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A multi-phenotypic cancer model with cell plasticity

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HIGHLIGHTS

- We established a multi-phenotypic cancer model with cell plasticity.
- Prove the stability of the nonlinear model of multi-phenotypic proportions.
- Cell plasticity explains the transient increase of cancer stem cells proportion.
- Overshooting of CSCs proportion arises only in multi-phenotypic case.

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ABSTRACT

The conventional cancer stem cell (CSC) theory indicates a hierarchy of CSCs and non-stem cancer cells (NSCCs), that is, CSCs can differentiate into NSCCs but not vice versa. However, an alternative paradigm of CSC theory with reversible cell plasticity among cancer cells has received much attention very recently. Here we present a generalized multi-phenotypic cancer model by integrating cell plasticity with the conventional hierarchical structure of cancer cells. We prove that under very weak assumption, the nonlinear dynamics of multi-phenotypic proportions in our model has only one stable steady state and no stable limit cycle. This result theoretically explains the phenotypic equilibrium phenomena reported in various cancer cell lines. Furthermore, according to the transient analysis of our model, it is found that cancer cell plasticity plays an essential role in maintaining the phenotypic diversity in cancer especially during the transient dynamics. Two biological examples with experimental data show that the phenotypic conversions from NCSSs to CSCs greatly contribute to the transient growth of CSCs proportion shortly after the drastic reduction of it. In particular, an interesting overshooting phenomenon of CSCs proportion arises in three-phenotypic example. Our work may pave the way for modeling and analyzing the multi-phenotypic cell population dynamics with cell plasticity.

1. Introduction

The cancer stem cell (CSC) hypothesis (Reya et al., 2001; Jordan et al., 2006) states that tumors or hematological cancers arise from a small number of stem-like cancer cells with the abilities of self-renewal and differentiation into other non-stem cancer cells (NSCCs). That is, the conventional cancer stem cell theory suggests a cellular hierarchy where CSCs are at the apex (Dalerba et al., 2007). Based on this paradigm, cancer stem cell models were widely investigated in previous literature on theoretical biology (Colijn and Mackey, 2005; Johnston et al., 2007; Boman et al., 2007; Dingli et al., 2007; Johnston et al., 2010; Antal and Krapivsky, 2011; Sottoriva et al., 2011; Werner et al., 2011; Stiehl and Marciniak-Czochra, 2012; Molina-Peña and Álvarez, 2012).

However, recent studies have highlighted the complexities and challenges in the evolving concept of CSC (Nguyen et al., 2012; Visvader and Lindeman, 2012). In particular, it was reported that reversible phenotypic changes can occur between stem-like cancer cells and more differentiated cancer cells. Meyer et al. showed that interconversion occurred both *in vivo* and *in vitro* between non-invasive, epithelial-like $CD44^+CD24^+$ cells and invasive, mesenchymal $CD44^+CD24^-$ cells in breast cancer (Meyer et al., 2009). Chaffer et al. (2011) showed both *in vivo* and *in vitro* that transformed (oncogenic) $CD44^{lo}$-HMECs (human mammary epithelial cells) could spontaneously convert to $CD44^{hi}$-CSCs. The results by Quintana et al. (2010) indicated that phenotypically diverse cancer cells in both primary and metastatic melanomas can undergo reversible phenotypic conversions *in vivo*. Scaffidi et al. showed that stem-like cancer cells can be generated *in vitro* from transformed (oncogenic) fibroblasts during neoplastic transformation (Scaffidi and Misteli, 2011). The conversion from NSCCs to CSCs was also *in situ* visualized

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by Yang et al. (2012) in SW620 colon cancer cell line. Besides, the phenotypic transitions between different NSCCs in breast cancer were reported both *in vivo* and *in vitro* (Gupta et al., 2011). These various types of phenotypic conversions among cancer cells, also known as *cancer cell plasticity* mechanisms (French and Clarkson, 2012), provide new thinking about the CSC hypothesis and related therapeutic strategy (Pisco et al., 2013).

Special attention has recently been paid to the mathematical models concerning cancer cell plasticity. Gupta et al. (2011) introduced a simple Markov chain model of stochastic transitions among stem-like, basal and luminal cells in breast cancer cell lines. Zapperi and La Porta (2012) compared mathematical models for cancer cell proliferation that take phenotypic switching and imperfect biomarker into account. A series works by dos Santos and da Silva (2013a,b) developed a model with the effects of stochastic noise and cell plasticity for explaining the variable frequencies of CSCs in tumors. Zhou et al. (2013) compared the transient dynamics of the bidirectional and unidirectional models of CSCs and NSCCs. Wang et al. (2014) showed that tumor heterogeneity may exist in the model with both CSC hierarchy and cell plasticity. Leder et al.'s (2014) model described the reversible phenotypic interconversions between the stem-like resistant cells (SLRCs) and the differentiated sensitive cells (DSCs) in glioblastomas, which revealed optimized radiation dosing schedules. These works demonstrated that cell plasticity provides new insight into cancer cell population dynamics.

To further explore how cell plasticity challenges the hierarchical cancer stem cell scenario, and in particular how cell plasticity influences tumor heterogeneity, one should incorporate cell plasticity into the development of cancer which is full of biological complexities. One particular and crucial complexity arises from highly diverse phenotypes in the population of cancer cells. The aforementioned mathematical models were mainly focused on the relation between CSCs and NSCCs (Zapperi and La Porta, 2012; dos Santos and da Silva, 2013a,b; Zhou et al., 2013; Wang et al., 2014; Leder et al., 2014), that is, their models simply classified the cancer cells into two "opposite" phenotypes. This simplification is effective for studying the reversible conversions between NSCCs and CSCs, but covers up various phenotype switchings between different cancer cells that are worthy of studying. As an exceptional case, Gupta et al.'s (2011) model consists of three phenotypes (stem-like, basal and luminal cells), but rigorous mathematical analysis for general multi-phenotypic models with cell plasticity is still lacking.

In this study, we try to provide a multi-phenotypic framework for integrating cell plasticity with conventional growth model of cancer cells. A generalized model comprising $1+m$ cellular phenotypes (one CSC phenotype and m different NSCC phenotypes) is put forward. Besides cell-state conversions from NSCCs to CSCs and phenotype switchings between different NSCC phenotypes, the cellular processes in classical cancer stem cell models (*i.e.*, asymmetric cell division, symmetric cell division and cell death) are also included in our model. When the cell population size is not large enough and subject to stochastic fluctuations, our model is formulated by a continuous-time high-dimensional Markov process. In the limit of large population size, the model can be governed by a system of linear ordinary differential equations (ODEs). Moreover, to investigate the dynamics of phenotypic proportions, the population model is converted into a nonlinear frequency one. It is shown that under very weak assumption, the nonlinear frequency model has only one stable steady state and no stable limit cycle. Not only does this result theoretically explain the *phenotypic equilibrium* phenomena reported in various cancer cell lines (Chaffer et al., 2011; Yang et al., 2012; Gupta et al., 2011; Iliopoulos et al., 2011), but it is also predicted that the phenotypic equilibrium should be universal in the population of multi-phenotypic cancer cells. Furthermore, it is also found that cancer cell plasticity greatly influences the transient proportions of cell phenotypes. In particular, two concrete examples with experimental data are presented, showing that the cell-state conversions play an essential role in the transient growth of CSCs proportion shortly after the drastic reduction of it. In particular, an interesting *overshooting* phenomenon of CSCs proportion arises in the S–B–L model with cell plasticity. Note that two-phenotypic models never perform overshooting (Zhou et al., 2013; Jia et al.), overshooting can be a result of interplay between cell plasticity and diversity of phenotype. Moreover, it has been investigated in ecology and population genetics that phenotypic variability can serve as an advantageous strategy for biological populations in fluctuating environments (Wolf et al., 2005; Kussell and Leibler, 2005; Lu et al., 2007; Acar et al., 2008; Kaneko, 2012), our findings thus enrich this idea that cell plasticity as a surviving strategy might be more essential in maintaining the phenotype diversity (heterogeneity) of cancer especially during transient dynamics.

The paper is organized as follows. The model framework is formulated in Section 2. In Section 3, we investigate the frequency model and phenotypic equilibrium. The roles of cell-state conversions in transient dynamics are discussed in Section 4. Conclusions are presented in Section 5.

2. Model description

2.1. Assumptions

This section describes the assumptions of the model investigated in this study. Consider a population of cancer cells comprising $1+m$ phenotypes: CSC represents cancer stem cell, and NSCC_1, $\mathrm{NSCC}_2, \ldots, \mathrm{NSCC}_m$ represent m different phenotypes of non-stem cancer cells. In this model, cell plasticity is integrated with the growth model of cancer cells. According to conventional cancer stem cell scenario, not only can CSC divide asymmetrically into two unequal daughter cells (one CSC and one NSCC) (Reya et al., 2001), but it can also divide symmetrically into two daughter CSCs (Todaro et al., 2010).[1] So for CSC we assume that

- *Symmetric division*: $\mathrm{CSC} \xrightarrow{\alpha_{00}} \mathrm{CSC}+\mathrm{CSC}$.
- *Asymmetric division*: $\mathrm{CSC} \xrightarrow{\alpha_{0j}} \mathrm{CSC}+\mathrm{NSCC}_j$ $(1 \le j \le m)$.
- *Cell death*: $\mathrm{CSC} \xrightarrow{\alpha_0} \varnothing$.

For NSCCs, besides the symmetric division, two types of cell plasticity mechanisms that have been reported in previous biological literature are included in our model, *i.e.*, the cell-state conversions from NSCCs to CSCs (termed as *de-differentiation*) (Yang et al., 2012) and phenotype switchings between different NCSSs (Gupta et al., 2011). In this way, for NSCC_i $(1 \le i \le m)$ we assume that

- *Symmetric division*: $\mathrm{NSCC}_i \xrightarrow{\alpha_{ii}} \mathrm{NSCC}_i+\mathrm{NSCC}_i$.
- *De-differentiation*: $\mathrm{NSCC}_i \xrightarrow{\alpha_{i0}} \mathrm{CSC}$.
- *Phenotype switching*: $\mathrm{NSCC}_i \xrightarrow{\alpha_{ij}} \mathrm{NSCC}_j$ $(i \ne j)$.
- *Cell death*: $\mathrm{NSCC}_i \xrightarrow{\alpha_i} \varnothing$.

We list the elements of the model in Table 1 (see Fig. 1 for the example of three phenotypes). If we denote $X_t^0, X_t^1, \ldots, X_t^m$ as the

[1] It should be noted that, another type of symmetric division that CSC divides into two daughter NSCCs (termed as symmetric differentiation, Morrison and Kimble, 2006) is not accounted for in our model, however it is shown in Appendix F that the main results achieved in this study are still valid for the model including symmetric differentiation, implying the kinetic equivalence between the two models.

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