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Evolution of cell motility in an individual-based model of tumour growth

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ABSTRACT

Tumour invasion is driven by proliferation and importantly migration into the surrounding tissue. Cancer cell motility is also critical in the formation of metastases and is therefore a fundamental issue in cancer research. In this paper we investigate the emergence of cancer cell motility in an evolving tumour population using an individual-based modelling approach. In this model of tumour growth each cell is equipped with a micro-environment response network that determines the behaviour or phenotype of the cell based on the local environment. The response network is modelled using a feed-forward neural network, which is subject to mutations when the cells divide. With this model we have investigated the impact of the micro-environment on the emergence of a motile invasive phenotype. The results show that when a motile phenotype emerges the dynamics of the model are radically changed and we observe faster growing tumours exhibiting diffuse morphologies. Further we observe that the emergence of a motile subclone can occur in a wide range of micro-environmental growth conditions. Iterated simulations showed that in identical growth conditions the evolutionary dynamics either converge to a proliferating or migratory phenotype, which suggests that the introduction of cell motility into the model changes the shape of fitness landscape on which the cancer cell population evolves and that it now contains several local maxima. This could have important implications for cancer treatments which focus on the gene level, as our results show that several distinct genotypes and critically distinct phenotypes can emerge and become dominant in the same micro-environment.

1. Introduction

Cancer cell motility is a crucial aspect of tumour invasion as it facilitates invasion of the healthy tissue in a more efficient way than only cell proliferation can. Cells with motile capabilities can access new nutrient sources and infiltrate the surrounding tissue and this process is instrumental in the formation of metastases, as the cancer cells need to actively move to and from the blood vessels which transport them to new sites in the body. The transition from cancer cells which are predominately proliferative to cells which are motile could therefore be a crucial step in the progression of the disease, and a greater understanding of this process could lead to improved treatment of the disease.

It is an established fact that evolution plays an important role in the development of a tumour (Nowell, 1976; Merlo et al., 2006; Smalley et al., 2005), and the emergence of motile cancer cells therefore has to be viewed from an evolutionary perspective. This view implies that cell motility will only evolve if it confers a selective advantage in the micro-environment in which the tumour grows. It is generally believed that cancer cells cannot move and proliferate simultaneously, a mechanism known as the "go-or-grow" hypothesis (Giese et al., 2003), and this suggests that the cancer cells are faced with a trade-off: in a harsh low nutrient micro-environment they might be more likely to survive if they migrate, but on the other hand they will be less likely to proliferate and consequently spread their genetic material. Migratory behaviour therefore has a dual effect on the fitness of a cell, it increases the probability that the cell will survive, but at the same time reduces the likelihood that the cell will divide. This suggests that the question of when and how a motile subclone emerges (under the assumption that the initiating subclone is non-motile) is far from trivial and is influenced by the complex interactions between the cancer cell population and the micro-environment of the tumour. However, there are many cell types (e.g. fibroblasts, lymphocytes) that have a predominantly motile phenotype and therefore this question is not applicable to them.

In this paper we present a mathematical model aimed at investigating the emergence of cancer cell motility in tumour invasion. The model is based on previous models of solid tumour growth (Gerlee and Anderson, 2007a, 2008, 2009), but is extended here in order to take cell movement into account. In particular we have focused on haptotaxis, cell movement driven up gradients in the extra-cellular matrix (ECM) density, which is known to be the

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dominant mode of movement in tumour invasion (Hood and Cheresh, 2002). In the model the cancer cells are treated as individual entities while extra-cellular factors such as oxygen and the ECM concentration are modelled as continuous quantities, making the model hybrid in nature. In order to capture the fact that tumours are heterogeneous and consist of a large number of subclones competing for space and nutrients, the behaviour of each cell in the model is determined from a response network which is subject to mutations when the cells divide. This means that the behaviour of the cells can change from one generation to the next, and implies that the model has the capability to capture the evolutionary dynamics of tumour growth.

1.1. Biological background

The model presented here will focus on the pre-vascular stages of tumour growth, and we will therefore discuss the structure of the tumour at this stage in detail. Although cancer cells have, due to mutations, escaped normal growth control (Hanahan and Weinberg, 2000), most avascular tumours exhibit a layered structure, which is due to the diffusion limited supply of nutrients (Sutherland, 1988). As the tumour grows, gradients of nutrients (e.g. oxygen, glucose) and waste products (e.g. lactate, hydrogen ions) develop, and when the tumour reaches a critical size, diffusion is insufficient to supply the inner parts of the tumour with nutrients. This leads to cell death or necrosis in the core of the tumour. Outside the necrotic core a rim of quiescent cells is found and further out a thin rim of proliferating cells. The mitotic activity therefore only takes place in a small fraction of the tumour, while the majority of the tumour consists of cells that are either quiescent or dead. It has been established that the limiting nutrient for avascular tumours is oxygen, and that the width of the proliferating rim is determined by the region where the oxygen concentration is in the viable range. Inside the proliferating rim the glucose concentration might still be high, but the usual aerobic metabolism of human cells requires oxygen to produce energy. There is one way for the cancer cells to circumvent this limitation, and that is to utilise the anaerobic metabolic pathway which only uses glucose and does not require any oxygen. In fact this seems to be a ubiquitous feature of solid tumour growth and will be included in the model (Gatenby and Gillies, 2004).

Another important aspect of tumour invasion is the capability of the cancer cells to degrade the surrounding ECM (Liotta et al., 1983; Stetler-Stevenson et al., 1993) and to migrate along gradients of ECM, a phenomenon known as haptotaxis (Lawrence and Steeg, 1996). The ECM is a complex mixture of macromolecules, containing collagens, fibronectin etc., which functions as a scaffold for the cells to grow on. Degradation of the ECM is accomplished by production of matrix-degrading-enzymes (MDEs) by the cancer cells. A large number of different MDEs have been identified, of which matrix metalloproteinases (MMPs) constitute a large family (Ennis and Matrisian, 1993). Most of these are soluble, but it has been shown that a considerable part of matrix degradation is accounted for by membrane anchored MMPs (MT-MMPs) and the plasminogen activator system (Hotary et al., 2000).

The ECM is known to play both a structural and signalling role influencing cell behaviour that includes migration, proliferation and survival (Hynes, 1992; Anderson et al., 2006). The mechanical/biological properties of the ECM are multiple and are dynamically modified by cell interactions, via degradation, alignment and production. The movement of cancer cells in the ECM is known to occur in two distinct modes: "path-generation" and "path-finding" (Friedl and Wolf, 2003). In the "path-generating mode" the cell degrades the ECM in the direction of movement and creates a path through the matrix, it then attaches to the matrix at the leading edge using integrins expressed at the cell surface and pulls itself forward. The other mode of movement occurs without degradation of the ECM and the cell instead pushes itself through existing gaps in the matrix and is therefore modulated by the ECM pore size (Zaman et al., 2005, 2006).

Cancer cell migration is tightly linked to metastases, an important step in tumour progression (Sahai, 2007). Metastases are formed from cells that break away from the main tumour mass, and form secondary tumours at new sites in the body. In order for a tumour to metastasise, one or several cancer cells need to go through a series of crucial steps: first the cell needs to migrate away from the primary tumour, and then enter the blood stream through a process known as intravasation. The cell then needs to survive long enough in the blood stream to get the opportunity to exit the vessel via extravasation. The final step in this chain of events is that the cell has to be able to migrate into and proliferate in the new tissue to form a tumour. If the metastases are formed in vital organs such as the liver or intestine this might be fatal. The acquisition of motile capabilities is the first step in this sequence of events and understanding how and why it occurs could lead to improved prevention and treatment of metastases.

1.2. Previous work

Mathematical modelling of tumour growth and invasion has a long history dating back to the work of Burton (1966), who was the first to propose that tumour growth is limited by the diffusion and consumption of nutrients. Subsequent work using a different modelling approach took into account the mechanical properties of the tissue and in particular considered the pressure inside the tumour (Greenspan, 1975). This model introduces a velocity field for the tumour cells which depends on the pressure in the tumour and assumes that the cells flow though the ECM according to Darcy's law, i.e. just like flow through a porous medium. This model has been further developed by introducing the effect of apoptosis (Byrne and Chaplain, 1996) or different cell types (Breward et al., 2002) and different cell responses (Chaplain et al., 2006). A more recent example of this modelling approach is the model by Cristini et al. (2003) in which they investigate the impact of the microenvironment and show that it plays a significant role in shaping the resulting tumour morphology. For a long time reaction–diffusion models were the dominant modelling approach (see for example Casciari et al., 1992b; Byrne and Chaplain, 1997; Anderson et al., 2000; Marchant et al., 2001; Swanson et al., 2003), but recently individual-based models of tumour growth have gained more attention (Anderson et al., 2007). A wide range of approaches have been used for single-cell modelling such as off-lattice models (Drasdo and Forgacs, 2000; Palsson and Othmer, 2000), cellular Potts models (Stott et al., 1999; Hogeweg, 2000), cellular automata (Deutsch and Dormann, 2005) and hybrid continuous–discrete models (Anderson et al., 1997; Anderson and Chaplain, 1998; Schofield et al., 2005; Anderson, 2005).

Mathematical modelling of the evolutionary dynamics of tumour growth has generally been constrained to models where the fitness of the mutant cells is predefined, and have mostly focused on the modelling of mutational pathways (Iwasa et al., 2006; Nowak et al., 2006; Komarova, 2006). These models have provided useful insight into the evolutionary dynamics of early tumour growth, for example investigating the role of chromosomal instability (Komarova et al., 2003) and the impact of tissue architecture in colon cancer (Michor et al., 2004).