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SELF-SUSTAINING SUB-POPULATIONS OF PROGENITOR CELLS

RONALD BEGG, MOHAMMAD KOHANDEL AND SIV SIVALOGANATHAN

Abstract. It has been established in several types of cancers, that the growth and maintenance of many cancers is due to a (typically small) sub-population of cells with stem-like properties: cells which are capable of indefinite self-renewal and of giving rise to all the different types of cells present in the cancer. The origins of these stem-like cancer cells are not entirely clear, and it has not been established if they originate from healthy stem-cells, healthy self-sustaining sub-populations of progenitor cells or even from mature, fully differentiated cells by way of dedifferentiation. In this paper we investigate some mathematical problems which arise when one considers the possibility of cancer stem-cells arising from healthy progenitor cells (normally possessing limited division potential) which have been perturbed in some way, such as through mutation. For example, glial progenitors have been previously proposed as a possible source of gliomas. We model the progression from stem cell to mature cell where at each cell division we include a probability of a cell either advancing or regressing in maturity. Whereas in normal, healthy cell populations, cells will be more likely to advance in maturity, we suggest that the tendency to advance or regress in maturity may be altered by changes in the cell population such as mutation, and that this may cause the subpopulation of progenitor cells to become self-sustaining, leading to uncontrolled growth of this subpopulation. The conditions, according to our model, under which a population of progenitor cells is self-sustaining are then discussed.

Key words. cancer, stem cell hypothesis, progenitor cell, differential equation

1. Introduction

The standard model for the generation of mature tissue involves the progression from undifferentiated stem cells, through several intermediate stages where the degree of differentiation progressively increases (progenitor cells), to fully differentiated mature cells. Stem cells are distinguished by two key features: the ability to generate multiple mature cell types, and the capability to self-renew indefinitely. Progenitor cells, however, have a limited capacity for self-renewal and may be able to produce only one or two mature cell types.

The cancer stem cell hypothesis suggests that a small subset of cancer cells possess stem-like properties, having the capacity to self-renew, and the capacity to produce all other cell-types present in the cancer. These cells are thought to be responsible for the growth and maintenance of the cancer cell population. Hence, treatment which targets these cells would therefore be strongly desirable [5].

The fact that cancer can arise through dedifferentiation has been proposed by various researchers over the last few decades. As far back as 1993, Sell [22] highlighted the two major non-exclusive hypotheses of the cellular origins of cancer malignancies, namely that they arise: (1) from stem cells as a result of maturation arrest or (2) from dedifferentiation of mature cells that retain the ability to proliferate.

The latter hypothesis was raised again more recently by Oku et al [18] where they were able to identify molecular mechanisms for dedifferentiation in colorectal cancer using gene expression analysis. In a 2009 Nature paper, Kawamura et al [15] also

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linked the p53 tumour suppressor pathway to somatic cell reprogramming. Daley [7] discusses the reprogramming of somatic tissues to a pluripotent state by ectopic expression of a cocktail of transcription factors and points out that the factors that drive reprogramming are oncogenes or have been linked to cellular transformation which strongly suggests that tumorigenesis and somatic cell reprogramming might share the common mechanism of dedifferentiation. Most recently, Kumar et al [16] suggest that the cancer stem cell phenotype is dynamic and may be acquired through dedifferentiation.

Thus, in recent years, there has been increasing experimental evidence lending credence to the belief that dedifferentiation does play a crucial role in the development of cancer malignancies. In 2004, Katoh et al [14] studied dedifferentiation in the context of the social amoeba Dictyostelium discoideum. Their work established dedifferentiation as a genetically determined process, and also suggests the existence of a developmental checkpoint that ensures a return path to the undifferentiated state.

In light of this mounting body of evidence, we examine, in this paper, the possibility that some tumours may be driven by this mechanism, arising through dedifferentiation from progenitor cells whose normal function has been perturbed (most likely via mutation). The possibility of this occurring is discussed in a biological context, in [19] and [3]. Normally, the proliferative potential of progenitor cells varies a little, but is finite [25]. The possibility of tumour growth being driven by progenitor cells arises if the normal controls on the progenitor sub-population are altered or removed. The way in which stem-like and progenitor-like cancer cells may differ is discussed in [3], referring to the fact that cells in gliomas are similar to glial progenitors in many ways.

The mechanisms controlling the proliferative potential of progenitor cells are not fully understood, although it is known that certain changes in the microenvironment of the progenitor cells can change their proliferative behaviour [4, 9, 11, 17, 20, 21].

Examples of previous mathematical work on the progression from stem-cell to mature cell in the case of colon cancer may be found in [2, 8, 13, 26]. A related model which separates cancer cells into stem and differentiated cell compartments and includes parameters representing genetic instability has been proposed and studied by [23]. In [27], Turner et al study both a stochastic model and a deterministic model of stem-cell differentiation in the context of brain-cancer growth and treatment.

Our model differs from these by including a mechanism which counts the number of cell divisions which a progenitor cell has undergone. Our model does not include parameters related to genetic instability or mutation rate, although it is assumed that mutations in the cell population may change the parameters of the model.

A model of the telomere-length distribution in a cell population is studied in [1], which addresses the question of when a population will be self-sustaining. This may be considered to be the continuous analogue of the case presented in this paper.

In this paper we specifically wish to investigate conditions under which the progenitor cell subpopulation might become self-sustaining, without input from the stem cell compartment. This situation is of interest because for progenitor cells to be the source of a cancer (as hypothesised in [3] in the case of gliomas), it is necessary that the progenitor cell subpopulation be able to sustain itself without external input from other cell compartments. One may think of a subpopulation of progenitor cells that has become self-sustaining as having become stem-like, possibly becoming the stem-like subpopulation of a cancer.