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Replicator dynamics of cancer stem cell: Selection in the presence of differentiation and plasticity

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ABSTRACT

The cancer stem cell hypothesis has evolved into one of the most important paradigms in cancer research. According to cancer stem cell hypothesis, somatic mutations in a subpopulation of cells can transform them into cancer stem cells with the unique potential of tumour initiation. Stem cells have the potential to produce lineages of non-stem cell populations (differentiated cells) via a ubiquitous hierarchal division scheme. Differentiation of a stem cell into (partially) differentiated cells can happen either symmetrically or asymmetrically. The selection dynamics of a mutant cancer stem cell should be investigated in the light of a stem cell proliferation hierarchy and presence of a non-stem cell population. By constructing a three-compartment Moran-type model composed of normal stem cells, mutant (cancer) stem cells and differentiated cells, we derive the replicator dynamics of stem cell frequencies where asymmetric differentiation and differentiated cell death rates are included in the model. We determine how these new factors change the conditions for a successful mutant invasion and discuss the variation on the steady state fraction of the population as different model parameters are changed. By including the phenotypic plasticity/dedifferentiation, in which a progenitor/differentiated cell can transform back into a cancer stem cell, we show that the effective fitness of mutant stem cells is not only determined by their proliferation and death rates but also according to their dedifferentiation potential. By numerically solving the model we derive the phase diagram of the advantageous and disadvantageous phases of cancer stem cells in the space of proliferation and dedifferentiation potentials. The result shows that at high enough dedifferentiation rates even a previously disadvantageous mutant can take over the population of normal stem cells. This observation has implications in different areas of cancer research including experimental observations that imply metastatic cancer stem cell types might have lower proliferation potential than other stem cell phenotypes while showing much more phenotypic plasticity and can undergo clonal expansion.

1. Introduction

According to clonal evolution theory, most tumours arise from single cells through multiple genetic alterations accumulated over time. However, the cancer stem cell hypothesis suggests that cancer cells with similar genetic background originate from a transformed cell which can initiate the rest of tumour population [1–4]. This subpopulation of tumour initiating cells, known as cancer stem cells, are hypothesized to be a result of somatic mutations of a normal adult stem cell giving it a proliferative advantage and as a result generating clonal outgrowth in the tissue which leads to the formation of a neoplasm [5–7]. Combination of these mutation/proliferation mechanisms and microenvironmental factors leads to different stages of cancer progression [8,9], which results in genetically and phenotypically heterogeneous tumours [4,10].

Stem cells can divide both symmetrically into two daughter stem cells (self-renewal) or two daughter progenitor cells (full differentiation), or asymmetrically into a daughter stem cell and a progenitor cell (partial differentiation). Progenitor cells then divide hierarchically into a population of fully differentiated functional tissue cells which lack proliferative potential [11]. This polarity in cancer stem cell division is observed in different cancer types. For breast carcinomas, it has been shown that activating the ErbB2 oncogene increases the self-renewal potential of cancer stem cells significantly [12]. Similarly, p53 inactivation leads to not only almost immortal stem cells but also a higher divisional polarity [12]. p53 is also reported to impose an asymmetric proliferation potential on other non-stem cell linages [13]; see also [14].

In addition to the tumour initiating potential of cancer stem cells, another distinctive feature of cancer cells is their high phenotypic

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plasticity. One aspect of such plasticity is the dedifferentiation potential possessed by stem cell progenitors. During dedifferentiation progenitors (or differentiated cells) can transform back spontaneously into a stem cell thus lending further credence to the vivid concept of cancer stem cells as tumour initiating cell [15]. Recent in-vitro experiments have demonstrated the dedifferentiation potential of different cancer type cell lines. For breast cancer, purified populations of non-stem cells, $CD44^{low}/CD24^{hi}$ (basal and luminal cell lines), created a population of $CD44^{hi}/CD24^{low}$, which is a marker for stemness [16]. It has been also shown that a population where the majority are non-stem cells, $CD44^{low}/CD24^{hi}$, gives rise to a higher mammosphere formation rate which is a measure of stemness [17]. The role of dedifferentiation in intestinal tumorigenesis is investigated in [18], where it is shown that elevating the levels of the transcription factor $NF-\kappa B$, which modulate Wnt signaling, induces dedifferentiation in the (non-stem cell) intestinal epithelial cell population and thus can lead to tumourigenesis. In the context of leukaemia, the leukemia-initiating cell marker $CD34^{+}CD38^{-}$ has been observed in the fraction of non-leukemia initiating cells [1,19].

It has been suggested that as cancer progresses towards more aggressive metastatic phenotypes, the dedifferentiation potential increases [15]. The dedifferentiation of non-stem cells may arise due to (stochastically) genetic or epigenetic mutations, or the epithelial-mesenchymal transition (EMT), a cellular differentiation process wherein epithelial cells adopt mesenchymal features [15]. It has been shown that EMT induced cells have a higher dedifferentiation potential while at the same time they display features resembling stem cell [20–22]. Thus, beside the mutation/clonal expansion model of cancer progression which leads to genomic heterogeneity in the tumour population, inclusion of hierarchal stem cell proliferation and the dedifferentiation potential of cells leads to more phenotypic heterogeneity inside a tumour. More importantly, cell plasticity shadows the concept of stem cells, in the sense that we cannot compare the two populations of normal and cancer stem cells competing via their corresponding proliferation strengths, but rather the population of non-stem cells has to be included in the picture of the selection process and Darwinian evolution of the tumour.

Mathematical models of selection processes so far have treated the selection mechanism among cancer stem cell populations and normal population assuming higher division rate for mutants due to activation and inactivations of oncogenes/tumour suppressor genes that regulate the growth factor signalling pathways inside the cell. These models were able to successfully describe the selection process occurring prior to each new clonal expansion (due to a new mutation). The dynamics of tumour suppressor gene inactivation in particular has been investigated in the literature in detail [23–25]; see [26] for a thorough review of evolutionary modeling in cancer. However, there has not been much work with regard to stem cell hierarchy proliferation potential and its effect on selection dynamics. Some recent works have focused on the asymmetric nature of stem cell division. Dingli, Traulsen and Michor [27] studied the time to fixation of mutant stem cell selection using a simplified birth-death model of two stem cell population which divides asymmetrically, ignoring the population progenitors and differentiated cells (perhaps for simplicity). A recent computational study by Sprouffske et al. [28], has investigated the effect of an asymmetric division scheme for stem cells by simulating stem cells with random fitness and have discussed Darwinian selection and the existence of disadvantageous subpopulations in the formation of neoplasms. Shahriyari and Komarova [29] have also addressed the evolutionary advantage/disadvantages of symmetric versus asymmetric differentiation by constructing a Moran-type process for one and two-hit mutation models and have analyzed the effect of differentiated cell compartment in the effectiveness of the mutations among stem cell compartment. More recently, Jilkine and Gutenkunst [30] considered a stochastic model for differentiation and dedifferentiation and investigated time to mutation acquisition in the presence of dedifferentiation mechanism for progenitors of stem cells. They also discussed how asymmetric versus symmetric differentiation can affect the efficiency of dedifferentiation process. The cancer stem cell hypothesis has also been applied in the context of drug resistance as an evolutionary process by Leder et al. [31].

The present work aims to provide a general framework to study the selection dynamics of cancer versus normal stem cells by including asymmetric differentiation, in addition to stem cell self-renewal. This introduces a more challenging mathematical model which now contains two competing stem cell populations and a third differentiated cell compartment, which now both stem cells populations are competing with. By introducing a Moran-type stochastic model for this three-compartment model, we derive replicator-type dynamics for the three populations of cancer stem cells, normal stem cells and differentiated cells as a function of time. We show that the condition for successful invasion by the cancer stem cells not only depends on their higher division rate or lower death rate, but also on differentiation rate or polarity of their asymmetric division. In constructing the birth-death model we assume three independent parameters for the death rates of mutant stem cells, normal stem cells and the differentiated cell population. An important feature of our model is that dedifferentiation events can be naturally added to the model. We discuss dedifferentiation (assumed only for cancer stem cells) in detail and show that the proliferation advantage is not only a function of relative fitness of two stem cells and their corresponding differentiation rates but also depends on the strength of plasticity and on the population of non-stem cells. We plot a phase diagram between advantageous and disadvantageous regimes in the space of fitness, plasticity and, differentiation probabilities. We show that assuming finite dedifferentiation rates (consistent with numerical estimate from experiments) a seemingly disadvantageous mutant can successfully initiate clonal expansion into a neoplasm.

The paper is organized as follows: In Section 2 we formulate a Moran-type model of stem cell differentiation and dedifferentiation and report the replicator dynamics in the presence of differentiation and dedifferentiation potentials. We also discuss the analytical result of the fixation time for this model in the absence of dedifferentiation. In Section 3 we discuss numerical solutions of the replicator dynamics and investigate the population dynamics and average time to fixation of a mutant stem cell as one varies division rates of the stem cell population, relative death rates of stem cells and differentiated cells and differentiation probabilities. Similarly, we look at time to fixation and whether a mutant is advantageous or disadvantageous by varying both relative division rates and dedifferentiation potential. In Section 4 we discuss the implications for cancer therapeutics and also possible future directions of investigation.

2. Replicator dynamics of differentiation and dedifferentiation

We consider a model of two stem cell populations and a population of partially/fully differentiated cells (Fig. 2). Normal stem cells divide with a rate r_1 and die with rate d_1 per generation. In each division event, a stem cell can divide (1) symmetrically into two daughter stem cells with probability ω_1, (2) asymmetrically into one daughter stem cell and one progenitor with probability u_1 and (3) fully differentiate into two daughter progenitor cells with probability v_1 (Fig. 3). The probabilities ω_1, u_1 and v_1 add up to unity. Similarly, mutant stem cell proliferation and death rates are denoted by r_2 and d_2. Correspondingly, self-renewal and differentiation probabilities are ω_2, u_2 and v_2. In the hierarchal stem cell proliferation scheme, the number of transient progenitors are finite thus by including all differentiated cell population into one compartment, we assume that the only possibility for this population to increase is the case in which a stem cell differentiates symmetrically or asymmetrically. Thus we assume