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Stem cell self-renewal in regeneration and cancer: Insights from mathematical modeling

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Abstract

Self-renewal is the process by which stem cells give rise to stem cells. Recent insights from experimental and theoretical models suggest that self-renewal not only influences the stem cell population but has a crucial impact on dynamics of non-stem cells. Efficient production of mature cells in tissue regeneration requires up-regulation of stem cell self-renewal. Increased self-renewal confers a competitive advantage on cancer cell clones by leading to aggressive expansion of both stem and non-stem cancer cells. Recent models suggest that self-renewal is the key parameter to understand clonal competition, selection and emergence of resistance in cancer cell populations.

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Keywords

Stem cell, Mathematical model, Self-renewal, Regeneration, Cancer, Resistance.

Introduction

Adult stem cells, also referred to as tissue stem cells, possess the ability to give rise to all cell types of a tissue. The most prominent example is provided by hematopoietic (blood forming) stem cells, which are responsible for formation of all blood cell types [1]. Other important examples include neural stem cells [2] and intestinal stem cells [3]. The ability to give rise to different types of mature cells is referred to as multipotency. Another important property of adult stem cells is the ability to maintain their own population throughout the life of an organism. This is accomplished by self-renewal, a process of stem cells giving rise to stem cells. The opposite scenario, where stem cells give rise to non-stem cells is referred to as differentiation [1]. Self-renewal affects not only the stem cell population but has a significant impact on time dynamics of non-stem cell populations. For this reason, self-renewal is most important in multiple physiological and pathological conditions over the life of multi-cellular organisms.

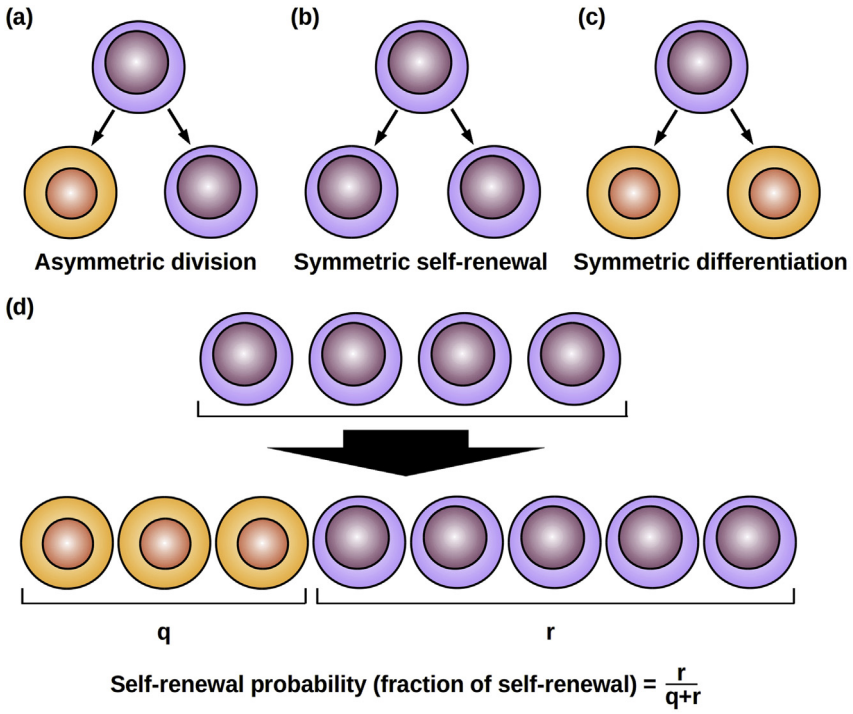
The dynamics of stem cell systems is dictated by a number of key parameters describing the stem cell self-renewal, proliferation, death, cell–niche interaction, flux of cells into various differentiation pathways and mutations. The multi-factorial nature of stem cell control seriously limits the intuitive interpretation of experimental data. Some parameters, such as self-renewal of stem cells, cannot be measured directly and predictions of the quantitative effects of system perturbations are inaccurate and frequently impossible without mathematical and computational modeling. In the following, we summarize recent modeling results underpinning the importance of self-renewal in health and disease.

Self-renewal on cellular and population level

On the cellular level two different scenarios of self-renewal exist [4]: asymmetric self-renewal in which a stem cell produces one stem cell and one non-stem stem cell, and symmetric self-renewal in which a stem cell produces two stem cells (Figure 1a, b). Another scenario, in which a stem cell produces two differentiated cells is referred to as symmetric differentiation (Figure 1c) [4]. All three have been observed [5–8]. If stem cells divided only asymmetrically, their population size would remain constant, assuming no death. Therefore, all scenarios where the stem cell population expands have to include symmetric divisions. It cannot be concluded from studies at the cell population level whether under homeostatic conditions stem cells divide only asymmetrically. Nevertheless, if in homeostatic conditions stem cells can die or be removed through symmetric differentiation, symmetric self-renewal is also required in homeostasis [9]. The biology of asymmetric divisions has been reviewed elsewhere [10,11]. The role of the different types of division in development, regeneration and cancer is summarized in Ref. [4].

To quantify self-renewal, the fraction of self-renewal (in the terms of a cell population) or probability of self-

Figure 1



Self-renewal on cellular and population level. (a) Asymmetric division: One progeny cell adopts the fate of the parent cell whereas the other adopts a more differentiated fate. (b) Symmetric self-renewal: Both progeny are of the same type as the parent cell. (c) Symmetric differentiation: Both progeny become more differentiated than the parent cell. (d) The fraction of self-renewal (self-renewal probability) is used to quantify self-renewal in large cell populations. It is the fraction of progeny that adopt the fate of the parent cell.

renewal (in the terms of a single cell) has been introduced [12,13] (Figure 1d). It is equal to the probability that a progeny cell is of the same cell type as the parent cell that gave rise to it. If the population is large and therefore robust to stochastic fluctuations, the fraction of self-renewal allows quantifying stem and non-stem cell dynamics without regard to the symmetric or asymmetric division mode. Cell labeling experiments [14–17] and dynamic imaging [18•] provide insights into proliferation and self-renewal properties of different cell types. Mathematical modeling is an important tool to interpret data obtained from labeling studies [17] and to check if they are in line with biological hypotheses [17,19••]. Treating somatic mutations as genetic labels allows to apply the mathematical theory of labeling experiments also to human tissues. For example, stochastic models and deep sequencing data can be used to study in vivo stem cell dynamics in human tissues [19••].

Self-renewal is an inherent feature of stemness

Different cell types comprising tissues are organized as a hierarchy. The stem cell population resides at the top of the hierarchy and gives rise to different types of progenitor cells which in turn produce precursors which finally give rise to mature cells [1]. From the point of view of population dynamics, the stem cell population is exceptional in the sense that it is the only cell population that is independent of influx of differentiating less specialized cells [14,20]. If we use this property as a definition of the stem cell population, stemness is a trait that emerges from the dynamic interaction of different cell populations [20]. If there exists a signal that down-regulates proliferation and self-renewal when there exist too many mature cells, mathematical models suggest that the stem cell population is also the one that needs less signal stimulation to maintain its size than all other cell populations [20]. It is usually accepted that stem cells divide slower than non-stem cells in order to reduce the number of somatic mutations in the stem cell population [21]. Since, hypothetically, death rates are small for all primitive cell types, this is mathematically equivalent to the assumption that stem cells have the highest self-renewal probability of all cells. How the number of non-stem cell types, their self-renewal potential and their proliferation rates influence the risk of mutations is studied in Ref. [22]. The relation of symmetric self-renewal and telomere length is addressed in Ref. [23••].

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