1. Two-dimensional cellular model. A) An isolated cell is modeled as a disk. B) A cell is modeled as a disk segment when contacting other cell(s). C) A cell completely surrounded by other cells is represented as a polygon. D) Forces at the junction vertex of three cells a , b , and c . Tension is tangential to the edge (black). Pressure is normal to the edge (blue).

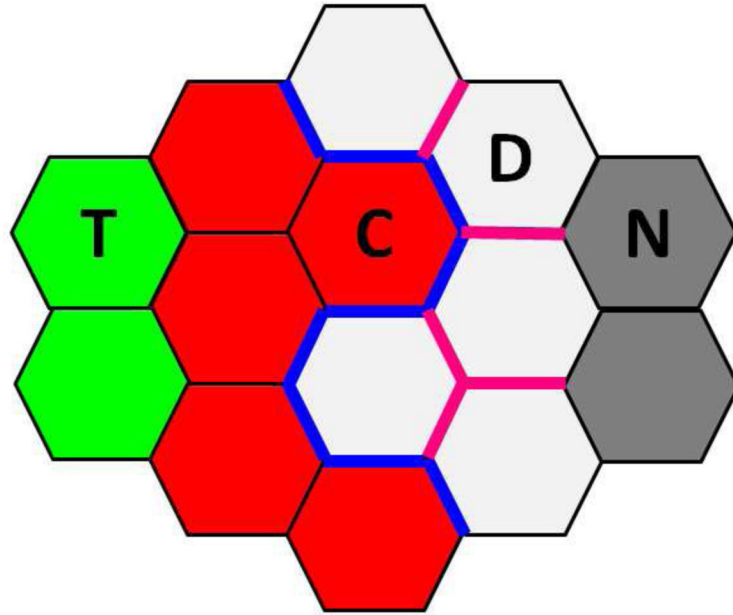


Fig. 2.

Illustration of cell types and mechanical properties within tumor and its microenvironment. Non-invasive tumor cells (T, green) are surrounded by invasive cancer cells (C, red). Invasive cancer cells are at the tumor-host interface, directly degrading the ECM. Degraded ECM (D) are white, and normal ECM (N) far away from the invasive cancer cells are gray. During tumor invasion, tension on the edge between invasive cancer cells and degraded ECM (blue) changes due to the lost adhesion between tumor cells and intension to adhere to the ECM. Tension on the edge among degraded ECM (pink) changes due to degradation by invasive cancer cells and increased stiffness of the ECM.

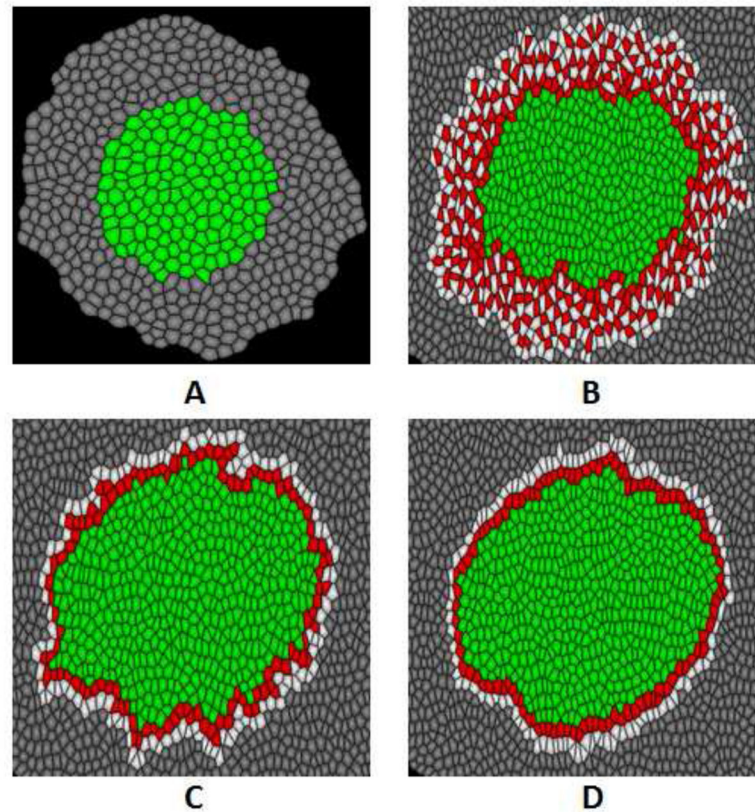


Fig. 3. Simulated tumor morphology with different tension coefficients η_{CD} . Tension coefficient $\eta_{DD} = 1.0$ for all simulations. (A) Initial tissue is composed of non-invasive tumor cells (green) and normal ECM cells (gray) before tumor invasion starts. (B) Invasive tumor morphology occurs with $\eta_{CD} = 0.5$. Invasive cancer cells invade into the extracellular matrix, forming an irregular and loose tumor-host interface. (C) Tumor morphology with $\eta_{CD} = 1.0$. Invasive cancer cells do not invade into the extracellular matrix, but the shape of tumor-host interface is slightly irregular and loose. (D) Tumor morphology with $\eta_{CD} = 1.5$. Invasive cancer cells do not invade into the extracellular matrix, restricted to the primary tumor and forming a stiff tumor-host interface.

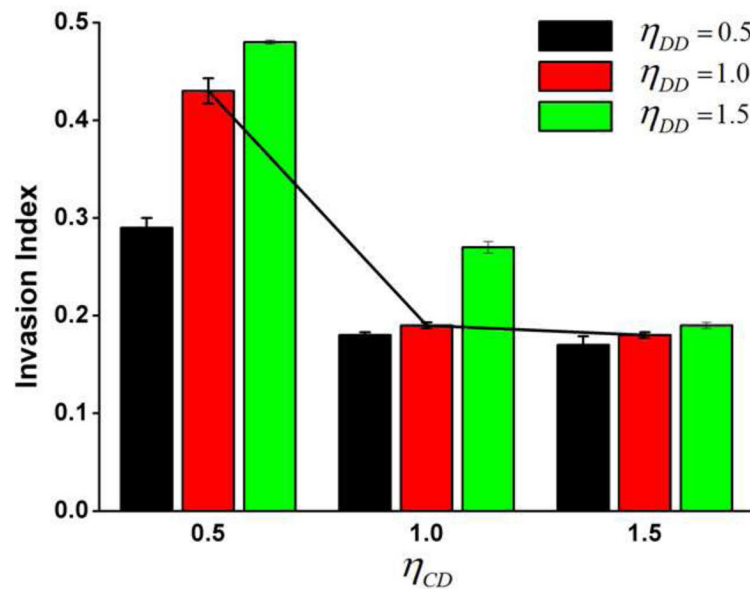


Fig. 4.

Invasive index with different tension coefficients η_{CD} and η_{DD} . Invasive index decreases when η_{CD} increases despite of the value of η_{DD} (black line for visual representation). When $\eta_{CD} = 0.5$, tumor is most invasive, indicating that increased adhesion to ECM cells and decreased adhesion to tumor cells result in invasive tumor behavior. Invasive index responds to η_{DD} differently dependent on the value of η_{CD} . When $\eta_{CD} = 0.5$, invasive index increases with η_{DD} significantly. When $\eta_{CD} = 1.0$, invasive index increases with η_{DD} slightly. When $\eta_{CD} = 1.5$, invasive index is not influenced by with η_{DD} .

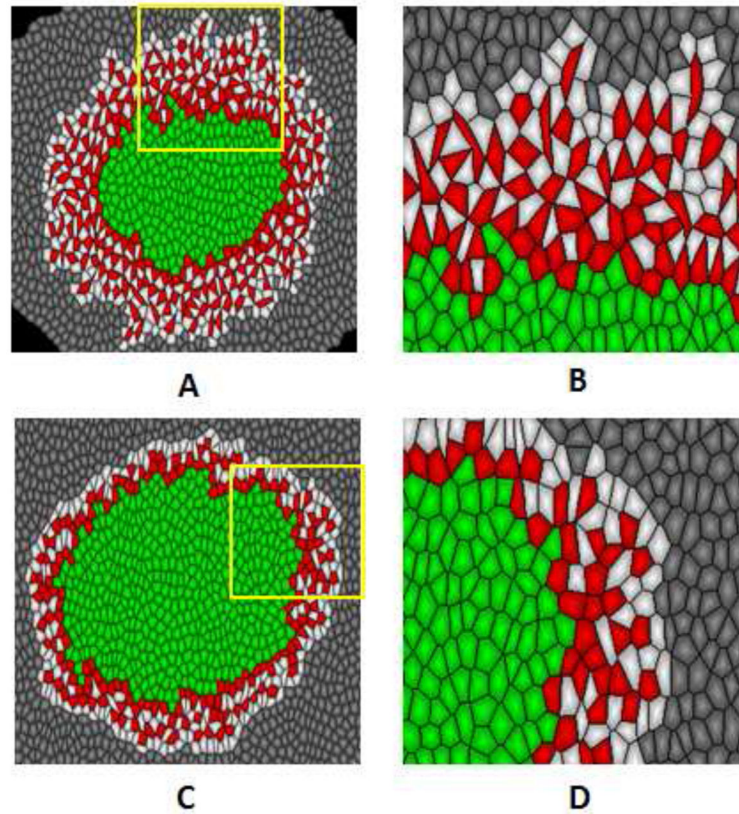


Fig. 5. Simulated tumor morphology and shape of invasive cancer cells with tension coefficients $\eta_{DD} = 1.5$ and $\eta_{DD} = 0.5$. Tension coefficient $\eta_{CD} = 0.5$ for all simulations. (A) When $\eta_{DD} = 1.5$, tumor represents aggressively invasive behaviors with large number of invasive cancer cells invade into extracellular matrix. (B) Magnified picture of the yellow square region in (A). Invasive cancer cells forms elongated irregular cell shapes, protruding towards the extracellular matrix. (C) When $\eta_{DD} = 0.5$, tumor represents less invasive behaviors. (D) Magnified picture of the yellow square region in (C). Invasive cancer cells forms regular cell shapes as the non-invasive tumor cells.