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A multiphase model of tumour segregation in situ by a heterogeneous extracellular matrix

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ABSTRACT

Normal and tumour cells live in a fibrous environment that is often very heterogeneous, even characterized by the presence of basal membranes and regions with high density of collagen fibres that physiologically compartmentalize cells in well defined regions, as for in situ tumours. In case of metastatic tumours these porous structures are instead invaded by cancer cells. The aim of this paper is to propose a multiphase model that is able to describe cell segregation by thick porous structures and to relate the transition rule that determines whether cells will pass or not to microscopic characteristics of the cells, such as the stiffness of their nucleus, their adhesive and traction abilities, the relative dimension of their nucleus with respect to the dimension of the pores of the extra-cellular matrix.

1. Introduction

Recent experiments by Wolf et al. [28] show that cell migration strongly depends on the density of the three-dimensional collagen network they move through and more specifically on the typical size of the pores of the network. They also evaluate the dependence of the cell speed from the pore cross-section, finding a relation that can be considered linear in the range considered (from 5 up to 20 μm^2). In our opinion, the most relevant feature is however the presence of a minimal cross section necessary to allow motion through the three-dimensional extracellular matrix (ECM). Below this threshold, cells try to penetrate with their cytoplasm in the fibre network, but because of the presence of a stiff nucleus, they remain essentially in place (see Fig. 1d bottom). At this point, if the cell is able to express metallo-proteinases (MMPs), these proteins will partially degrade the fibres leading to a local increase in the pore size of the collagen network, forming paths that the cells can use to invade the ECM. Recent experiments by Wolf et al. [28] show that cell migration strongly depends on the density of the three-dimensional collagen network they move through and more specifically on the typical size of the pores of the network. They also evaluate the dependence of the cell speed from the pore cross-section, finding a relation that can be considered linear in the range considered (from 5 up to 20 μm^2). In our opinion, the most relevant feature is however the presence of a minimal cross section necessary to allow motion through the three-dimensional extracellular matrix (ECM). Below this threshold, cells try to penetrate with their cytoplasm in the fibre network, but because of the presence of a stiff nucleus, they remain essentially in place (see Fig. 1d bottom). At this point, if the cell is able to express metallo-proteinases (MMPs), these proteins will partially degrade the fibres leading to a local increase in the pore size of the collagen network, forming paths that the cells can use to invade the ECM. On the other hand, cells in which MMP expression is inhibited (like the GM6001 cells in Fig. 1) are not able to penetrate into the network with their entire body, unless the pores are large enough (as in Fig. 1d top). In fact, after 18 h the border of the multicellular spheroid shown in Fig. 1c has not moved in the rat tail case and has advanced in the bovine case.

Several other experimental papers study the penetration of cells in microchannels [10,14,22] interfering with the adhesive and mechanical properties of the cells. On the basis of these experiments and of energy arguments Giverso et al. [6] identified a criterium of penetration involving the comparison of the ratio of adhesion forces exerted by the cells and nucleus stiffness with a given function of the ratio of the microchannel size with respect to the nucleus diameter. In particular, if the size ratio is too restrictive, then the cell cannot penetrate into the micro-channel. However, keeping the same geometrical characteristics, cell clones with higher traction abilities or softer nuclei might be able to penetrate the microchannel. The same dependence was obtained by Scianna et al. [23–25] who simulated cell migration both over adhesive substrates, and through three-dimensional ECM and microchannels using a cellular Potts model.

Coming back to the experiments by Wolf et al. [28] the above discussion means that the threshold value they find cannot be

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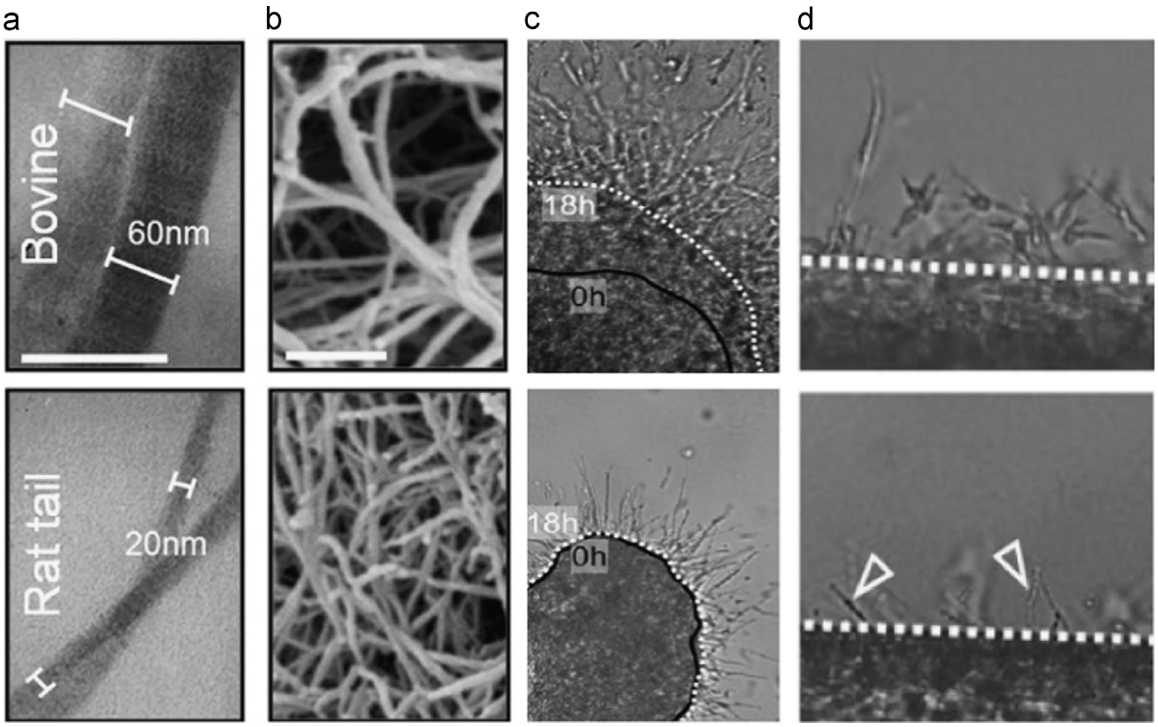

Fig. 1. Morphological characteristics of rat tail and bovine collagen fibrils ((a) transmission electron microscopy, bar=0.1 μm) and network ((b) scanning electron microscopy, bar=1 μm). In (c) invasion into rat tail (bottom) and bovine (top) collagen when MMP is inhibited. The rat tail collagen is characterized by a finer mesh and the cell cannot penetrate. The arrowheads in the magnified pictures in (d) indicate long cytoplasmic extensions of cells with the nucleus stuck below the collagen. Partially modified from [28] (with permission).

considered constant, but depends on the geometrical and mechanical properties of the cells.

The same mechanism works for multicellular spheroids as well, as shown in Fig. 1c, d and in the supplementary material (Video 3) of [28]. When the spheroid of MMP inhibited cells is embedded in a collagen network which is not too thick, or better with a pore size that is not sterically restrictive, the cells at the boundary of the spheroid tend to invade the gel. On the other hand, if the collagen network is characterized by a pore size that is too small, cells at the boundary tend to protrude into the network but their nucleus remains trapped at the border of the spheroid, so that it cannot follow and there is no invasion of the tissue.

Starting from the above experiments in this paper we propose a multiphase model that is able to describe cell segregation by thick porous structures. Previous models were not able to include this effect, because they mainly described multicellular spheroids as a fluid (viscous or inviscid) and related the velocity of cells to cell pressure through a sort of Darcy's law with a permeability coefficient that was usually constant or weakly depending on the ECM volume fraction (see the reviews [4,15,20,26,27]). This implied that any cell pressure would have led to penetration in porous structures, possibly slowed down by the decreased porosity, but segregation was impossible to be achieved.

The model presented here focuses on the term that governs cell motility in the porous ECM. The proposed structure allows us to describe situations in which thick regions of ECM can be invaded or not depending on the stiffness of the cell nuclei, on the adhesion and traction ability of cells, on cell pressure on the ECM, and on the relative dimension of the cell nucleus with respect to the dimension of the pores of the ECM.

The paper then develops as follows. After this introduction and a section presenting the modelling framework, Section 3 contains the main modelling novelties focusing on cell motility. Section 4 discusses the output of the simulation in the case of a single growing population, starting from a control case in which the tumour grows in situ without invading the surrounding tissue. Then several effects leading to tumour invasion are considered such as higher ECM porosity and activation of matrix degrading enzymes. Section 5 generalizes the model to several cell populations, having in mind the goal of describing the growth of a tumour in a normal tissue focusing in particular on the cases in which the tumour population is less sensitive to contact inhibition and have decreased nucleus stiffness, or increased traction ability by the cells.

2. The basic mathematical model

We consider the cell aggregate living in a rigid extracellular matrix (ECM) as a mixture composed of cells and ECM components in the interstitial fluid. Denoting by ϕ_c, ϕ_m, and ϕ_ℓ the volume ratio of cells, ECM, and interstitial fluid and by $\mathbf{v}_c$ and $\mathbf{v}_\ell$ the corresponding velocities, following [3], we can write the following multiphase model:

$$\begin{cases} \dfrac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{v}_c) = \Gamma_c \\ \nabla \cdot \mathbf{T}_c + \mathbf{m}_c = \mathbf{0}, \\ \dfrac{\partial \phi_m}{\partial t} = \Gamma_m, \\ \dfrac{\partial \phi_\ell}{\partial t} + \nabla \cdot (\phi_\ell \mathbf{v}_\ell) = \Gamma_\ell, \\ \phi_\ell \mathbf{v}_\ell = -\dfrac{\mathbf{K}}{\mu} \nabla P, \end{cases} \tag{2.1}$$

where Γ_c, Γ_m and Γ_ℓ are respectively the supplies of cells, ECM and interstitial liquid, $\mathbf{T}_c$ is the stress tensor for the cell population, P is the interstitial pressure, and $\mathbf{m}_c$ is the interaction force between cells and the other constituents. Since our focus will be on growth phenomena in heterogeneous environments, as discussed in [9], the mechanical interactions between the interstitial