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

How to Characterize Stem Cells? Contributions from Mathematical Modeling

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Abstract

Purpose of Review Adult stem cells play a key role in tissue regeneration and cancer. To translate findings from stem cell biology into clinics, we require a quantitative characterization of stem cell dynamics in vivo. This review explores how mathematical models can help to characterize stem cell behavior in health and disease.

Recent Findings Mathematical models significantly contribute to quantification of stem cell traits such as proliferation, self-renewal, and quiescence. They provide insights into the role of systemic and micro-environmental feedback loops during regeneration and cancer. Computer simulations allow linking stem cell properties to tumor composition, clinical course, and drug response. Therefore, models are helpful in personalizing treatments and predicting patient survival.

Summary Mathematical models coupled with tools of parameter estimation and model selection provide quantitative insights into stem cell properties and their regulation. They help to understand experimentally inaccessible processes occurring in regeneration, aging, and cancer.

Keywords Cancer stem cell · Mathematical model · Tumor heterogeneity · Clonal evolution · Bone marrow transplantation · Patient prognosis · Differential equations

Introduction

In early phases of stem cell biology, tremendous efforts have been undertaken to identify stem cells among all tissue cells. These efforts were driven by applications in regenerative medicine with a hope that stem cells can be isolated from tissues, multiplied, and then transplanted into patients. However, fundamental problems of stem cell medicine remain unresolved [1, 2]. Specifically, (i) multiplication of stem cells in culture is challenging or even impossible, as in the case of hematopoietic stem cells (HSC) [3], and (ii) for many stem cell types, successful transplantation with long-term clinical benefit is still not possible [4, 5].

These problems indicate that for successful clinical applications, techniques of stem cell identification and separation have to be complemented by a detailed characterization of stem cell properties in vivo. Such a characterization of stem cells has to involve diverse aspects including response of stem cells to systemic and micro-environmental regulatory loops, epigenetic and metabolic state, plasticity and kinetic properties such as proliferation rates and self-renewal probabilities (Fig. 1A).

The cancer stem cell hypothesis is another reason why stem cell dynamics and their regulation should be understood. According to the hypothesis, cancer stem cells are required to maintain tumor growth and, due to their high resistance to therapy, they trigger relapse [6]. The most prominent example of a stem cell-driven cancer is acute myeloid leukemia (AML), a frequent hematological cancer [7]. Other potential examples include breast cancer [8], prostate cancer [9], glioblastomas [10], and sarcomas [11]. To treat cancer, it is crucial to understand how cancer stem cells differ from their benign counterparts and to quantify these differences. Important aspects are depicted in Fig. 1A.

In the following, we summarize recent examples of mechanistic mathematical models contributing to characterization of stem cell function. First, we discuss mathematical tools and concepts. Then we focus on specific applications, namely (i) the use of mathematical models to quantify stem cell parameters

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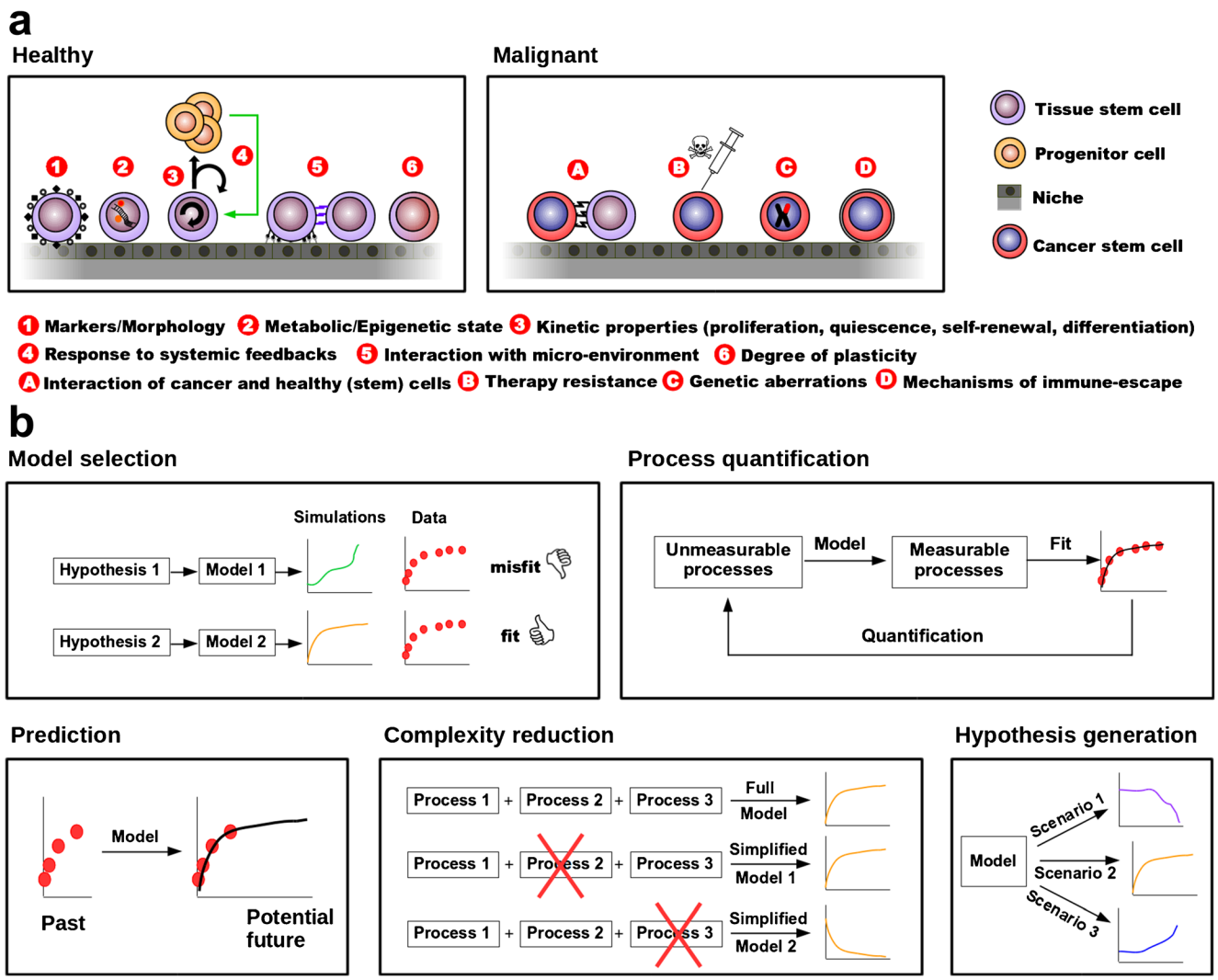

Fig. 1 **a** Stem cell dynamics evolve from the interplay of multiple traits. A quantitative understanding of these traits is required to predict and optimize stem cell-driven processes. Left: Stem cell traits relevant to tissue dynamics in health and disease. Right: Cancer stem cell traits relevant to understand cancer progression, therapy, and relapse. **b** Applications of mathematical models to biological questions. Comparisons of model simulations to data can provide evidence of whether a given hypothesis is in agreement with observations or not. Mathematical models can contribute to quantify processes that are not directly observable and help to predict future time evolution of a system based on existing data. Model reduction techniques help to identify relevant components of complex systems. Model simulations can allow to generate new hypotheses and to plan experiments

that account for population dynamics; (ii) the application of mathematical models to understand regulatory feedback loops, including systemic and micro-environmental signals; and (iii) mathematical models of treatment resistance. All aspects are discussed in the context of regeneration and cancer.

Mathematical Frameworks to Model Stem Cell Dynamics

Mathematical models have already a long history of applications to stem cell problems. The choice of the mathematical framework depends on the considered biological system and the question of interest. Ordinary differential equations (ODEs) are useful when the modeled cell populations are large and well-mixed. This seems approximately fulfilled for hematopoietic cells in the bone marrow or for certain chemical species in cytoplasm. The obtained results are usually interpreted as average concentrations/densities, and the equations describe time dynamics of such quantities. Whenever it is possible to subdivide a given system into a finite number of large and well-mixed subsystems, so-called compartment models can be used. Each compartment represents one of the subsystems, and its time evolution is described by an ODE. These models arise naturally in the context of stem cell-driven systems, where stem, progenitor, and mature cells correspond to the different compartments [12, 13]. In such models the pace of commitment is usually dictated by successive divisions. If the system exhibits a continuum of different cell

types or states, so-called structured population models can be used. Such models arise if we describe continuous cell transitions such as aging or continuous cell maturation. These models have the form of transport or integro-differential equations [14, 15, 16]. In case of a small number of individuals, stochastic effects may significantly impact population dynamics. To include stochasticity in a model, different approaches can be chosen. Stochastic differential equations allow including noise (random fluctuations) into a differential equation and solving it numerically or analytically [17••]. A well-established method to simulate stochasticity originating from random choices among different possible behaviors, such as cell division, quiescence, and cell death, is Gillespie algorithm [18••]. These approaches allow studying population dynamics in the presence of random events, albeit without tracking individual histories of population members. The latter can be accomplished using so-called individual-based models which are usually computationally intensive. Possible applications include populations with high heterogeneity (only a small number of identical individuals) or cases where it is relevant to know the history of each individual [19•, 20••]. Spatial heterogeneity can be accounted for by individual-based and partial differential equation models. There exist multiple examples of bridging these approaches [17••, 21•, 22••, 23].

Applying Mathematical Models to Biological Questions: a List

Based on literature review, a number of commonly used concepts emerge (Fig. 1B). These include:

- Model selection and hypothesis testing: Different biological hypotheses are formulated as mathematical models. Comparison of modeling output to data helps to falsify hypotheses and to decide which model fits data best. Examples of this approach include ref. [12, 17••, 18••, 24••, 25••].
- Quantification of unmeasurable quantities: Models help to relate experimentally inaccessible (microscopic) quantities to measurable (macroscopic) quantities. Assuming that the model is based on correct assumptions the fitting to data can help to quantify the unmeasurable processes. Examples of this approach include ref. [17••, 24••, 26••].
- Correction of measurement-related processes: Transfection of cells with genes fused with luminescent proteins such as GFP alters dynamics of signaling pathways. Similarly, repeated illumination of biomolecules by laser beam results in photobleaching. Mathematical models allow developing requisite corrections.
- Data-based predictions: Models can help to predict future evolution of a system based on data about its current state. Examples for this approach include ref. [20••, 25••, 26••, 27••].
- Complexity reduction: Model analysis can help to identify which sub-processes have a relevant impact on an outcome of interest and which can potentially be neglected or simplified. Examples of this approach include ref. [26••, 28].
- Exploration and hypothesis generation: Mathematical models help to explore dynamics of complex systems and to understand which processes or assumptions may affect distinctive dynamical features. This allows proposing novel biological hypotheses. Examples include ref. [19•, 21•, 22••, 29•, 30, 31, 32, 33•].

In the following sections, we discuss specific insights obtained from application of these concepts to stem cell systems.

Mathematical Models Allow Quantifying Proliferation, Self-Renewal, and Quiescence

Proliferation rates, self-renewal probabilities, and the fraction of quiescent cells determine key characteristics of a cell population such as growth dynamics and stem cell frequency. These parameters are relevant to the understanding of tissue regeneration and malignant cell growth [34]. Mathematical models have contributed a lot to the understanding of complex population dynamics.

One example of this is adult neurogenesis. Modulation of cognitive functions requires generation of new neurons throughout lifetime. The neurons are derived from neural stem cells (NSC) that are located in specific regions of the brain, such as the hippocampus. Experiments show a saturating decline of hippocampal NSCs in aging mice [18••]. However, the fraction of actively cycling cells is constant over time. The data themselves do not allow a direct conclusion about the age-related changes of cell properties such as proliferation, self-renewal (the probability that a stem cell gives rise to stem cells), and activation from quiescence. To address this question, a family of ODE models has been developed, which describe time evolution of the numbers of NSC and of the active subset. Each model assumes a different age-related change of cell properties. Fitting of the different models to data suggests that, among a number of alternatives, only an age-related decrease of the rate of activation of quiescent NSC combined with a decreased depletion is a mechanistic explanation for the experimental findings [18••].

Similar questions arise in the context of the hematopoietic system. The hematopoietic stem cells (HSC) are responsible for life-long blood cell production. However, it is unclear how HSC proliferation and self-renewal change with age. HSC can perform symmetric and asymmetric divisions. Symmetric divisions lead to two identical offspring, i.e., two stem cells in case of symmetric self-renewal and two non-stem cells in case of symmetric differentiation. Asymmetric divisions give rise to one stem and one non-stem cell. One approach to assess the

age-specific fraction of symmetric self-renewal among all divisions is the study of telomere length distributions and their change with age. Mathematical models suggest that telomere length decreases slower if stem cells perform symmetric self-renewal compared to the scenario where stem cells divide only asymmetrically. This conclusion follows from stochastic simulations and analytical calculations of age-dependent telomere length distributions based on a deterministic approximation. The analytical results allow to study how the probability of symmetric self-renewal impacts on telomere length distributions. A quantitative comparison of the analytical expressions with data from humans at different ages supports the hypothesis that symmetric HSC self-renewal is frequent during adolescence and asymmetric divisions increase with age [24••].

Another approach to understand in vivo stem cell dynamics employs labeling experiments. Due to their high complexity, mathematical modeling is required to interpret the experimental readouts. The labels can be either experimentally induced genetic modifications [35••] or naturally occurring mutations [36••]. Using somatic mutations as neutral genetic labels, clone size distributions can be derived from mathematical models [36••]. Comparison of the theoretically derived clone size distributions to sequencing data provides insights into clonal evolution. Application of this framework to sequencing data from the human epidermis suggests that most somatic mutations do not lead to growth advantages (so-called neutral competition) [36••]. Application to a xenograft model of glioblastoma suggests that growth dynamics of most clones can be explained by neutral competition and a hierarchical organization of the cell population [37••]. Similar results have been obtained for hepatocellular carcinoma [38], although the model used in this latter paper has been questioned [39].

According to the cancer stem cell hypothesis, cancers are maintained by a population of stem-like cancer cells, so-called cancer stem cells that give rise to the tumor cell bulk. To establish a cancer cell population, cancer stem cells have to acquire a growth advantage that allows them expanding within a homeostatic tissue. For a long time, increased proliferation has been considered a hallmark of cancer [40]. This view is supported by agent-based models of low-grade glioma showing that experimentally measured total and proliferating cell densities can be reproduced under the assumption that proliferation of malignant cells is increased compared to healthy cells [41]. However, mathematical models of acute leukemia suggest that increased self-renewal of cancer stem cells leads to efficient expansion, whereas a sole increase in proliferation rate confers only a minor growth advantage to cancer stem cells [42, 43]. These insights follow from computer simulations and stability analysis of ordinary differential equation models describing growth of cancer stem and non-stem cells under environmental feedbacks. Especially, if stem cells divide asymmetrically under homeostatic conditions, i.e., 50% of their offspring are again stem cells, a mutation that leads to high proliferation rates will not result in an increase of the mutant stem cell population [34, 42]. The same models suggest that even cancer cells with proliferation rates lower than those of healthy cells can expand rapidly if their self-renewal is high enough. This could explain resistance against classical chemotherapy observed in relapsing leukemia [29•]. Models of colon crypts point in a similar direction. Numerical simulations of a delay differential equation model with randomly chosen parameter values show that tumors resistant to in silico treatment have a reduced stem cell differentiation rate compared to therapy sensitive tumors [30].

The cancer stem cell hypothesis suggests that the cancer cells can be subdivided into cancer stem cells with the potential of indefinite self-renewal and proliferation, progenitor-like cells with limited self-renewal and proliferative potential, and post-mitotic maximally differentiated tumor cells. So far, it remains unknown how proliferation and self-renewal of cancer stem and progenitor-like cells impact on the growth dynamics of the cancer. Mathematical models of AML suggest that proliferation and self-renewal of cancer progenitor-like cells have a negligible impact on the total malignant cell dynamics compared to the respective properties of cancer stem cells [26••]. This insight led to the hypothesis that observable leukemic cell dynamics are the result of the cancer stem cell properties which could, therefore, be estimated based on clinical data. Parameter estimations for individual patients suggest that high self-renewal and high proliferation are linked to poor survival. Application of the framework to patients with multiple relapses indicates changes in self-renewal and/or proliferation in the course of the disease [26••]. This result is complemented by modeling studies suggesting increase of leukemic stem cell self-renewal with time. This change of cell properties can be either caused by new mutations [21•] or by selection of pre-existing small clones [14, 29•]. Simulations of ODE models describing competition of healthy cells and multiple leukemic clones suggest that clones with highest self-renewal out-compete clones with lower self-renewal [29•]. This result has been rigorously shown in the case of a continuum of different cell clones (i.e., a trait-structured system of integro-differential equations) [14]. Population-based models of clonal competition considering emergence of new clones due to mutations lead to the conclusion that a high self-renewal of the new clone increases the probability that it reaches detectable size and acquires further mutations [21•]. This mechanism might explain an increase in self-renewal over time and help to predict the impact of newly detected mutations.

Systemic Feedback Regulations Govern Regeneration and Cancer Growth

Systemic feedbacks allow coordinating mature cell output with the activity of stem and progenitor cells. A detailed

knowledge about such regulations is crucial to understand stem cell maintenance, tissue regeneration, and cancer growth.

A paradigmatic example to study tissue regeneration is bone marrow transplantation (BMT). As treatment of hematological cancers, host's bone marrow is eliminated by chemotherapy and radiation. To restore blood cell production, hematopoietic stem and progenitor cells from a donor are infused. For treatment optimization, it is important to understand how stem cell self-renewal and proliferation change during the regeneration phase. Numerical and analytical study of a set of ODE cell population models, each imposing regulation of a different parameter, suggests that the clinically observed speed of mature cell production cannot be explained by a sole increase in proliferation rates [12]. However, mathematical models assuming increased self-renewal during regeneration are able to capture quantitative data from BMTs [12, 31, 44•]. This type of models is also helpful to understand complications of BMT and how they could be rescued [31].

The stem cell population is exceptional in the sense that it is the only cell population that is independent of influx of differentiating cells. It is a fundamental question what kind of signals are required to maintain such a hierarchy and how stem and non-stem cells respond to them. Steady-state analysis of ODE models of hierarchically organized cell populations, controlled by a negative feedback signal from mature cells, implies that stem cells are the subpopulation requiring less signal stimulation to maintain its size than any other subpopulation [13]. This result shows that stemness can be understood as a property that dynamically evolves from interaction of cells and systemic signals.

It is an open question if and how malignant cells respond to systemic signals. Cell culture and xenotransplantation studies [45] have shown that AML cells of some patients require growth factors, so-called cytokines, to multiply. Cells from other patients can grow autonomously, i.e., in absence of cytokines. It is unknown whether this difference has an impact on the course of the disease. Computer simulations and analytical results suggest that autonomous leukemic cell growth is linked to a poor prognosis and a fast increase of malignant cell load [25••]. This hypothesis is supported by model-fitting studies. Patient data that are compatible with the model of autonomous leukemic cell growth and incompatible with the model of cytokine-dependent leukemic cell growth are correlated with a poor prognosis [25••]. In the context of hematopoietic malignancies, another important factor seems to be reduction of heterogeneity of healthy HSC due to recurrent infections, which reduces competitiveness of HSC with respect to leukemic stem cells (LSC) [46].

Cytokines play a role in various cancers beyond AML. Mathematical modeling and experimental data suggest that cytokines originating from chronic inflammation can trigger development and progression of myeloproliferative neoplasms, a group of blood cancers characterized by excess production of red cells, white cells, or platelets [47]. Another example for a cytokine inducing tumor growth is IL6 in head and neck squamous cell carcinoma (HNSCC). Treatment using antibodies against the IL6 receptor has been investigated by a quantitative mathematical model of HNSCC xenografts [22••]. The model consists of ODEs describing evolution of tumor stem cells, progenitor cells, and terminally differentiated cells. Self-renewal and death rates of the different cell types depend on cell counts and on the fraction of occupied IL6 receptors. Time evolution of free and bound IL6 and of therapeutic IL6 antibodies is described by separate ODEs. Simulations lead to the conclusion that the drug has a more pronounced effect on the increase of tumor cell death compared to the reduction of self-renewal. The model suggests that tumor reduction is robust with respect to changes in drug dose and administration interval [22••].

Healthy and Cancer Stem Cells Compete for Micro-environmental Factors

It is well accepted that stem cells depend on complex interactions with their micro-environment, the so-called stem cell niche.

One of the best studied niche systems is the hematopoietic stem cell niche. A distinguishing feature of the hematopoietic stem cells is their dynamic attachment to and detachment from the niche. Under homeostatic conditions, HSC can detach from the niche, travel through circulation, and reattach at a different site. In ref. [17••], these processes have been formulated as an individual-based stochastic model, the average dynamics of which are given by a system of ODEs. Steady-state analysis of this model allows to relate measurable steady-state cell counts to so far unknown rates of niche detachment and attachment. Niche traffic also plays a role in malignancy. Mutated cells have to spread inside the niches. Using the master equation and stochastic differential equations, the average time required for a new clone to reach a certain size can be calculated. This suggests that clones without proliferative advantage cannot reach a dominant size within the lifetime of a mouse [17••].

Competition of leukemic and healthy cells for spaces in a joint human bone marrow niche has been modeled in ref. [32••]. According to the ODE model, dislodgement of HSC by LSC can reduce the number of HSC long before the clinical manifestation of the disease. The higher the probability that a LSC can dislodge a HSC, the lower the HSC count at the time of diagnosis and the poorer the patient survival. The correlation between low HSC counts and poor prognosis has been detected in clinical data [32••]. Simulations predict that the decline of HSC before clinical manifestation of the disease is a unique feature of models that include a competitive interaction between stem cells. It cannot be explained by systemic

feedback signals that act simultaneously on all differentiation stages [32••]. The modeling results and the clinical observation that HSC decline before AML relapse support the relevance of the stem cell niche for human disease dynamics.

Stem cell dynamics emerge from integration of local (micro-environmental) and global (systemic) signals. Mathematical models are a helpful tool to investigate whether hypotheses derived from experiments are sufficient to explain observed phenomena. One example for this approach is given in ref. [48], where experimentally derived feedback mechanisms acting on healthy and dysplastic hematopoietic cells have been formulated as ordinary differential equations. The experiments indicate that self-renewal could be regulated by local and proliferation by systemic signals. Simulations of the obtained model show that the hypothesized feedbacks are sufficient to reproduce cell dynamics observed in MDS patients.

Cancer Stem Cell Heterogeneity, Plasticity, and Resistance Contribute to Cancer Relapse

Resistance to treatment and subsequent relapse of the cancer are major clinical problems. In the simplest scenario, a subset of cancer cells is a priori resistant to the administered drug [19•, 29•]. In this case, the treatment leads to an enrichment of resistant cells. Since eradication of sensitive cells results in the availability of free resources, the resistant cells potentially show enhanced multiplication in the post-treatment period. This phenomenon is investigated in ref. [29•] using an ordinary differential equation model of competing AML clones in the presence of a nonlinear systemic feedback signal. Computer simulations propose that at the time of diagnosis most cells proliferate fast and have a high self-renewal probability. If slowly cycling cells are endowed with high self-renewal probabilities, relapse can occur shortly after treatment since high self-renewal accelerates cell expansion [29•]. This mechanism could explain the observation of early and treatment-resistant relapses in AML patients. Similarly, computer simulations based on ODE models of radiotherapy of breast cancer propose that it might not be sufficient to aim at maximal reduction of tumor volume. The authors simulate different treatment protocols and conclude that in cases where cancer cells cannot be totally eradicated, therapy should aim to counterbalance the reduction of tumor burden and outgrowth of resistant cells [33•].

Induced drug resistance describes the phenomenon whereby cancer cells become resistant in response to drug exposure. This phenomenon is an example of phenotypic plasticity, i.e., a potentially reversible change of cell properties. Mathematical models are a helpful tool to evaluate whether experimental observations can be explained by phenotypic plasticity and to discriminate them from selection phenomena, imperfect marker expression, or other mechanisms [49–51]. Simulations of chemotherapy using a cellular automaton model of solid tumors suggest that treatment response strongly depends on the mechanisms of drug resistance. In the simulations, very high doses lead to selection of primary resistant cells whereas low doses can increase induced resistance [19•]. Two recent works for ovarian [52•] and colorectal cancer [20••] demonstrate how mathematical models can help to predict treatment response and to personalize treatment choice.

To understand resistance to novel targeted therapies, intercellular heterogeneity of cell signaling pathways has to be taken into account. Mathematical models coupling activity of signaling pathways and tumor cell phenotype allow to simulate the impact of novel treatment agents and the impact of cellular heterogeneity on the outcome [27••]. Similarly, the interaction of tumor and immune system seems to have impacts on treatment outcome, especially in case of immune therapies [20••, 53, 54, 55]. Another process that might interfere with treatment response is the conversion of non-cancer stem cells into cancer stem cells. Depending on the context, this type of plasticity can be either advantageous or disadvantageous for survival of the cancer cell population [56•]. Other variables influencing cancer growth and drug response are the genetic, epigenetic, and metabolic state of cancer cells. Corresponding models have been reviewed elsewhere [57–59].

Summary

The multi-factorial and nonlinear nature of stem cell regulation significantly limits our intuitive understanding. Further complications arise due to the restricted experimental accessibility of stem cells, which are often located in protective niches. Although mathematical models cannot ultimately prove whether a biological hypothesis is correct, they can contribute to our mechanistic understanding of complex systems and help to overcome experimental limitations. Mathematical models allow comparing rigorously competing hypotheses and to design experiments that help to distinguish between them [12, 18••, 25••, 37••, 51]. Comparisons of model simulations to experimental data can provide evidence of whether a given hypothesis is in agreement with data or not [18••, 37••, 58]. Using parameter estimation strategies, mathematical models can contribute to quantify processes that are not directly observable [17••, 26••]. Sensitivity analysis and model reduction tools allow simplifying rigorously the complexity of the studied system by identifying sub-processes with negligible impact on the overall dynamics, see e.g., [28]. The examples discussed above demonstrate how mathematical models provide valuable insights into relevant stem cell traits such as self-renewal, proliferation, or response to signals. They allow quantifying these traits and inferring trait differences between individual cells and trait evolution over

time. Mathematical models contribute to understand how processes on the level of single cells are integrated with regulatory signals and population dynamics. Modeling tools help to compose multiple insights to an increasingly complete picture of stem cell dynamics that can be applied to simulate clinical scenarios and to personalize treatment decisions [19•, 20••, 22••, 25••, 26••, 33•, 52•].

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Compliance with Ethical Standards

Conflict of Interest Thomas Stiehl and Anna Marciniak-Czochra declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies and experiments involving human or animal subjects performed by the authors have been previously published and complied with applicable ethical standards as defined in the Helsinki declaration and its amendments, institutional and national research committee standards, and international/national/institutional guidelines.

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