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MATHEMATICAL MODELS OF STEM CELL BEHAVIOUR (M KOHANDEL AND M PRZEDBORSKI, SECTION EDITORS)

Cancer Stem Cell Division: Mathematical Models and Insights

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Abstract

Purpose of Review Tumors consist of heterogeneous cell types, which present challenges to effective therapeutics. This review intends to explore existing mathematical models to better understand the influence of these different types of cells on tumor growth and survival.

Recent Findings Cancer stem cells are often the instigator of tumor development and drug resistance. The replenishment of the stem cells by other stem cells and progenitor cells impacts the efficacy of treatments. Multiple treatments are required to attack the multiple tumor cell types and induce remission. Mathematical models can be used to explore the behavior of these heterogeneous tumor cells, as well as predict the long-term efficacy of different therapies.

Summary Cell division plays an integral role in the development of tumors. While mathematical models are generally robust, they must be updated frequently to accommodate the brisk pace of biological advances. Usable data to inform the models is scarce calling for better collaboration between these sciences to help advance the field of cancer therapeutics.

Keywords Mathematical oncology · Cell division · Dedifferentiation · Cancer stem cells · Mathematical models

Introduction

After hypothesizing the existence of cancer stem cells (CSCs) in solid tumors in 2001, biomedical researchers quickly established the presence of these self-renewing cells [1–3]. Since then, the cancer stem cell hypothesis has been supported in multiple cancer types [4–9] and further refined to explain the role of CSCs in tumor growth and characteristics that could lead to better treatment options (reviewed in [10]). The last decade has been largely spent determining specific biomarkers for CSC targeting [11, 12], finally leading to testing therapeutics in the past 4 years [13–16].

Rhodes and Hillen [17] argue that mathematical models not only allow us to confirm experimental results but also provide possible explanations to why the system is behaving in a certain way. Despite groundbreaking biological discoveries, mathematical models of cancer have not focused on including CSCs. For instance, relevant searches in both PubMed and Google Scholar from 2006 to 2021 indicate approximately 2% of cancer models mention cancer stem cells (33/1707 in PubMed and 2900/116,000 in Google Scholar as of 10 March 2021), when compared to mathematical models of cancer in general (using the title search terms "cancer stem cell" AND "mathematical model" vs "cancer" AND "mathematical model"). And yet, CSCs have been linked to poorer clinical prognosis and cancer relapse (reviewed in [18]), making them a key component of tumor treatment. Beginning in 2006, Ganguly and Puri made the first attempts at incorporating this new biology [19, 20] followed by others [21–23]. In the past decade, as biologists focused on finding appropriate CSC biomarkers, mathematical models began to explore the role of CSCs in tumor biology, with a focus on growth kinetics

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[24–27, 28•, 29–31], cellular plasticity [21, 32–35], the tumor microenvironment [36–40, 41•, 42], and therapies [43, 44•, 45, 46•, 47, 48•, 49, 50]. From approximately 2017 onward, these models have begun to increase in complexity to better mirror biological mechanisms.

In this review, we consider the current state of mathematical models of cancer which incorporate CSCs and determine the gaps which must be addressed in future studies. As models that focus on populations that change in time, differential equations allow us to consider long-term behavior and act as a way to predict what will happen under certain conditions, thus allowing for less expensive and more timely answers than with experiments. As with any model, a mathematical model will not necessarily represent a biological process in its entirety. Particular aspects, with necessary assumptions, are explored in different models which can be combined to get a fuller description of the biological process. Here, we focus on the models that are relevant to the cancer stem cell division and dedifferentiation which describe a critical process that likely leads to tumor growth and recurrence. First, we explore the division of cells and then focus on the process of dedifferentiation. Next, we look at how the impact of dedifferentiation on tumor growth can be understood in the steady state of the models. Finally, we consider how the models can inform the effectiveness of combining therapies.

Cell Division

Cells in a human body can be classified into three groups: stem cells, progenitor cells, and differentiated cells. Stem cells are capable of differentiating into all other cell types and are known for their longevity. Stem cells can divide symmetrically into two stem cells or two progenitor cells, or asymmetrically, into one stem cell and one progenitor cell. Progenitor cells proliferate into more specific cell lineages, eventually producing fully differentiated cells (see Fig. 1). Moreover differentiated cells may defifferentiate acting again like stem cells, as described below. Fully differentiated cells typically have a finite lifespan and make up the majority of cells within tissues.

With every division, there is a chance of mutation for both the stem and progenitor cells. Once a stem cell is mutated, it may then produce mutated stem or progenitor cells; possibly creating a malignant tumor. There are two potential explanations for the origin of a CSC: (i) mutations within existing stem cells and (ii) reprogramming of differentiated cancer cells into CSCs [51, 52].

The probabilities of dividing symmetrically into two cancer stem cells or asymmetrically into one cancer stem cell and one non-stem cancer cell are driven by gene expression. Mukherjee et al. examine how cells regulate asymmetric division [53]. For example, cell-fate determinants such as

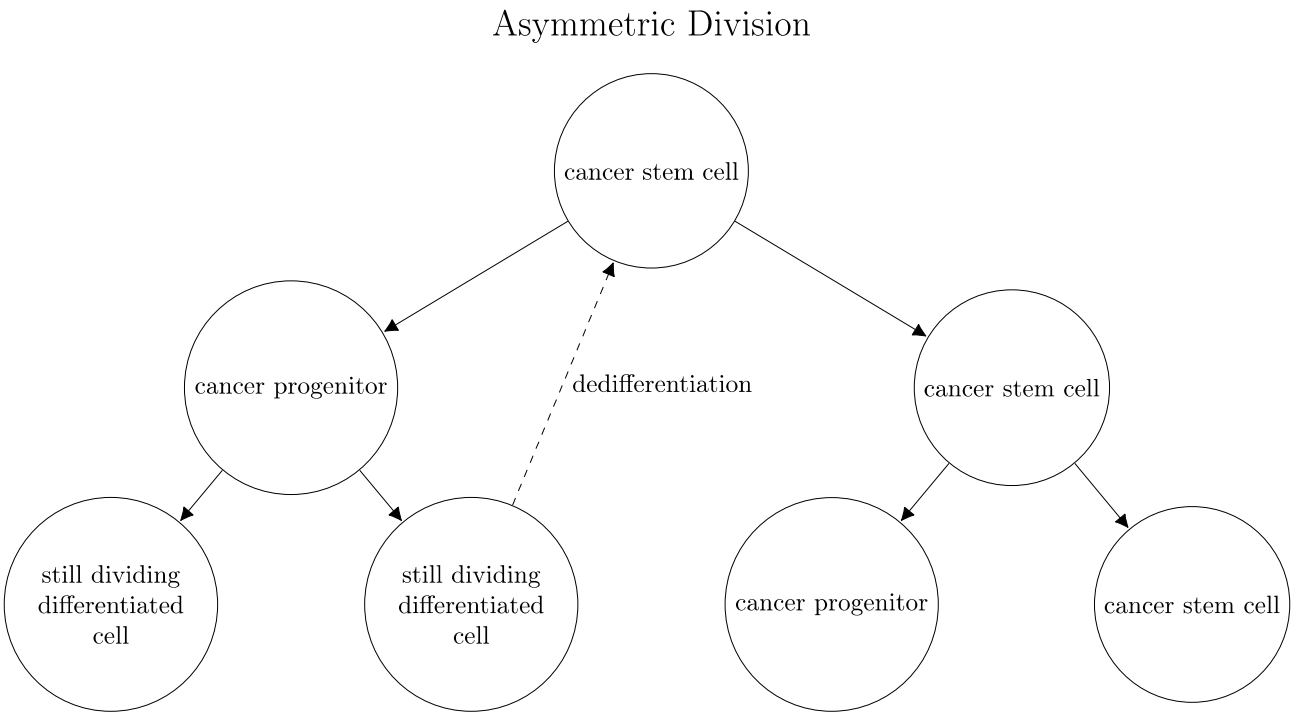

Fig. 1 Cancer stem cells asymmetrically divide into progenitor cells and replicants of themselves. The progenitor cells go on to form differentiated cells which then can dediferentiate

microRNAs regulate homeostasis, developmental cell-fate decisions, and oncogenesis. Bu et al. find that high levels of miRNA-34 cause differentiation of cancer stem cells in colon cancer, whereas low levels result in self-renewing stem cells [54]. For gliomas, the presence of high levels of EGF/bFGF regulates CSCs to divide symmetrically more than 80% of the time [55]. A novel view of CSCs posits that whether a CSC will produce zero, one, or two daughter cells that are also CSCs depends on the size of the stem-cell niche [56]. Stem cells reside in a special tissue microenvironment which allows both undifferentiated and self-renewable cells to be actively present. The progenitor cells made by CSCs help lessen the cell-division load of the stem cells, by driving differentiation into other cell types, thus allowing for CSCs to proliferate at low levels [57].

Historically, cells have been thought to have a hierarchical structure where a stem cell creates a progenitor cell which then undergoes a set number of divisions before it becomes a terminally differentiated cell. The differentiated cell is subsequently eliminated at the end of its lifespan. This age-structured progression has been well-modeled using systems of ordinary differential equations in the form of a compartmental model [19, 30, 58, 59, 60•]. The mathematical modeling for the cancer stem cell (CSC) division is commonly expressed as exponential growth. Benitez et al. design a two-population model for tumors, including CSCs and non-stem cancer cells to show that substrate stiffness (hardness of the environment) has an impact on stem cell division with soft substrates yielding symmetric division and hard surfaces leading to asymmetric division [61].

The dynamic process of symmetric division and differentiation and that these probabilities are not constant during oncogenesis has been addressed by [27, 49, 62, 63]. Of particular note, Bessonov et al. design a Markovian model for CSC population that aims to understand the "instructive signals" for cancer cell population stabilization and cell-to-cell communication that impacts probabilities of cell division [62]. Their model provides insight into the cellular dynamics of tumors.

Dedifferentiation

Hierarchical models, incorporating different numbers of subpopulations, are the traditional form of a model for cell division and are generally a system of ordinary differential equations. However, some argue [64] that this method is archaic and suggest that continuum models which allow for a spectrum of ages should be implemented using a partial differential equations model. There is mounting evidence that in specific scenarios, fully differentiatiated cells are able to move in the opposite direction and enter into a previous age class [65–68]. This dedifferentiation can cause cells to adopt a more stem-like phenotype, in essence partially reversing the typical pathway of increased specialization seen in normal cells. In investigating stem cell division, Bessenov et al. explore the probability of differentiation type and incorporate a time dependence because the underlying field biochemical signals may influence the division probabilities [62]. They find that in all biologically relevant cases, there is a nonzero probability that dedifferentiation occurs. This model could aid an experimentalist in determining what biochemical factors are supporting the different division types. Zhou et al. expands a hierarchical model to incorporate the impact of dedifferentiation in two ways: (i) the progenitor cell dedifferentiates into the previous age class, and (ii) the progenitor cell dedifferentiates into a stem cell. Dedifferentiation is shown to have the greatest impact when young populations have the largest self-renewal rates, and it becomes less common as the dominant self-renewal rate moves to later populations [69•]. Jilkine et al. found that the inclusion of even a small amount of dedifferentiation drastically speeds up carcinogenesis, especially in cases where fewer cells are initially in the cancer environment [70].

An alternative to the ordinary differential equations (ODE) hierarchical model is a partial differential equation (PDE) model as a function of time and age. Scott et al. present such a model that incorporates the clonogenicity of a cell based on the stage of differentiation and microenvironment influences [64]. Working with the general stem cell population, Wang et al. study the population density of stem cells incorporating a decrease in proliferation and self-renewal as a cell ages [71]. As a counterargument, Molina-Pena et al. argue that hierarchical models are still relevant because intermediate progenitor cells are able to form and sustain tumors [28•].

The dedifferentiation process, a form of a feedback loop, can be invoked when the stem cell population is near extinction. Proliferation is dependent on the size of a population and incorporated using feedback loops for various different types of cells. Feedback loops can promote or inhibit the proliferation of cells. The most common mathematical form of a feedback loop is the Hill function [72–74]. Renardy et al. regulate the progenitor population size through the replication and differentiation probabilities of stem and progenitor cells [60•]. Weiss et al. examine feedback on the self-renewal probability, division rate, and death rate [75•]. Rhodes and Hillen suggest that the Survivin protein, which is emitted when a cell dies, may instigate the dedifferentiation process in an effort to maintain a cancerous cell population [17].

Impacts of Dedifferentiation

When considering a cancer treatment, there are two measurements of success: the short-term efficacy of the treatment

and the long-term cancer development. Mathematically, we can determine the long-term behavior by studying the steady states of the system. Delay differential equations are implemented in the case of hematological cancers to account for the time, approximately 96–144 h [76], needed for cell maturation during the transition from the bone marrow to peripheral blood [77]. In this case, three steady states exist: the trivial steady state, complete dominance of the malignant population in both the bone marrow and the peripheral blood over their healthy counterparts, and coexistence. The complete dominance equilibrium suggests that once a malignant state is entered, the cancer will take over both the bone marrow and the blood [36]. Afenya et al. expand the system to give cancer stem cells their own compartment and allow for transition from healthy bone marrow into cancer stem cells [37]. The examination of the steady states shows that incorporating large time delays in the cancer stem cell conversion does not cause the malignant dominance in both the bone marrow and the peripheral blood to break. This suggests that cancer stem cells are driving malignancy and can remain dormant for a long period of time before causing a late recurrence.

For a solid tumor, Benitez et al. use a simple predator-prey model for a solid tumor and find there is a tipping point, dependent on the symmetric division probabilities, between the tumor being homogeneous differentiated cells and a balance between stem cells and differentiated cells [78•]. The balance between stem cells, cancer stem cells, and differentiated cells is delicate and is dependent on the death rate, differentiation probabilities, and dedifferentiation. Kaveh et al. find without dedifferentiation, the system will converge to a steady state where the CSCs dominate the stem cells or are non-existent, depending on the parameter choices [79]. However, if dedifferentiation is included at a high enough rate, then a steady state where stem cells and CSCs coexist is attained, even if initially no stem cells were included in the model. This study supports the stochastic nature of cancer development.

Konstorum et al. incorporate the stochasticity by extending the ecological concept of the Allee effect, where a population becomes extinct because there are not enough species to maintain the cancerous population [80]. If enough CSCs are destroyed, then the tumor will be eliminated even if it has not disappeared by the end of treatment. There is an Allee region based on the parameter relationship between CSC and a chemical activator. When self-promotion is included and dedifferentiation is not, the CSC population is able to replenish itself when it is near extinction. When cancer cells are at low numbers, randomness plays a crucial role. In particular, in an effort to renew themselves, non-stem cancer cells are more likely to develop stem-like characteristics in the low cell number limit. The influence of just one mutant cell is studied by Mahdipour-Shirayeh et al. and Wodarz, but they come to contradictory conclusions [81, 82]. Mahdipour-Shiraveh et al. determine that increased plasticity of the mutant cell increases the potential of invasion while Wodarz finds that increased plasticity decreases the invasion potential. Eastman et al. remedy this contradiction by demonstrating that the disagreement is a result of parameter definition and model assumptions [83]. While the two models ultimately give the same results when the parameters are defined in agreement, the Mahdipour-Shirayeh model allows for differentiated cells to proliferate, which introduces additional regimes that Wodarz is not able to simulate. Tonekaboni et al. find surprising results that suggest there is a careful balance between plasticity and death rates [34]. For example, increasing plasticity may decrease the overall survival probability in the case of certain death rates, meaning that carefully controlling death rates, in other words not killing too quickly, may be better to hamper cell plasticity.

Incorporating Cancer Therapies

Traditional therapies for cancer attack the tumor cells, but the cancer stem cells remain virtually unscathed due to differences in biomarkers and proliferation kinetics. CSCs are then able to resurrect the tumor, causing a cancer recurrence. Promising treatments [63, 84, 85] are those which specifically target the CSC in the hopes of reducing the risk of relapse. In the model presented by Sigal et al., immune cells, dendritic, and T-cells are specifically trained to either attack CSC or non-stem cancer cells within mice [48•]. Symmetric and asymmetric differentiation is permitted along with dedifferentiation. The necessity and timing of different treatments, including chemotherapy and targeted immunotherapy, are examined for efficacy. While chemotherapy is most effective in reducing the current tumor burden, immunotherapy is most successful in decreasing future tumor development. This ultimately increases the complexity of relevant mathematical models of cancer therapies, which must incorporate multiple cell types within the tumor, various aspects of the host immune system, and combination therapeutics.

Radiation, a localized treatment for cancer, is believed to increase the CSC population due to the sudden death of the tumor cells. One explanation is that the dying cells produce Survivin which instigates the CSC proliferation process. Rhodes et al. study a treatment within a mouse model which combines YM155 infusions, a Survivin suppressor, with radiation [17]. Molina-Pena studied radiation therapies which target either the CSC or the progenitor cells, using both experimental mouse models and cell culture studies from patient-derived tissues [28•]. In these isolated treatment scenarios, the tumor regrew. However, when radiation therapy simultaneously targets CSC and progenitor cells for a sufficient length of treatment then the tumor can be eliminated with no relapse.

Incorporating Experimental Data

Mathematical models of cancer describe relationships between important biological components such as cells, proteins, and cytokines. Along with a variable to represent each of the relevant components, a parameter value is also included. When determining the validity of a model, the parameters are fit to data from an experiment. Published data may include in vitro cell culture models of samples from cancer patient tissues, in vivo experimental mouse models, or even human clinical trials data. To control aspects impossible in human studies and allow mathematical modelers to systematically test different aspects of the model, data from mouse models are often used to fit parameter values. The parameters are chosen in such a way so that there is a minimal error between the model and the data. When able to find reasonable parameter values to create an agreement between the model and the experimental results, the model is declared a success. In order to avoid overfitting of data, the model must be validated, which requires additional experimental data [86•]. Yet, mouse models cannot fully represent cancer within humans. Ideally, validated models would be tested using in vivo human data, which emphasizes the need for access to full datasets in order to create robust, validated models. This becomes especially critical as human biomarkers and personalized therapeutics become the norm for cancer therapeutics.

Conclusions

Cancer stem cells play an integral role in the development of a tumor. The relationship between CSC and non-stem cancer cells is frequently described using a hierarchical model where the cells move from one age class to the next. The rate of division of the cells is impacted by the cell microenvironment. However, recently, it has been discovered that cells do not necessarily move in a unilateral manner but can repopulate a previous age class, most alarmingly the CSC. This observation counteracted some of the treatment advances which were formed on the basis that elimination of the CSC would be a huge advancement toward curing cancer.

The use of mathematical models provides insight to the importance of CSC in tumor development. Specifically, the examination of long-term behavior made apparent that CSCs are the source of recurrence. These revelations are essential in advancing the knowledge related to the dynamics of cancer growth. Mathematical models are also used to test treatment strategies causing more effective treatments, sometimes solely based on treatment schedule. The models are generally robust in relation to the specifics of the type of cancer, primarily requiring adaptation of parameter values. Since there are so many relevant biological aspects, finding data to combine with a math model is often a challenge. By creating better forms of collaboration between the experimentalists and the modelers, science could be advanced much more substantially.

Declarations

Conflict of Interest The authors declare no relevant conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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