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MATHEMATICAL MODELS OF STEM CELL BEHAVIOR (M KOHANDEL, SECTION EDITOR)

Mathematical Modeling of Normal and Cancer Stem Cells

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Abstract
Purpose of Review Stem cells are fundamental to tissue maintenance and repair; they also play a critical role in cancer development and in determining the outcomes of cancer treatment. This review explores recent mathematical and computational models that address stem cell dynamics in the context of normal tissue regulation and cancer.
Recent Findings Quantitative approaches have yielded significant insight into the processes of tissue regulation in normal hierarchically organized tissues. Modeling of cancer stem cells has also illuminated important mechanisms involved in cancer initiation and progression. In particular, mathematical studies have been instrumental to our current understanding of the role of stem cells in cancer therapy, resistance, and relapse.
Summary The use of quantitative methods to understand stem cell behavior has greatly expanded in recent years. In the future, mathematics will be an increasingly important and necessary tool necessary to fully unravel the complexity of stem cell dynamics.

Keywords Stem cells · Hierarchically organized tissues · Tissue homeostasis · Cancer stem cells · Cancer therapy · Mathematical modeling

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Introduction

Stem cells are unspecialized, undifferentiated cells that are characterized by two properties, their ability to maintain their own numbers through self-replication (called self-renewal), and by cell potency, the ability to differentiate into specialized cell types. Embryonic stem cells are pluripotent, being capable of giving rise to nearly all cell types in the body. Adult stem cells are multi-potent, having the ability to generate progeny of distinct cell types of a specific tissue [1]. Adult stem cells maintain and repair the tissues in which they are found and they are the focus of this review.

Many experimental techniques such as lineage tracing and genetic labeling have begun to identify the dynamics and exact mechanisms involved in determining the fate of stem cell populations [2]. However, it is becoming increasingly apparent that quantitative and modeling methods are also necessary to gain a thorough understanding of stem cell dynamics. In this article, we review recent findings from mathematical models of stem cell behavior. We focus on three aspects of stem cell dynamics: The role of stem cells in tissue maintenance and homeostasis in hierarchically organized tissues, the importance of cancer stem cells in carcinogenesis and tumor evolution, and stem cells in the context of cancer therapy.

Stem Cells and Hierarchically Organized Tissues

Normal tissues are organized hierarchically into cell lineages. At the start of these lineages are stem cells, characterized by their ability to maintain their own numbers through self-replication. Differentiated cells are the end products of tissue-specific sequences of cell divisions that originate in stem cells and progress through different stages of differentiation [3]. Cells at these intermediate stages of differentiation are called

progenitors or transit amplifying cells. The association of specific cell markers with different degrees of differentiation has led to the notion of cell compartments as a sequence of distinct differentiation steps, where each compartment represents a different stage of differentiation [4]. This characterization is central to multi-compartment models of cell lineages. These models are concerned with important features that affect tissue dynamics, such as the number of compartments, their division rates and self-renewal capabilities, and the number and location of forks in the differentiation pathways, which allow stem cells to generate all the differentiated cell types of a particular tissue [3, 5].

The importance of stem cell dynamics and cellular hierarchy is clearly illustrated by models of the colon crypt. In humans, the intestinal epithelium is renewed every few days. This renewal process is driven by the proliferation of stem cells, which reside near the bottom of the colon crypt, and their direct progeny, transit amplifying cells, which migrate outward and out of the crypt [6]. Mathematical modeling can complement lineage-tracing experiments to elucidate crypt dynamics. This approach is exemplified by a recent study that looked at mtDNA mutations [7]. Modeling of crypt dynamics is also useful in the quantification of the functional number of stem cells as well as their mutation rate [8]. It is also valuable to understand signaling pathways in the colon, including TGF-β and Wnt/β-catenin signaling [9, 10].

The spatial arrangement and hierarchical organization within the crypts has important consequences. Two-dimensional modeling of the human colon crypt suggests that cell type, phenotype, and spatial location can influence the clonal expansion of mutated cells [11]. Crypt architecture and cellular hierarchy also suppress the sequential accumulation of mutations [12]. A recent study combining modeling and experiments indicates that stochastic events can lead to the replacement of stem cells carrying colon cancer mutations by wild-type stem cells, supporting the role of crypt architecture in suppressing mutant accumulation [13••]. Mathematical models of intestinal stem cell dynamics during homeostasis, tumorigenesis, repair, and development have led to better understanding of crypt dynamics and indicate future directions in the field of intestinal stem cells [14–16]. For a detail review on multi-scale mathematical modeling of the colon crypt, we refer the reader to [17].

In normal tissues, cell lineages are highly regulated to maintain tissue homeostasis and to promote the rapid regeneration after an injury. The control mechanisms involved have different performance objectives, which include the fast regeneration from a variety of initial conditions, the maintenance of high ratios of differentiated to undifferentiated cells, and the robustness of target population size to perturbations [3]. The study of these objectives lends itself quite naturally to mathematical modeling and analysis.

Feedback loops that act in a paracrine or autocrine fashion are fundamental to establish homeostatic control and the nature of these control mechanisms determines the dynamics and stability of the system [18]. Of especial importance are the regulation of stem proliferation and the probability of stem cell self-renewal vs. differentiation [3, 19–22]. In particular, the stability properties of two and three cell compartment models for cell lineages have been extensively studied in cases where the regulation of stem cell proliferation is modeled using Hill equations [23–25]. The use of Hill equations to model control of stem proliferation has also been successful at describing data from a wide range of experimental systems, including measurements from the process of hematopoiesis and data obtained from the experimental manipulation of the mouse olfactory epithelium [3, 26].

Different aspects of control networks have been investigated. An important adaptation is the ability of systems to recover rapidly after an injury and maintain high ratios of differentiated to undifferentiated cells while keeping a low variance with regard to the equilibrium number of cells. It has been shown, for example, that there is a trade-off between requiring a small equilibrium fraction of stem cells and the speed at which a system is able to recover from a perturbation [24, 27]. Furthermore, besides the aforementioned importance of feedback on stem cell proliferation, mathematical modeling also suggests that the interplay between genetic and epigenetic regulation plays an important role in adult stem cell regeneration [28•].

While most models assume a certain functional form of control loops that regulate stem cell lineages, a different approach was adopted in [29••]. The goal was to identify mathematically the different types, possible numbers, and directions of control loops that ensure stability, keep the variance low, and possess some robustness. It was found that exactly two possible minimal control networks exist in a two-compartment system, and 20 minimal control networks in a three-compartment model [29••]. A general methodology termed "stochastic near equilibrium calculus of stem cells" was subsequently developed in [30••] that generalized these results to lineages with any number of compartments, and allowed to calculate the means and the variances of cell numbers in all the compartments based on local properties of the controls. Applications to the airway epithelium were investigated in [30••], and the role of symmetry of stem cell divisions in tissue stability was studied in [31].

The basic principles of cell lineage regulation apply to a wide variety of tissues. From a modeling perspective however, blood presents an especially attractive system. Since blood has no spatial structure, it is especially amenable to modeling with ordinary differential equations. This technique is central to a recent sequence of mathematical models dealing with cell lineage regulation in blood [32–34]. These studies focused on the process of hematopoiesis of white blood cells, stem cell

dynamics in acute leukemias, and myelodysplastic syndromes caused by problems in feedback signals affecting hematopoietic stem cells [32–34].

Several of the studies previously discussed follow the multi-compartment model of cell differentiation. However, in some systems, it has also been proposed that cells can change their differentiation level independently of cell division, for example, by moving away from the stem cell niche [35]. Moreover, for certain tissues, the different differentiation stages are not well identified [36]. These types of scenarios can be modeled by assuming that cell differentiation occurs as a continuous process, rather than progressing through a discrete sequence of differentiation stages [37]. Alternatively, a hybrid formulation is possible by considering a differentiation process that consists of discrete and continuous transitions [38]. For a comparison of two discrete and continuous mathematical approaches applied to hematopoietic networks, including advantages and constraints, see [39].

Stem Cells and Cancer

Because the stem cell lineage is a basic unit of cellular proliferation that maintains tissue turnover, its dynamics are intimately related to the origins of cancer. In fact, the design principles that shape the architecture of SC lineages have been hypothesized to be under selection to minimize the risk of malignant transformations [40•]. In [41•], the generation of two-hit mutations was studied (which is important in the context of e.g., tumor suppressor gene inactivation events). It was suggested that not only are hierarchical tissues more effective in delaying the generation of two-hit mutants compared with non-hierarchical ones, but also that symmetrically dividing stem cells lead to slower cancer generation compared to asymmetrically dividing SCs. Refs [42, 43] further explored spatial SC lineage models, focusing on division patterns that minimize mutation generation.

There is growing evidence that only a rare subset of cells, referred to as cancer stem cells (CSCs), are the driving force behind tumor growth, resistance, and recurrence. These CSCs share a number of similarities with normal adult stem cells. In particular, CSCs have the ability to self-renew and differentiate, giving rise to all the differentiated cell types that make up the bulk of the tumor. Like normal stem cells, they also have a large proliferative potential being the only cancer cells capable of repopulating a tumor and initiating metastasis. John Dick observed the first CSC in acute myeloid leukemia in 1994, and accumulating evidence since then has supported the existence of CSCs in many different types of cancers [44].

The modeling literature on CSCs is vast. Mathematical models of cancer have provided important insights into the processes of carcinogenesis, tumor evolution, and metastasis [45, 46, 47•, 48, 49]. Recent quantitative methods can help elucidate the type of phenotypic transitions that lead to uncontrolled cellular growth in stem cell-driven tumors [20]. Tumor characterization via quantitative methods can also occur at an individual patient-specific level as shown in a recent framework called the Spatial Cell Ancestral Inference (SCAI) [50]. Modeling can also aid in the measurement and identification of crucial parameters relevant to carcinogenesis. This type of approach can lead to excellent agreement between clinical data and theoretically derived results [51]. Researches have also explored mathematically the role of CSCs in hematopoietic malignancies. In leukemias, for example, a study based on ordinary differential equations characterized how changes in parameters describing proliferation rates and self-renewal properties can lead to the expansion of the leukemic cell population [52]. Stochastic modeling is also an important tool to understand the dynamics of blood cancers. In particular, for chronic myeloid leukemia (CML), stochastic fluctuations in the number of stem cells are important to explain some of the variability observed in treatment responses [53•]. The importance of tracking down fluctuations in hematopoietic stem cells is also important to accurately describe the process of hematopoiesis in CML [54]. In addition, modeling can help to characterize the tumor growth dynamics in terms of the strength of the inhibitory signals still acting in non-spatial cancers [55]. Recent quantitative studies also focused on the role of stem cells in the epithelial-mesenchymal transition in the context of cancer [56, 57].

The CSC paradigm assumes that tumor formation results from the unidirectional differentiation of CSCs. In some tumors however, new evidence supports the existence of a bidirectional hierarchy, in which non-CSCs can dedifferentiate. This phenomenon is referred to as plasticity between CSC and non-CSC populations [58]. Recent quantitative studies have investigated this possibility [59]. Modeling results suggest that the probability of a non-CSC dedifferentiating into a CSC influences the likelihood of carcinogenesis [60]. Indeed, in a three-compartment Moran-type model, dedifferentiation was found to be a crucial contributor to mutant fitness [61•]. Cellular plasticity was also implicated in the probability of cancer cell survival [62]. In contrast, a different modeling study suggests that perceived tumor plasticity is really the consequence of imperfect cell markers not identifying all CSCs in a tumor [63].

Normal somatic cells are capable of only a limited number of divisions; this phenomenon known as Hayflick's limit or replicative senescence acts a tumor suppressive mechanism. Stem cells and the majority of cancers (~90%) escape replicative limits by expressing the enzyme telomerase at sufficiently high levels. The remaining cancers escape senescence through the alternative lengthening of telomeres (ALT) pathway [64].

A simple approach to model replicative senescence is to associate a number, called the replication or proliferation capacity, to every non-stem cell [5]. When a non-stem cell

divides, the replication capacity of the daughter cells will be one unit less than that of the parent cell. When the replication capacity of a cell is exhausted, cell division is no longer possible. This approach has been used to explore the role of replicative senescence as a possible evolutionary force behind commonly observed features of cell lineages [5] (including the self-renewal probability, division rate, and number of intermediate cell compartments, and as a mechanism acting against precancerous non-neoplastic mutations in healthy tissue [65]. This basic idea has also been used to model competition between CSCs and non-CSCs in solid tumors [66]. In another recent study related to senescence, mathematical modeling was used to reconstruct the cell division dynamics of hematopoietic stem cells [67].

There is debate over the cell of origin of CSCs, whether they originate from normal stem cells or from more differentiated cell types that acquire stem cell characteristics. In multiple cancers, there is evidence that the initiating mutations originate in cells with limited proliferative potential, such as progenitors [68]. Furthermore, frequent somatic mutations that activate the core promoter of telomerase have been identified in multiple types of cancers [69], which suggest a possible tumor origin in more differentiated telomerase-negative cells. Indeed, mathematical modeling has shown that in an expanding clonal cell population, the probability of escaping replicative limits through telomerase activation is far from negligible [70]. Moreover, modeling results also suggest that the fact that most cancers are telomerase positive is not an indication that tumors initiate in telomerase-positive cells [71].

Stem Cells and Cancer Therapy

Cancer therapy is limited by our incomplete understanding of the mechanisms governing cancer dynamics. Over the years, treatment has evolved into more personalized, targeted therapy [72]. As biological experiments may be expensive and time consuming, mathematical models are extremely useful in investigating different potential scenarios of carcinogenesis and treatment. These models are able to investigate such things as the efficacy of drug treatment or combination therapy, and cancer relapse and treatment resistance.

Critical to more effective, cancer therapy is the understanding and characterization of tumor growth. Computational models, such as the model introduced by Pappalardo et al. that simulates interactions in the pathways potentially involved in the development of melanoma, can be used to suggest new therapeutic strategies and improve drug treatment [73]. Another method of modeling tumor growth and the dynamics of tumor subpopulations is a "chemical reaction" approach where each event related to cell division, differentiation, and cell death is modeled as a chemical reaction. Following this approach, one recent study considered a three-compartment system consisting of stem cells, transit cells, and differentiated cells and identified kinetic relationships necessary for solid tumor growth. This study suggests that inducing stem cell differentiation may improve the efficacy of cancer treatment when combined with other types of cancer therapy [74].

One interesting set of studies deals with the so-called tumor growth paradox. When spatial constraints are taken into account, quantitative models suggest that while increasing the cell death rate results in short-term tumor reduction, the freeing of CSCs and the formation of self-metastases could result in higher tumor burdens in the long-term [66, 75•]. These studies provide modeling support to as of yet limited, but intriguing data that suggest that under certain conditions, therapeutic interventions might lead to higher tumor growth [76, 77].

Mathematical modeling performed in tandem with biological experiments can aid in the identification and measurement of key parameters that drive tumor progression. This is exemplified by a recent model that investigated the initial phase of tumor growth using data from in vivo and in vitro experiments of $ErbB2^{+}$ mammary cancer [78]. The identification of important tumor-related parameters could also inform the design of effective drug therapy. Recently, a statistical framework was developed to quantify the effect of multiple drugs on the response of genes controlling tumor growth, as well as the effect of those drugs on inhibiting tumor growth in individual patients [79]. This approach aims to characterize stem cell response to therapy and to provide information necessary for more effective personalized drug treatment. Surprisingly, due to intra-tumor heterogeneity, mathematical models have shown that the most effective drug combination may not include drugs that have been shown to be most effective against any particular tumor cell subpopulation [80, 81]. Thus, knowing the predominant tumor cell subpopulation in a heterogeneous tumor may not be helpful in determining the best drug combination. Recent models search for drug combinations capable of overcoming the challenges imposed by intra-tumor heterogeneity [82].

Effective use of chemotherapeutic drugs in cancer therapy must overcome several difficulties, one of which is the timing of drug administration. Dosing schedules can influence the probability of developing treatment resistance as well as the total number of drug-resistant cells. This information can in turn be used to optimize the scheduling of chemotherapeutic drugs [83]. For example, one mathematical model based on glioblastomas detected two optimal dosing schedules, which were validated in mouse models [84]. These schedules exploit intra-tumor heterogeneity and the dynamic instability of radioresistance. Another approach to identify optimal drug schedules for individual patients uses the circadian expression of clock genes. One such study modeled optimal drug scheduling based on drug toxicity in colorectal cancer [85].

Another well-recognized obstacle to effective anticancer drug treatment is drug resistance. In [86•], stochastic modeling of resistance of CML to small molecule inhibitors (e.g., imatinib) was described, including topics such as cross-resistance, the role of cell quiescence, drug combinations, and optimal treatment strategies. Resistance to the new drug ibrutinib in chronic lymphocytic leukemia (CLL) treatment was studied in [87].

In cancers that follow the CSC paradigm, mathematical modeling suggests that the CSC subpopulation might expand under current anticancer therapies resulting in treatment resistance and relapse [88–90]. For instance, a mathematical model driven by information from patients with chronic myeloid leukemia being treated with the drug imatinib predicted that after a year of targeted treatment, the proportion of CSCs will increase 100-fold and will continue to increase up to 1000-fold after 5 years of treatment [91•]. These findings suggest that complete and efficient tumor treatment necessitates the eradication of the entire CSC population. Indeed, modeling and clinical evidence from malignant tumors indicate that the repopulation of treatment-resistant tumors by only a small population of resistant tumor cells may occur within several months post-treatment [92]. Modeling can also contribute to our understanding of important mechanisms behind treatment resistance, such as the impact of cell density and mutation frequency in multi-drug resistance [93]. A recent study also examined the different levels of resistance that resulted from various chemotherapeutic and cytostatic treatments [94].

Stem cell dynamics could also influence the efficacy of radiotherapy treatment. Evidence suggests that there is a distinct radiosensitivity between CSCs and differentiated cancer cells. In particular, glioma stem cells have been shown to be highly radioresistant through preferential activation of the DNA damage response [95, 96]. Computer simulations reveal that tumor heterogeneity and radioresistance of CSCs can modulate the kinetics of tumor repopulation after therapeutic irradiation [97, 98]. Identification of the optimal doses of radiation is of particular interest in cancer modeling. Heterogeneous tumors for instance may be more effectively targeted by radiation dosimetries specifically designed to boost radiation in areas containing more CSCs [99].

In addition to drug resistance, effective cancer therapy must overcome the phenomenon of cancer relapse. Computational studies of acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) suggest that relapse is due mainly to the selection of pre-treatment clones rather than mutations acquired during therapy [87, 100]. A model of acute leukemias found that clonal selection is highly influenced by self-renewal and that highly self-renewing but slowly proliferating cells trigger relapse [100]. Recent findings in breast cancer also suggest that decreasing the rate of self-renewal of CSCs, along with the disruption of inflammatory feedback loops contributes to the elimination of mesenchymal and epithelial breast CSCs, significantly reducing the probability of relapse [101].

Quantitative models of CSCs have enhanced our understanding of cancer biology and treatment [102]. Despite these numerous contributions, there are many areas where quantitative approaches are still sorely needed. One of these areas is in the emerging field of immunotherapy, which aims to treat cancer by using the patient's own immune system [103]. CSCs may possess the ability to evade host antitumor immunity and be the source of immunotherapeutic resistance [104, 105]. There are multiple valuable models of immunotherapy (see e.g., [106, 107]). There are however, very few recent modeling studies of immunotherapy that consider the role of CSCs and the possibility of treatment resistance [108]. On important future challenge will be the development of comprehensive mathematical models of immunotherapy that take into account tumor stem cell dynamics and intra-tumor heterogeneity.

Conclusion

Mathematical modeling in biology is a relatively new discipline. Yet, it has already provided fundamental insights into the fields of stem cell dynamics and cancer development and treatment. In this article, we focused on recent mathematical and computational studies related to stem cell dynamics. We began by looking at the role of adult stem cells in tissue regulation and maintenance of homeostasis. As part of this discussion, we examined models in the context of hematopoiesis and tissue regulation of the colon crypt. We then looked at the CSC paradigm, and discussed the concepts of stem cell plasticity, replicative senescence, and tumor-initiating cells. We ended by surveying recent mathematical research in the area of cancer therapy. In particular, we discussed studies dealing with quantitative approaches to understand radio and chemoresistance and the mechanisms of cancer relapse. While our quantitative understanding of normal and CSCs has increased significantly in the last few years, many challenges remain ahead. One important future direction will involve the modeling of stem cell dynamics in novel cancer treatment strategies, including oncolytic viruses, telomerase inhibitors, and immunotherapy.

Compliance with Ethical Standards

Conflict of Interest Lora D. Weiss, Natalia L. Komarova, and Ignacio A. Rodriguez-Brenes declare that they have no conflict 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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- •• Of major importance

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