Modelling tumour invasion

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Abstract

In the framework of the vast literature about cancer modelling the question of tumour invasion mechanisms is more and more attracting the attention of mathematicians. It is well known that this problem presents an extreme complexity, because a variety of phenomena may concur to the spreading of malignancies within the body. Metastasis takes place through intra- and extravasation (i.e. crossing the epithelial tissue of vessels) of cancer cells, which in that way use lymph and blood as natural carriers. The interactions between cells and blood vessels has been investigated extensively (see e.g. [2]) as well as the mechanics of cell displacements over a substrate (see e.g.[1]). Cells increased motility has been recognized as an important factor of tumour invasiveness. It is known that most of the times tumours consists of several different cellular species , owing to mutations. Mutations towards more mobile and more aggressive phenotypes are among the phenomena included in a model of considerable generality developed primarily by A. Anderson [3,4,10], and based on the so-called hybrid approach: cells are disposed on a lattice and they perform various actions (one step displacements, replication, mutation, death, etc.) with probabilities chosen according to some simple rules, influenced by the local value of continuous fields (like nutrients concentrations, the gradient of the extracellular matrix concentration (ECM), etc.). Models of such complexity can reproduce interesting features. For instance simulations show that increasing the heterogeneity of ECM may lead to more irregular shapes (and the same happens reducing oxygen concentration). High irregularity of the tumour boundary is somehow associated to its potential invasiveness. The main limit of this class of models, besides the computational complexity, is the presence of a large number of parameters and of many arbitrary options (for instance type and number of possible mutations). In this lecture we want to review some much simpler (and consequently less ambitious) models, aimed at showing how invasion processes stimulated by the active role of cancer cells can be described on the basis of reaction-diffusion systems. During the last decade quite a few papers have been addressed to the class of the so called acid-mediated invasion processes. The key feature of acid-mediated invasion is the regression of the host tissue under the chemical aggression of an excess of H+ ions (lowering the local pH). Such increased acidity is the result of the so called

anaerobic pathway of glucose metabolism, adopted by tumour cells either because of hypoxic conditions, as a consequence of mutations selecting anaerobic phenotypes, which eventually prevail (for the joy of Darwin). Indeed this is the way in which cancer cell exploit their ability to survive to acidic environment (up to some extent: they will die too when pH becomes too low). Glucose metabolism is fundamental for the production of ATP (adenosine triphosphate) within cells (a process somehow measuring the cell viability). The anaerobic pathway is associated with a reduced efficiency of ATP production, accompanied at the same time by an increased glucose consumption and by a significant production of lactate. The latter substance migrates out of the cell and is responsible for liberating an excess concentration of H+ ions. The possible death of tumour cells induced by an exceedingly low ATP production rate has been investigated recently in [5,13,15]. The formulation of a reaction diffusion system describing acid-mediated invasion in [9] opened a research line in this direction. In [9] the authors had the goal of showing the possible occurrence of a necrotic gap interposed between the tumour and the host tissue (a situation confirmed by experimental evidence). They consider a population of cancer cells advancing over a population of normal cells which are killed by the acid produced by the tumour. The displacement mechanism of the advancing cells is diffusion. The diffusivity plays the role of a small parameter. According to this scheme the tumour progression is described by a nonlinear diffusion equation (diffusivity depends on the concentration of the residual normal tissue). The host tissue does not diffuse and reacts with the H+ ions, which in turn are produced by the tumour and diffuse. In one space dimension one can look for a travelling wave solution, which indeed exhibits a gap when the sensitivity of normal cells to the acid is beyond some threshold. In [9] waves profiles corresponding to the supposedly smallest velocity have been computed. A more systematic analysis of the same waves has been performed very recently in [8], using mainly a matched asymptotic technique. It has been shown that there are two classes of waves: slow waves, whose velocity tends to zero as some power of the cells diffusivity (rescaled by the ions diffusivity) , and fast waves which are insensitive to the smallness of diffusivity. The slow waves structure has been studied carefully. The critical power of diffusivity is $\frac{1}{2}$ (there are no solutions for larger exponents), to which there corresponds the smallest speed. The differential equation for the tumour cells reduces in that case to the well known Fisher equation. Slow waves fall into three categories, according to the level of sensitivity of the host tissue to acid: (a) waves with a fraction of normal tissue surviving the passage of the front, (b) waves with some overlapping of the two species, (c) waves exhibiting the gap at the front (the most interesting case). A simple formula has been provided to evaluate the width of the overlapping region (case b), and of the gap (case c). Fast waves do not seem to have a biological relevance, but are nevertheless among the possible solutions and they possess the property of being linearly stable. The effect of tumour related acidity on the surrounding tissue has been studied in the paper [12] with specific reference to multicellular spheroids, both for the vascular and avascular case. Here the aim is not to construct travelling wave solutions, but instead to deal with spheroids evolving according

to a quasi-steady scheme. In [12] the nutrients dynamics has been disregarded and vasculature was supposed to remain unaffected by acidity. In the paper [6] a more complicated model was investigated in which the production rate of H+ ions was directly related to glycolysis, and vasculature reduction by the acid action was introduced. A much larger variety of situations arises and the model looks more realistic in many aspects (for instance the possibility of unlimited growth, contemplated in [12] was ruled out). Another paper adopting a scheme of plane travelling wave is [11], where the driving mechanism for tumour propagation is not diffusion but haptotaxis. Indeed in their model the authors consider the lysis of ECM by an enzyme (produced by the tumour). The ECM concentration gradient so created stimulate the migration of cancer cells. The corresponding system of travelling waves is qualitatively very different from the one examined in [9] and [8], since it possesses a degeneracy which substantially complicates the analysis. Finally, we will make a short reference to a generalization of the previous model, in which both diffusion and haptotaxis are considered, and a new phenomenon is analyzed, namely the increased cell motility stimulated by the presence of HTP (heat shock proteins), for which there exist experimental evidence. The corresponding reference is [14].

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