Chemical Engineering Science 191 (2018) 268–287

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

A multiphase model for exploring tumor cell migration driven by autologous chemotaxis

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HIGHLIGHTS

- A multiphase model is developed that can describe autologous chemotaxis consistent with in vitro experiments.
- The role played by fluid-ECM, cell-ECM, and cell-fluid interaction forces are included.
- The model illustrates how autologous chemotaxis can be used as a means for metastasis.

ARTICLE INFO

Article history:
Received 23 January 2018
Received in revised form 26 June 2018
Accepted 27 June 2018
Available online 30 June 2018

Keywords:
Cell-migration
Multiphase flow
Interstitial fluid
Interstitial fluid pressure
Lymphatic flow
Vascular flow
Autologous chemotaxis
Chemokine
Protease

ABSTRACT

It has been demonstrated that interstitial fluid (IF) flow can play a crucial role in tumor cell progression. In the seminal works by Swartz and collaborators (Fleury et al., 2006; Shields et al., 2007) it was discovered that due to this flow, chemokine ligands secreted by tumor cells selectively tend to bind to receptors (CCR7) on the downstream side of the cells that in turn stimulate cells to migrate in the direction of the flow. This migration process was denoted as autologous chemotaxis. Previous mathematical modeling of autologous chemotaxis apparently has been restricted to single-phase considerations. The purpose of this work is to explore how a multiphase approach can be used where the fluid and cancer cells are treated as two separate phases with their own momentum balance equations. A mathematical model is derived that sheds light on essential nonlinear coupling mechanisms and interactions that are involved. The role played by fluid-ECM (friction type of term) and cell-ECM interaction forces (adhesion forces) are demonstrated. In particular, a fluid generated stress term in the mathematical expression for the cell velocity is highlighted. This term reflects how the flowing fluid will try to push the cancer cells in the downstream direction whose effect must be counterbalanced by the cancer cells by creating a sufficiently strong cell-ECM resistance force. Moreover, in order to represent the autologous chemotaxis migration mechanism we include (i) a component to represent stagnant ECM concentration (collagen); (ii) a chemical component representing chemokine that can convect with the fluid; and (iii) a third chemical component to represent protease secreted by the cancer cells which is able to release ECM-bound chemokine through proteolytic activity. The resulting model allows us to demonstrate how the autologous chemotaxis transport mechanism is governed by formation of chemokine concentration gradients that are asymmetric and skewed in the flow direction. We test the model behavior for a flow system with an external imposed pressure gradient which is comparable with the laboratory experiments by Swartz and collaborators. Sensitivity to changes in circumstances like blocking of the CCR7 receptor needed for autologous chemotaxis and elimination of the pressure driven IF flow (i.e., no flow) are explored and discussed. We also illustrate the model behavior in an envisioned tumor setting where increased IF flow is produced from leaky blood vessels that sit on the inside of the tumor. An increased fluid flow towards the region on the outside of the tumor is then generated where it is adsorbed by lymphatic vessels and gives rise to a characteristic elevated IF pressure profile that decreases at the tumor periphery. In turn, this results in an autologous chemotactic driven migration of cancer cells at the rim of the tumor. The simulation illustrates how the autologous chemotactic cell migration mechanism discovered by Swartz and collaborators possibly can be used as a means for metastasis by generating aggressive cell migration towards lymphatic vessels.

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https://doi.org/10.1016/j.ces.2018.06.076
0009-2509/

1. Introduction

1.1. Interstitial fluid flow in the tumor microenvironment

Interstitial fluid flow, the movement of fluid around cells and through pores in the extracellular matrix (ECM), can have the ability to alter the tumor microenvironment which in turn can play a major role in tumor progression. One of the effects that interstitial fluid flow has on the tumor microenvironment, is creating a asymmetric pericellular gradient of chemotactic proteins which the cells migrate towards through chemotaxis. How such gradients arise are critical in order to understand these processes.

Some of the chemokines that tumor cell migration is sensitive to are CCL19 and CCL21, which are both ligands for the receptor CCR7. Autocrine signaling is a well-described phenomenon in cells, where the cell secrete chemokine, which may bind to the ECM to be subsequently released proteolytically and diffuse away from the cell. With the addition of interstitial fluid flow, this phenomenon takes on a new significance. The chemokine will still diffuse, but it will also advect in the direction of the flow, causing the cells to chemotactically migrate towards this asymmetric chemokine gradient created by the flow. See Fig. 1 for an illustration similar to the one used in Shields et al. (2007) which describes autologous chemotaxis as a means to metastasis. The flow direction is from the high pressure tumor toward the nearest low pressure draining lymphatic vessel, and this flow acts as a guidance mechanism for the cancer cells. This has been demonstrated in the seminal work by Shields et al. (2007) for breast cancer cells, which expresses a high density of CCR7 receptors such that the ligands can efficiently signal.

1.2. The mechanism suggested by Swartz and collaborators

The tumor cells often respond to extracellular cues based on gradients of morphogenetic and chemotactic proteins. One of these responses is a mechanism suggested in Shields et al. (2007) where tumor cells chemotact towards a draining lymphatic. The tumor cells create a pericellular gradient of proteins which in turn may be amplified under the influence of a subtle interstitial flow. The chemokine or morphogen has matrix binding properties (Patel et al., 2001) where the protein are secreted by the cells in precursor forms that contain specific motifs that bind to components of the ECM to be later released by cell-mediated proteolysis. A 2D mathematical model was presented in Fleury et al. (2006) based on single-phase considerations where the main objective was to demonstrate that the pericellular gradients formed by the cell-secreted morphogen can result in a significant asymmetry when interstitial flow is introduced. This asymmetry is what is thought to drive the chemotactic migration of the cells in the direction of the flow. The model is a steady-state convection-diffusion equation for the concentration of the solute C_i of the form:

$$v\nabla C_i = D_i\nabla^2 C_i + R_i \quad (i = p, m) \tag{1}$$

where v is the fluid velocity, solved using Brinkman's equation for a sphere, C_i refers to either protease C_p or morphogen C_m. In the case of cell-secreted protease the reaction term is assumed as a first-order protease degradation term, such that $R_p = -k_p C_p$ with a rate constant k_p. In the case of ECM-released morphogen the reaction term becomes $R_m = k_{ECM} C_p S$ where the morphogen bound to the ECM is only released by proteolysis (with rate constant k_{ECM} and S is the concentration of bound morphogen). The cancer cell is treated as a stationary semicircular disc which has either a constant surface concentration or a constant surface flux of protein. The interstitial fluid phase is considered as a constant velocity field which is used in the calculation of the gradients.

In the experimental results obtained in Shields et al. (2007), the tumor cells secreted the ligands CCL21 and CCL19 and expressed the receptor CCR7. When interstitial fluid flow was introduced, the tumor cells exhibited increased migration downstream. In the event of using antibodies to block the CCR7 receptor, the increased downstream migration ceased. Main observations from the experimental results in Shields et al. (2007) are schematically summed up in Fig. 2.

Further investigations are provided in the work by Shieh et al. (2011) where the role of fibroblasts and its interaction with cancer cells leading to increased cell migration, is elucidated. A main observation from these experiments, by examining the interplay between tumor cells, fibroblasts, and interstitial flow, is that flow guides fibroblast invasion, leading to concurrent and increased invasion of tumor cells through the ECM. Without interstitial flow, fibroblasts did not affect tumor cell invasion.

1.3. Interesting questions and challenges

However, to the best of our knowledge, its seems that previous modelling aimed at shedding light on basic mechanisms involved in autologous chemotaxis, have been restricted to single-flow descriptions. Such formulations typically are based on Darcy's equation or the more general Brinkman's equation, combined with appropriate transport-reaction equations that can account for the

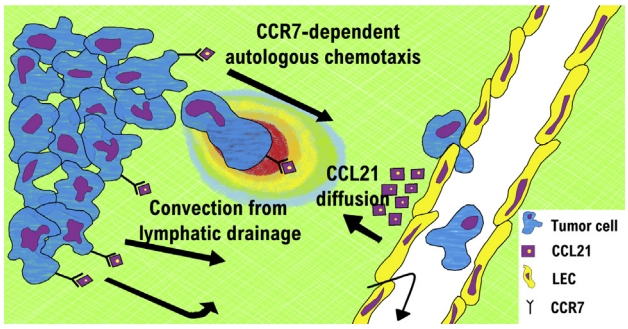

Fig. 1. Figure motivated by (Shields et al., 2007) illustrating the tumor microenvironment where lymphatics drain interstitial fluid, creating a fluid flow toward the lymphatics. This fluid flow causes chemokine CCL21 to advect toward the lymphatic vessel and thereby creating a chemokine gradient in the direction of flow. Tumor cells armed with CCR7 receptor can sense this gradient and migrate toward it.

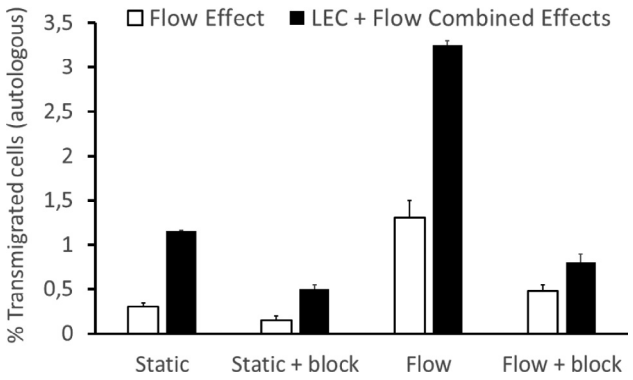

Fig. 2. This figure is a summary of the experimental results shown in Fig. 7A in Shields et al. (2007). We have focused on the results regarding the flow and its effect on cell migration as a function of ECM-released chemokine. The role of lymphatic endothelial cells (LEC) and secreted chemokine from them is not directly accounted for in the model we consider. In particular, we will assess the mathematical model in light of the results that show cell migration under flow, with and without CCR7 blocking, and static (no flow) conditions (white columns).