Simulation of Breast Tumor Growth from In-Situ to Invasive Cancer Using A Mathematical Model to Correlate with Lesion Phenotypes Shown on MRI

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Introduction

Cancer progression is a complex process. Several possible explanations have been put forward to explain why benign or in-situ tumors show different phenotypes than aggressive invasive tumors. Low rate of migration by the tumor cells, failure of cells to escape the well-defined tumor borders, and reduced proliferation rate are considered as the possible reasons. On the other hand, malignant or invasive tumors are thought to actively migrate into surrounding healthy tissue that leads to poorly defined margins. The constraint mechanism to limit cell proliferation is no longer functioning. Mathematical modeling provides a unique means to simulate different cancer growth patterns. While these models are mathematically valid, only functional information (e.g. limit or heterogeneity distribution of the nutrient) has been taken into consideration. The anatomical information (e.g. physical pressure between tumors and environmental structure) is important and needs to be considered. The works being reported so far have been focusing on understanding the influence of physiological mechanisms on tumor growth; few of them try to correlate with imaging findings. In this study, we incorporated environmental anatomical information into the models, specifically to simulate the breast cancer growth in the milk duct. The simulation result is further correlated with the MRI imaging findings of pure ductal carcinoma in-situ (DCIS) and DCIS with invasive components.

Methods

The tumor model consists of two components: a growth model that describes the evolution of the tumor inside the duct and a mechanical model that describes the deformation of the duct wall. By varying these key parameters: the nutrient concentration, the stiffness of the duct wall, the viscosity of the tumor fluid, etc., we simulate how the environmental constrains would affect the tumor growth in the breast duct and when the tumor cells break through the duct to become invasive cancer.

Tumor growth model:

$$\frac{\partial c(x,y,z)}{\partial t} = D\nabla^2 c - \lambda c + \lambda_B (c - c_B), \quad \nabla \cdot \vec{v} = = b\vec{c} - \lambda_A = -\frac{\kappa}{\mu} \cdot \nabla^2 \vec{P}, \quad \frac{dR}{dt} = v, \quad (P)_0 = \gamma \cdot \kappa = \gamma \cdot \frac{1}{R} \qquad \text{(Eqs.1)}$$

Where, c is the nutrient concentration, c_B is the nutrient concentration from the blood vessel, D is the diffusion rate, λ is the nutrient consumption rate, λ_B is the nutrient metabolic rate from the blood vessel, λ_A is the apoptosis rate, v is the velocity of the tumor surface deformation, κ was the permeability, μ is the viscosity and P is the pressure inside tumor, R is the tumor radius, while γ is surface tension.

Membrane deformation model:

The finite difference analysis is used to calculate the displacement of each point along the duct membrane. The displacement of the membrane $u_m=(u_m(n), u_m(t))$ could be solved using strain-stress equation with static equilibrium:

$$\vec{T} = \mu \cdot \vec{n}.\nabla(\vec{v} \cdot \vec{t}) + \frac{1}{3}\mu\vec{t} \cdot \nabla \cdot \vec{v}, \quad \vec{N} = p - 2\mu \cdot \vec{n}.\nabla(\vec{v} \cdot \vec{n}) + \frac{2}{3}\mu\nabla\vec{v}, \quad \frac{E}{2(1+\mu)}\nabla^2 u + \frac{E}{2(1+\mu)(1-2\mu)}\nabla(\nabla \cdot u) = B, \quad , \qquad \text{(Eqs.2)}$$

Where B is the body force, the tangential part is T while the normal part is N, E is the Young's modulus, while μ is the Poisson ratio.

Results

Nutrient concentration drops as cells diffuse towards the center of the duct as shown in color, leaving those in the center to become hypoxic and eventually to develop a necrotic region for high grade DCIS. Figs.1 and 2 show how the wall of the duct deforms and the tumor advances along the duct over time. The magnitude of the axial deformation is much greater than the radial deformation as cells move preferentially along the duct with least resistance. Pure DCIS is more likely to show linear enhanced pattern on DCE-MRI (Fig. 1(b)).

It is found that the direction of tumor growth within the duct and the degree of duct deformation depends on the mechanical properties of the duct wall. As shown in Fig.1, higher Young's modulus E (higher rigidity) of the duct allows the tumor to expand through the host resulting in elongated tumor pattern. While lower Young's modulus (lower rigidity) of the duct wall causes greater deformation of the duct wall. It is also found that the pressure is the highest in areas where the duct wall deforms the most. It would become easier for the cells to push against the membrane (and expand radially) than to spread along the duct. Eventually the cells break through the duct wall and become invasive cancer. As shown in Fig 2 this growth pattern would exhibit the typical linear enhancement of DCIS with invasive nodules, where cancer cells break the duct membrane and become invasive ductal carcinoma (IDC).

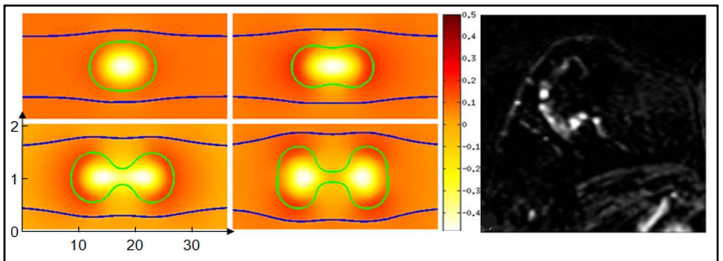

Fig. 1 (a) The deformation of the tumor and duct with higher Young's modulus. The tumor extends along the duct without invading. (b) Typical appearance of DCIS shown on MRI, which is linear enhancement

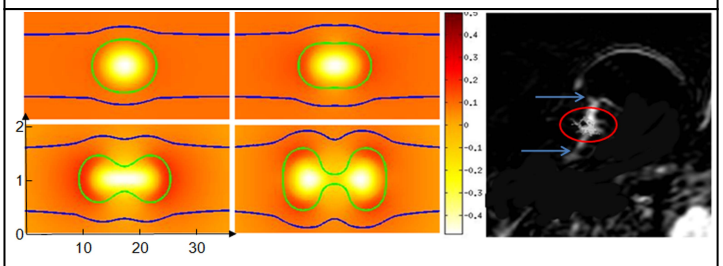

Fig. 2(a) The deformation of the tumor and duct with lower Young's modulus. This would eventually result the break-up of the duct wall, and cancer cell would invade. (b) Corresponding tumor appearance shown on MRI, it is a linear enhancement DCIS with invasive duct carcinoma in the center.

Discussion

The published models included very complicated realistic effects, such as nutrient and extracellular fluid transport limitations and variations in material properties, growth of angiogenesis etc. However, few of them considered the effect of environmental structure; as such these models are good for simulating in-vitro tumor growth, but cannot be correlated with in vivo phenotypes.

In this study, we simulated the breast tumor growth in the milk duct by assuming the duct is a deformable cylinder. By coupling tumor growth and membrane deformation models, we were able to describe the interactions between the expansive forces created by the tumor cell proliferation and the stresses in the basement membrane. This model may be used to simulate different stages of DCIS and identify the key mechanisms for DCIS to progress to invasive cancer. Understanding the biological growth pattern of DCIS may be used to further refine diagnostic criteria. In the future, it may be possible to incorporate the information obtained from simulation to computer-aided-diagnosis (CAD) system to indicate tumor types in addition to likelihood of malignancy.

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