Journal of Theoretical Biology 361 (2014) 41–60

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Mathematical modelling of cancer invasion: Implications of cell adhesion variability for tumour infiltrative growth patterns

Pia Domschke [a,b,*], Dumitru Trucu [b], Alf Gerisch [a], Mark A. J. Chaplain [b]

[a] Technische Universität Darmstadt, Fachbereich Mathematik, Dolivostr. 15, 64293 Darmstadt, Germany
[b] University of Dundee, Division of Mathematics, Dundee DD1 4HN, Scotland, UK

HIGHLIGHTS

- A model of cancer invasion is presented with a focus on the role of adhesion.
- We consider both cell–cell and cell–matrix adhesion.
- Changes in adhesion are investigated through time-dependent adhesion characteristics.
- The computational simulation results show a range of heterogeneous dynamics.
- Our results are qualitatively similar to observed tumour infiltrative growth patterns.

ARTICLE INFO

Article history:
Received 12 April 2014
Received in revised form
5 July 2014
Accepted 7 July 2014
Available online 24 July 2014

Keywords:
Solid tumour spread
Non-local model
Heterogeneity

ABSTRACT

Cancer invasion, recognised as one of the hallmarks of cancer, is a complex, multiscale phenomenon involving many inter-related genetic, biochemical, cellular and tissue processes at different spatial and temporal scales. Central to invasion is the ability of cancer cells to alter and degrade an extracellular matrix. Combined with abnormal excessive proliferation and migration which is enabled and enhanced by altered cell–cell and cell–matrix adhesion, the cancerous mass can invade the neighbouring tissue. Along with tumour-induced angiogenesis, invasion is a key component of metastatic spread, ultimately leading to the formation of secondary tumours in other parts of the host body.

In this paper we explore the spatio-temporal dynamics of a model of cancer invasion, where cell–cell and cell–matrix adhesion is accounted for through non-local interaction terms in a system of partial integro-differential equations. The change of adhesion properties during cancer growth and development is investigated here through time-dependent adhesion characteristics within the cell population as well as those between the cells and the components of the extracellular matrix. Our computational simulation results demonstrate a range of heterogeneous dynamics which are qualitatively similar to the invasive growth patterns observed in a number of different types of cancer, such as tumour infiltrative growth patterns (INF).

1. Introduction

The development and spread of cancer in the human body is a complex, multistage process, consisting of interconnected spatio-temporal multiscale phenomena, ranging from genes and molecules to cells and tissue. Invasion of the surrounding tissue by cancer cells plays a central role in solid tumour progression, and is a key stage in the metastatic spread of the disease. It is defined as one of the "hallmarks of cancer" by Hanahan and Weinberg (2000, 2011).

Cancer invasion itself is a complicated multiscale process, in which cell-scale dynamics both influence and are influenced by the tissue-scale evolution of the tumour, or cancerous mass, and the tumour microenvironment. By combining excessive proliferation with the secretion of a variety of matrix degrading enzymes, as well as altered adhesive properties and migratory behaviour, cancer cells have the ability to break through tissue compartments (Weinberg, 2006) and are able to invade locally the surrounding tissue. Coupled with tumour-induced angiogenesis, cancers possess a deadly ability to metastasise – spreading to secondary locations in the host body, giving rise to secondary tumours.

Besides enhanced proliferation, malignant tumour progression also involves the secretion of various matrix-degrading enzymes

* Corresponding author at: Technische Universität Darmstadt, Fachbereich Mathematik, Dolivostr. 15, 64293 Darmstadt, Germany.
E-mail addresses: domschke@mathematik.tu-darmstadt.de (P. Domschke), trucu@maths.dundee.ac.uk (D. Trucu), gerisch@mathematik.tu-darmstadt.de (A. Gerisch), chaplain@maths.dundee.ac.uk (M. A. J. Chaplain).

http://dx.doi.org/10.1016/j.jtbi.2014.07.010
0022-5193/

(MDEs) and a variable cell–cell and cell–matrix adhesion (Gao et al., 2005; Wolf et al., 2013). Several classes of proteolytic enzymes such as matrix metalloproteinases (MMPs) (Parsons et al., 1997) or the urokinase-type plasminogen activator (uPA) are produced and secreted by the cancer cells, and either completely degrade or locally change the composition of the extracellular matrix (ECM) (Andreasen et al., 1997, 2000; Pepper, 2001). The degradation of the matrix by these proteolytic enzymes creates space which can be exploited by highly migratory cancer cells, leading to further local expansion of the tumour (Newby, 2006). Whether distributed freely in the ECM or bound to the cancer cell membrane, once secreted, the different MMPs degrade at least one component of the ECM enabling further tumour progression (Visse and Nagase, 2003; Somerville et al., 2003; Sternlicht and Werb, 2001).

Recognised as playing a key role in all cell migratory dynamics, cell–cell and cell–matrix adhesion is particularly important during cancer invasion (Behrens et al., 1989; Byers et al., 1995; Larebeke et al., 1992; Le et al., 1998; Umbas et al., 1992; Zheng et al., 2005). The past few decades have witnessed intensive *in vivo* and in vitro research efforts focussed on exploring the impact of adhesion on the morphology and direction of migratory tumour cell patterns arising in cancer invasion (Friedl et al., 1995; Kolega, 1981; Pierce et al., 1978).

Among transmembrane proteins, *cadherins* have been identified as having a major contribution to cell adhesion (Weinberg, 2006). These are calcium-dependent adhesion molecules that interact with intra-cellular proteins, most notably *β-catenin*, to form adherence junctions between cells in human tissue (Juliano, 2002). The homeostasis of this important molecular process is essentially altered during cancer progression, where a reduction in cell–cell adhesion favours an increase in motility of highly migratory cancer cells within the invading tumour (Umbas et al., 1992). An important role in cell–cell adhesion is played by cell–cell signalling mechanisms based on the interactive dynamics between the calcium-sensing receptor distribution and Ca^{2+} ions from the extracellular matrix (Hofer et al., 2000; Hills et al., 2012; Ko et al., 2001), which is significantly changed during cancer invasion. The direct correlation between this calcium-based cell signalling mechanism and the regulation of E-*cadherin* and *β-catenin* was first discovered in colon carcinoma (Bhagavathula et al., 2007).

Complementing cell–cell adhesion, cell–matrix adhesion plays an equally important part in individual and collective cancer cell motility during the growth and development of solid tumours (Zamir and Geiger, 2001). This process is mediated by a family of cell-surface receptors known as integrins, whose extracellular domains bind to ECM ligands (Berrier and Yamada, 2007). As well as being in contact with various proteins in the ECM, integrins interact with the various actin cytoskeletal proteins whose intracellular dynamics enable the cells to acquire a direction to migration by establishing a leading edge and a trailing edge (Moissoglu and Schwartz, 2006). Furthermore, in addition to regulating the creation of new protrusions at the leading edge, actin molecules also contribute towards cell's contractile properties. Alongside other traction forces arising from the porosity, confinement, or viscoelasticity of the 3D ECM, cancer cells exploit their contractile abilities to enhance their migration (Mierke et al., 2010; Poincloux et al., 2011). Additionally, cancer cells usually facilitate favourable changes in extracellular matrix stiffness and exploit the ECM confinement to progress further into the surrounding tissue (Hung et al., 2013; Zaman et al., 2006; Pathak and Kumar, 2012).

The interplay between cell–cell and cell–matrix adhesion has been recognised to play an important role in determining patterns of invasive spread at the tissue level. The invasive growth pattern of a solid tumour can be examined and pathologically evaluated using the so-called infiltrative growth pattern (INF) classification. An invasive tumour can be classified histopathologically into three main categories – INFa, INFb and INFc – using the following definitions from the Japanese Gastric Cancer Association (2011):

- INFa – an invading tumour showing an expansive growth with a distinct border from the surrounding tissue/stroma.
- INFb – an invading tumour showing an intermediate pattern between INFa and INFc.
- INFc – an invading tumour showing an infiltrative growth with no distinct border from the surrounding tissue/stroma.

Fig. 1 shows all three types of tumour infiltrative patterns observed in oesophageal cancer and lung squamous cell carcinoma. As can be observed, there is progressively more heterogeneity of the patterns observed from INFa to INFb to INFc, with more mixing of cancer cells with stroma and a more poorly defined border between the cells and the normal tissue. Recently, the invasive infiltrative growth patterns of malignant solid tumours have been considered as potential prognostic factors for stomach, gallbladder, bladder and oesophageal cancer (Krüger et al., 2004; Luebke et al., 2005; Okada et al., 2009; Ito et al., 2012). The Japanese classification of oesophageal cancer notes that the differences between the three categories of the classification depend on the relative strength of invasion and proliferation in the peripheral area of cancer nests (groups of cancer cells) (Japan Esophageal Society, 2009). Cancer nests themselves often display heterogeneous invasive patterns (Japanese Gastric Cancer Association, 2011; Masuda et al., 2012; Ito et al., 2012; Ueda et al., 2007). Nonetheless, the classification is still rather basic and additional insight, such as that which could be provided by mathematical modelling, would be beneficial.

Other tumours may also show a range of invasive patterns. For example, Fig. 2a shows a phyllodes tumour (similar to a fibroadenoma and which accounts for 2.5% of all fibroepithelial lesions of the breast) and Fig. 2b an example ductal carcinoma in situ (DCIS). In each case in these examples the interface between the tumour and the adjacent normal tissue has a rounded non-invasive contour which correlates with clinical behaviour. Both of these lesion types have the potential to progress to invasion with characteristic alterations of their interfaces – more aggressive phyllodes' tumours with a tendency to local recurrence have a more infiltrative edge, while DCIS can transform into invasive tumours where one starts to see tongue-like projections extending into adjacent tissues.

Despite all the experimental advances, both *in vivo* and in vitro, that have increased our understanding of cancer growth, metastatic spread of cancer in the human body continues to be one of the main challenges for the medical and scientific community.

In addition to biomedical and clinical research into cancer growth spread, the past two decades have also observed an increase in the efforts of mathematical modelling and computational simulation to investigate and understand more fully not only local cancer growth and invasion of tissue (Anderson et al., 2009; Gatenby, 1995; Gatenby and Gawlinski, 1996; Perumpanani et al., 1996, 1999; Byrne and Chaplain, 1997; Byrne et al., 2001; Byrne and Preziosi, 2004; Chaplain and Lolas, 2005, 2006), but also other important aspects of cancer development such as angiogenesis (Orme and Chaplain, 1996; Chaplain et al., 2006) and metastasis (Anderson et al., 2000). Recently, these modelling efforts have been expanded to try to develop models which reflect the multiscale character of cancer invasion (Deisboeck et al., 2011; Macklin et al., 2009; Ramis-Conde et al., 2008; Trucu et al., 2013). The central role of cell–cell and cell–matrix adhesion in tumour cell invasion has received a special attention (Byrne and Chaplain, 1996; Andasari and Chaplain, 2012; Chaplain et al., 2011; Turner and Sherratt, 2002; Anderson, 2005; Ramis-Conde et al., 2008;