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A Study on Cancer-Cell Invasion Based on the Diffuse Interface Model

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***Abstract*—**In this study, a three-dimensional haptotaxis model to simulate the migration of a population of cancer cells has been proposed. The invasion of cancer cells is related with the hapto-attractant and the effect of the interface energies between the cells and the ECM. The diffuse interface model, which incorporates the haptotaxis mechanism and interface energies, is employed. The semi-implicit Fourier spectral scheme is adopted for efficient evaluation of the simulation. The simulation results thoroughly reveal the dynamics of cancer-cell migration.

***Keywords*—**Haptotaxis, Cancer Cells, Cell Migration, Interface Energy, Diffuse Interface Model

I. INTRODUCTION

CANCER-CELL invasion is a complex biological process involving cell migration through the extracellular matrix (ECM). Cancer cells have an ability to escape from a primary tumor and invade the surrounding tissues by the process of cell migration [1]. Cell migration is governed by a variety of factors. The main mechanism by which a cancer cell migrates is known as haptotaxis. Haptotaxis is a phenomenon in which cancer cells are directed toward a higher concentration of hapto-attractant by a surface gradient. In the process of cancer-cell migration, the gradient is usually present in the ECM [2].

Previous experiments have shown that the migration and invasion of cancer cells are influenced by factors such as random mobility and the haptotaxis coefficient [3-5]. Most systematic studies of these cell properties have been conducted in a two-dimensional culture system, which limits our understanding of the mechanism of cancer-cell migration [6]. Recently, a three-dimensional culture system was developed and cancer cells were organized in three-dimensional patterns surrounded by other cancer cells as well as the ECM [7]. It is possible to clearly and precisely detect the properties of cancer cells using this system.

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Over the last 10 years, models for the invasion of cancer cells had been developed [8-10]. A discrete approach that considered individual cancer cells was adopted; however, the main drawback of the individual-based model was its high computational complexity [9]. Recently, a continuum model that considered cell–cell adhesion was developed [10]. However, this model just introduced the cell–cell adhesion that develops because of surface tension at the tumor surface and excluded the cell–matrix adhesive effects. Previously developed haptotaxis models were single-cell models; these models were accurate in the modeling of processes involved in cellular adhesion [2]. Thus, in order to elucidate the interaction between the adhesion of the cells and that of the ECM, cell-population models were developed.

In this study, we develop a haptotactic model consisting of a population of cancer cells and ECM. The migration of the population of cancer cells was governed mainly by haptotaxis in response to the density gradient of the ECM. We propose a three-dimensional dynamic model to examine the haptotaxis-governed migration process of the population of cancer cells in detail. We employ the diffuse-interface model to develop multi-components and multi-physics model; this model incorporates multiple mechanisms, especially, interface energies. The developed model will be the basic framework for the further study, which is considerably complicate biological phenomena related with haptotaxis such as the invasion of cancer cells.

II. COMPUTATIONAL METHOD

To develop a three-dimensional model for a population of cancer cells, we assume that they are free particles and that they can interact with each other. In this continuum model, we assume that the migration of the population of cancer cells is driven by haptotaxis in response to the density gradient of the ECM. As shown in Fig.1, we model the population of cancer cells in a three-dimensional geometry. In this model, it is assumed that the hapto-attractant is produced only along the x_2 direction. A periodic boundary condition is assigned along the x_1 and x_3 directions so that the effect of the surrounding boundary on cell migration can be avoided.

We propose a three-dimensional dynamic model incorporating the surface energies of the cancer cells and the haptotaxis mechanism. To overcome the computational

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complexity that arises as a result of considering cell-evolution that is dependant on related with multiple driving forces, a diffuse-interface approach is adopted. Similar approaches have been applied in previous studies related with morphological evolutions of nano- and microstructures and have demonstrated the reliability and effectiveness of such approaches [11-13]. In contrast to the interface-tracking methods such as the boundary elements method, the surfaces are not modeled explicitly but are indicated implicitly by a concentration field where a surface is represented by a thin continuous transition region. Thus, complex interface changes will not cause any additional computational difficulties. Here, two different concentrations fields c_1 and c_2 are introduced to represent the concentrations of cancer cells and the ECM, respectively. We define the concentration c_1 as the fraction of cancer cells to the total number of cells at a particular site; thus, c_1 = 1 when we only have cancer cells at a site and c_1 = 0 when there are no cancer cells at a site. The density c_2 is defined as the fraction of ECM to the total number of cells at a particular site; thus, c_2 = 1 when we only have ECM in the site and c_2 = 0 when there is no ECM in the site. The concentrations of cancer cells and the ECM are regarded as spatially continuous and time-dependent functions $c_1(x_1, x_2, x_3, t)$ and $c_2(x_1, x_2, x_3, t)$, respectively.

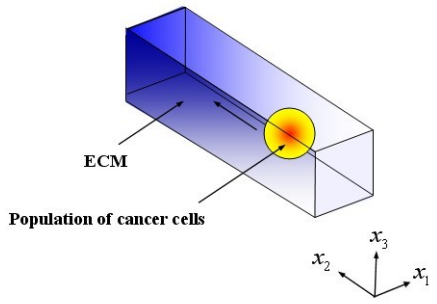


Fig.1 Schematic representation of haptotaxis in ECM. Darker region corresponds to higher density of hapto-attractant.

A number of mathematical models have been proposed for the taxis phenomenon. The most widely used one is the model of Keller and Segel [14]. They derived an expression for the cancer-cell flux $\mathbf{J}_c$ induced by external stimuli given by $\mathbf{J}_c = \chi c \nabla \phi$, where χ is the taxis sensitivity, $c(\mathbf{x})$ is the concentration of the cancer cells, and ϕ is the attractant density. In this paper, the cancer-cell flux $\mathbf{J}_c$ indicates that the haptotactic response of cancer cells depends on the hapto-attractant gradient field. Thus, we introduce the cancer-cell flux caused by haptotaxis using the expression $\mathbf{J}_c = \chi c_1 \nabla \phi$, where χ is the haptotaxis sensitivity, $c_1(\mathbf{x})$ is the concentration of cancer cells centered in the spatial domain, and ϕ is the hapto-attractant density. By employing the diffuse-interface framework, we define the mobility of the cancer cells as $M_1(c_1) = M_0\left[\left\{\int c_1^2(1-c_1)^2 dc_1 / \int_0^1 c_1^2(1-c_1)^2 dc_1\right\}(1-c_1)\right]$, where M_0 is a material constant and the other term given in the square brackets represents the cancer cells precisely [11, 12, 15-19]. Note that $M_1(c_1)$ does not exist outside the interfacial region of the population of cancer cells. Since the mobility of the cancer cells is proportional to the haptotaxis sensitivity χ [20], we define the cancer-cell flux induced by the haptotactic response as $\mathbf{J}_c = M_1 \beta \nabla \phi$, where β is the sensitivity constant and $M_0\beta$ corresponds to the haptotaxis sensitivity χ.

At the same time, another driving force that relates the cancer-cell flux $\mathbf{J}_c$ to chemical potentials μ_1 and μ_2 is given by $\mathbf{F}_{d1} = -\nabla \mu_1^0$ and $\mathbf{F}_{d2} = -\nabla \mu_2^0$, respectively. We represent the flux of the population of cancer cells and the ECM flux induced by chemical potentials (μ_1^0 and μ_2^0), which are related to the interface energies of the cells, as $\mathbf{J}_{d1} = -M_1 \nabla \mu_1^0$ and $\mathbf{J}_{d2} = -M_2 \nabla \mu_2^0$, respectively. Thus, the net flux of the population of cancer cells can be expressed as

$$\mathbf{J}_1 = -M_1 \nabla \mu_1^0 + M_1 \beta \nabla \phi, \quad (1)$$

$$\mathbf{J}_2 = -M_2 \nabla \mu_2^0 . \quad (2)$$

Taking into account the net flux of the population of cancer cells, it is indicated that the haptotactic response of cancer cells depends on the hapto-attractant gradient field. At the same time, the chemical potential is related to the free energy of the system; therefore, using the Cahn–Hilliard equation [21], we obtain

$$G = \int_V \left\{ f_c(c_1, c_2) + h_{11}(\nabla c_1)^2 + h_{22}(\nabla c_2)^2 + h_{12}(\nabla c_1 \nabla c_2) \right\} dV \quad (3)$$

The first term $f(c_1, c_2)$ represents the chemical energy in the system and the next three terms account for the interface energy among the population of cancer cells, the interface energy of the ECM, and the interface energy between the cancer cells and the ECM, respectively; h_{11}, h_{12}, and h_{22} represent material constants. By combining this equation with the mass-conservation relation $\partial c_1 / \partial t + \nabla \cdot \mathbf{J}_1 = 0$, we get a nonlinear diffusion equation:

$$\frac{\partial c_1}{\partial t} = -\nabla \cdot (-M_1 \nabla \mu_1^0 + M_1 \beta \nabla \phi) \quad (4)$$

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We normalized the governing equations with a characteristic length L_c and time $t_c = L_c^2 / M_0 f_0$ as

$$\frac{\partial c_1}{\partial t} = \nabla \cdot \left(M_1 \nabla \mu_1 \right) \tag{5}$$

$$\mu_1 = \left(2c_1 + c_2 \quad 1\right)\left(2c_1^2 \quad 2c_1 \quad 2c_1 c_2 \quad c_2 \quad 2c_2^2\right) + \tag{6}$$

$$-ch_{11}^2 \nabla^2 c_1 \quad \frac{1}{2} ch_{12}^2 \quad ^2 c_2 \quad \alpha\phi \quad \nabla \quad -$$

$$\frac{\partial c_2}{\partial t} = \nabla \cdot \left(M_2 \nabla \mu_2 \right) \tag{7}$$

$$\mu_2 = \left(c_1 + 2c_2 \quad 1\right)\left(2c_1^2 \quad c_1 \quad 2c_1 c_2 - 2c_2 \quad 2c_2^2\right) \tag{8}$$

$$-ch_{22}^2 \nabla^2 c_2 \quad \frac{1}{2} ch_{12}^2 \quad ^2 c_1 \qquad \nabla$$

where $\alpha = \beta\phi_0 / 2 f_0$ and represents the significance of the haptotaxis. The mobilities M_1 and M_2 and the initial hapto-attractant density ϕ are dimensionless numbers normalized by M_0 and ϕ_0. ch_{11}, ch_{12}, and ch_{22} are the Cahn numbers, which represent the relative significance of the interface energy between the cancer cells and the ECM.

III. RESULTS

We have performed a series of simulations, as shown in Fig.2. The figures show snapshots of cancer-cell migration at selected time steps. The domain size is $100 \times 50 \times 50$ in the simulation. We select the characteristic length L_c and Cahn numbers to be 1.0 mm and $ch_{11} = 1$, $ch_{12} = 1$, $ch_{22} = 1$, respectively. The

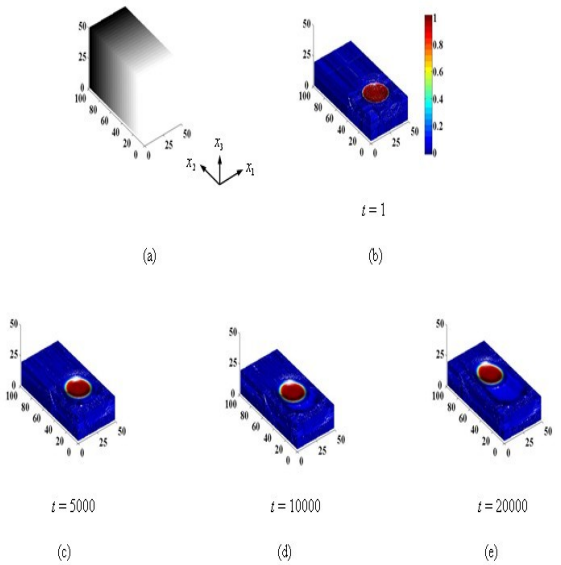


Fig.2 Evolution sequence of population of cancer cells in haptotaxis. Cancer cells migrate to region with higher hapto-attractant density during simulation.

characteristic length and the radius of a cancer cell are considered to be 0.1 cm and $3.6 \times 10^{-3} cm$, respectively; this gives a typical cancer-cell volume of 1.5×10^{-8} cm^3 per cell [8, 22]. In the spatial domain, cancer cells are initially positioned at (25, 25, 25). The hapto-attractant gradient field is illustrated using a color bar graph, as shown in Fig.2 (a). The darker region corresponds to a higher density gradient and the brighter region corresponds to a lower density gradient. The hapto-attractant is introduced from the left end of the domain, and the linear hapto-attractant gradient field from the left to the right is assigned as α = 4.0. Figs.2 (b)–(e) show the evolution sequence of the cancer cells from $t = 0$ to $t = 20000$. As observed, the population of cancer cells migrates to the higher hapto-attractant density-gradient region in the simulation.

Previous simulations for a population of cancer cells were unable to clarify the migration of the cancer cells in detail, especially in a three-dimensional domain. However, using the diffuse-interface model, we can calculate the velocity of the population of cancer cells by tracing their displacement from the simulated results. The measured velocity is approximately 16.55 μm/s, which is consistent with the experimentally observed velocity value of approximately 20 μm/s [23, 24]. This simulation result confirms the reliability of the proposed model. Moreover, we suggest that this model can be used to quantify cell properties, for example, it can be used to accurately calculate the cell velocity.

IV. CONCLUSION

This paper presents a three-dimensional model that clearly reveals, in detail, the process of cancer-cell migration, which is governed by haptotaxis as well as by the interface energies among cells and those between the cells and the ECM. The diffuse-interface model is employed, and it incorporates the cancer-cell flux related with both the interface energies and the haptotactic response of the cancer cells. The proposed model is mathematically evaluated using the semi-implicit Fourier spectral method. Simulations have demonstrated a haptotactic migration of cancer cells toward the higher density gradient of the ECM. We can also calculate the velocity of the cancer cells; the result is consistent with the experimentally observed velocity value. This simulation result confirms the reliability of the proposed model and provides a solid framework for further study on cancer-cell invasion.

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