Development of Cell Trajectory Analysis for Revealing Interactions of Cancer Cells

Attachment Format #3 No. 1

Doctoral Dissertation Abstract

Major 総合創成工学専攻

Course 繊維先端工学分野

Name Xin Zhuohan

1. Dissertation Title (If in English, add the Japanese translation.)

Development of Cell Trajectory Analysis for Revealing Interactions of Cancer Cells

がん細胞の相互作用の解明に向けた細胞軌跡の解析技術の開発

2. Abstract (Roughly 2,000 Japanese characters or 800 English words)

Collective cell migration is a major mechanism of cell movement, especially in cancer metastasis. Invasion of cancer cells can spread between tissues. During this migration process, cells metastasize as single and multicellular cells through vascular and other pathways. During tumorigenesis, various stimuli of the microenvironment can induce epithelial mesenchymal transition (EMT) through different signaling pathways. EMT refers to a morphological transformation in which epithelial cells are transformed into a mesenchymal phenotype and acquire a greater ability to migrate. It allows epithelial cells to detach from the tissue and migrate elsewhere. EMT is one of the bases of tumor metastasis. Many studies support the roles of mesenchymal and epithelial cells as leaders and followers, respectively. These previous experimental results support the mechanism of coordinated cellular interactions in collective migration.

Leader cells regulate interconnections through feedback mechanisms mediated by molecular and mechanical signals. Cell-cell interactions are strongly dependent on Cadherin, a calcium-dependent transmembrane protein that constitutes a major component of attachment junctions. During EMT, a simultaneous down-regulation of E-cadherin expression and an up-regulation of N-cadherin expression is usually observed. This switch between cadherins involves a weakening of cell-to-cell junctions. Cells migrate through actin aggregates at the leading edge of cell populations, giving rise to lamellipodia. For adhesion, they are mainly generated by a molecular mechanism consisting of integrins and associated adhesion proteins. These interactions include molecular mechanisms and

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have been extensively described in combination with mechanistic models. The forces between cells and the matrix typically include traction forces driving the cells and frictional forces between the cells and the matrix. Adhesion forces between cells are mediated by transmembrane protein complexes. Frictional forces between cells are associated with the sliding of attachment proteins. Three-dimensional hydrogels made from ECM proteins or two-dimensional materials can be used to remodel the specific ECM composition. Topographical features of the extracellular matrix can be recreated by spinning polymers into fibers and depositing them on the surface as a thin layer to which cells can adhere. Electrospinning techniques have been widely used in simulating the extracellular matrix, among other things. In this paper, we construct a quantitative analysis based on the interaction between leader and follower cells. Different proportions of both cells were tracked and the migration characteristics of single cells in collective cell migration were analyzed. The results show that a certain proportion of leader cells has an effect on the relevant properties of collective migration, but an extremely high proportion leads to a weakening of the facilitation mechanism.

To clarify the complexity of the migration phenomenon, the researchers developed experimental methods to capture the collective behavior of the cells. Initial protocols were based on living imaging of monolayers of cells cultured on flat substrates. Image processing generally relies on particle image velocimetry to measure velocity and on manual or semi-automatic cell segmentation to extract cell shape and number. In addition, different specific traction microscopes can generate traction or stress maps of cell populations. These methods can put all the cells together and get an overall impression of the migration pattern. They are difficult to separate cells by certain properties. This is because migration patterns are influenced not only by internal factors but also by external factors. It is a challenge to detect all factors at the same time. Therefore, we propose a method using machine learning to study hidden relationships based on cell trajectories.

In biology, the target of study often involves a large number of cells or genes. Each of these individuals has unique characteristics and they are related to each other. Finding individuals with similar characteristics in a population is useful for collective events and large-scale analysis. The first step is to extract features of the target, such as speed, location, fluorescence intensity, and direction. These features also change

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with the time dimension. Such high-dimensional data cannot be compared directly and it is difficult to understand the high-dimensional data. The combination of bioinformatics and computer vision provides a new approach for biological applications. Many dimensionality reduction algorithms can project data from high to low dimensions. The high-dimensional data is visualized while maintaining the original structural features. The reduced dimensional data is obtained by measuring the similarity of each target and iterating until the minimum similarity between groups is obtained, and the algorithm can perform clustering based on the similarity. The method shows excellent performance when dealing with huge datasets. Our analysis is based on cell migration trajectories, which are sliced throughout the migration process at different observation time windows. The obtained high-dimensional trajectory information is dimensionally reduced and all data are clustered based on similarity. The results show that after normalizing the initial positions of the trajectories, the cells still exhibit positional similarity to each other. The method was further optimized by comparing different algorithms and parameters. The effect of leader cells on collective cell migration occurred in different proportions of leader and follower cells. The observed phenomena in the optimized method support the previous conclusion that a certain proportion of leader cells has a promoting effect on the migration of the colony. The proposed method provides a new perspective for studying the collective migration of cancer cells and offers new insights into the interactions between cells. The method is not only applicable to this model, but can also be applied to other models capable of tracking cell trajectories for even broader future applications.