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Systems mapping of genes controlling chemotherapeutic drug efficiency for cancer stem cells

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Cancer can be controlled effectively by using chemotherapeutic drugs to inhibit cancer stem cells, but there is considerable inter-patient variability regarding how these cells respond to drug intervention. Here, we describe a statistical framework for mapping genes that control tumor responses to chemotherapeutic drugs as well as the efficacy of treatments in arresting tumor growth. The framework integrates the mathematical aspects of the cancer stem cell hypothesis into genetic association studies, equipped with a capacity to quantify the magnitude and pattern of genetic effects on the kinetic decline of cancer stem cells in response to therapy. By quantifying how specific genes and their interactions govern drug response, the model provides essential information to tailor personalized drugs for individual patients.

Introduction

The discovery of cancer stem cells in malignancies of hematopoietic origin and in some solid tumors has changed our vision of the biological processes involved in carcinogenesis and chemotherapeutic practices. Just as normal cells are maintained by self-renewing stem cells, malignant tumors are produced through the mutations of stem cells and their subsequent proliferation [1–5]. For example, leukemia is believed to arise from a stem cell that gives rise to a large population of clones that proliferate into malignancies. Therefore, by developing specific therapies targeted at cancer stem cells, malignant tumors can be controlled and prevented and, finally, eradicated through blocking the recurrence of cancer cells [6–8].

To make it effective to treat cancer based on the cancer stem cell hypothesis, two essential questions need to be addressed. First, how can we distinguish cancer stem cells from cancer non-stem cells in terms of their origin, property and function [3]? Second, through which mechanisms do cancer stem cells respond to chemotherapeutic drugs [9]? The availability of genetic, genomic and proteomic expression data provides an unprecedented opportunity to detect and define expression patterns of cancer stem cells and predict the clinical outcome of patients who receive a particular drug therapy [10,11]. By contrast, mathematical modeling has exemplified increasing vitality to uncover and explain many still unknown aspects of cell behavior, tissue function and network organization [12–14]. More recently, an avalanching interest has emerged in applying differential equations to quantify the proliferation and differentiation of normal stem cells and cancer stem cells and detect the differences of these two types of cells [14,15].

Wang *et al.* [16] have for the first time integrated expression data with mathematical models to identify genes and proteins or their expression patterns that are linked with the formation, proliferation and programming of cancer stem cells. This integration can potentially lead to understanding of the genetic and molecular mechanisms of carcinogenesis and the complexity of its progress and dynamics. Here, we argue that the model described by Wang *et al.* can be reformed to map genes that control the response of cancer stem cells to chemotherapeutic drugs. The new model is constructed on a mapping approach – systems mapping – by incorporating chemotherapeutic drug efficacy that describes the kinetic reduction of abnormal cell populations in response to therapy [17,18]. It provides an analytical tool to test the temporal effects of genes on drug response and can be used to assess the efficacy of treatments in arresting tumor growth.

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Systems mapping

The formation of phenotypic traits is one of the most complex processes in nature. Traditional approaches for genetic dissection of complex traits is to associate genetic variation with phenotypic variation in a trait measured at a particular time point. These approaches have proven to be instrumental for identifying quantitative trait loci (QTLs), but they have not considered the complexity and dynamics of phenotypic formation. A new computational model, known as systems mapping, has been recently developed to enhance the biological relevance of QTL mapping [19]. Systems mapping views a complex phenotype as a dynamic system, dissects it into its underlying interconnected components and organizes and connects different components through mathematical equations in biological laws [20,21]. By mapping specific genes that govern each component and its mutual connections with other components, this model has a capacity to help understand not only the behavior of the components but also how these components act together to form the behavior of the whole. As a bottom–top model, a systems approach can identify specific QTLs that govern the developmental interactions of different components that lead to the function and behavior of the system. By estimating and testing mathematical parameters that specify the system, systems mapping enables the prediction or alteration of the physiological status of a phenotype based on the underlying genetic control mechanisms.

Genetic mapping of complex traits is constructed by a mixture model in which different mixture components are presented by QTL genotypes that are segregating among individuals in a mapping population [22,23]. Because QTLs cannot be observed directly, the proportions of mixture components are specified by conditional probabilities of QTL genotypes given observable marker genotypes. Phenotypic values of individuals carrying a particular QTL genotype are assumed to follow a distribution function, such as the normal distribution, characterized by expected mean (denoted as the genotypic mean) and variance. Systems mapping embeds a system of ordinary differential equations (ODEs) into a genetic mapping setting containing dynamic measures of phenotypic values. Unlike traditional approaches that estimate genetic effects directly, systems mapping specifies and estimates genotype-specific mean vectors by ODE parameters and a covariance matrix by a parsimonious statistical model. Mathematical tools, like the fourth-order Runge–Kutta algorithm, have been incorporated to estimate ODE parameters for individual QTL genotypes contained within a mixture-model framework [24,25]. Structural approaches have been used to model the covariance matrix for longitudinal traits, which include (i) parametric stationary [26], (ii) parametric nonstationary [26,27], (iii) nonparametric [28] and (iv) semiparametric models [28]. Each of these approaches has advantages and disadvantages regarding computing efficiency, flexibility and power.

Mapping QTLs for chemotherapeutic efficiency

Mathematical models for efficacy of a chemotherapeutic drug

Based on the cancer stem cell hypothesis [29], Ganguly and Puri [12] described a basic model for healthy and cancer stem cell pathways (Fig. 1). Normal stem cells (SC) are of two types, one that performs self-renewal with a probability, P_{SC}, and the other

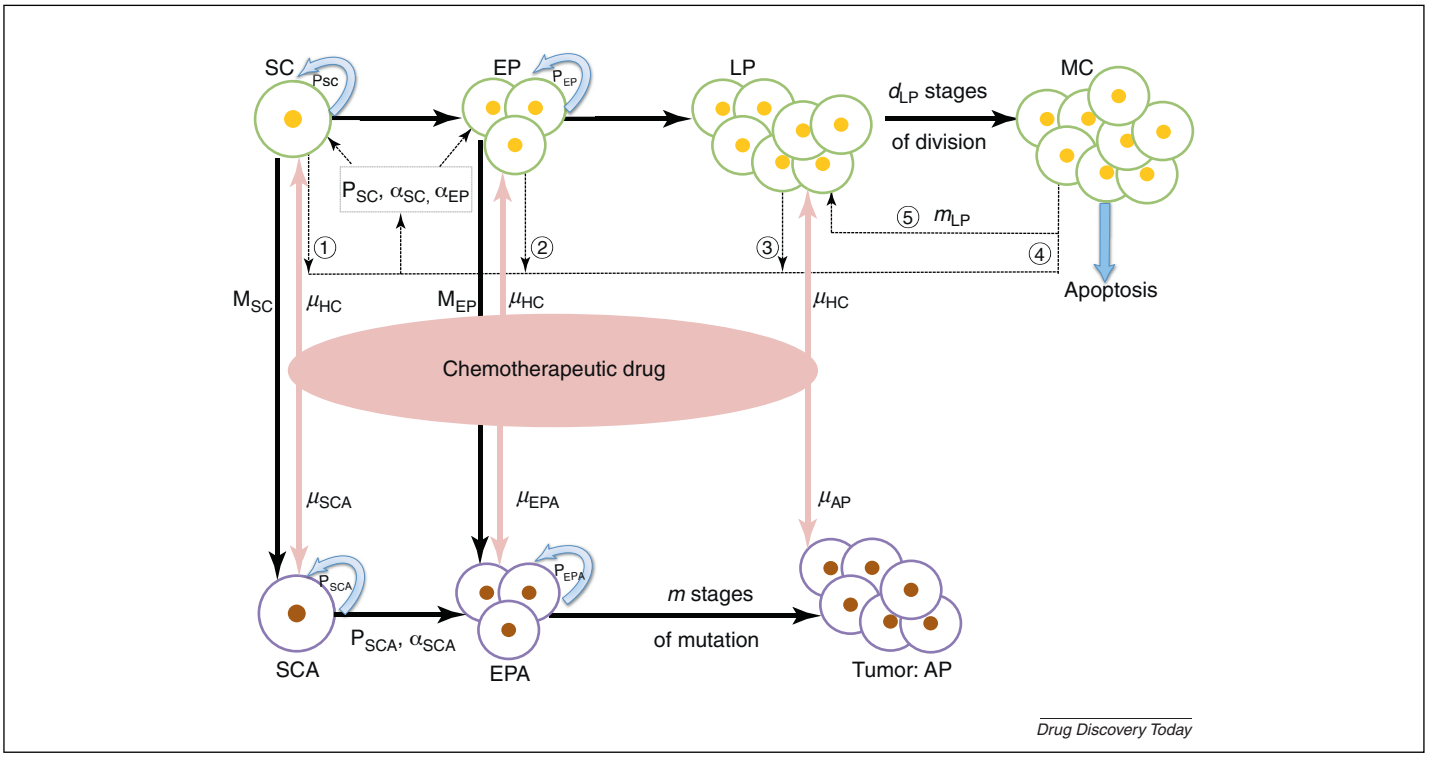

FIGURE 1

Cancer stem cell model showing the cell signaling pathway and the action of a chemotherapeutic drug. Arrowed dotted lines represent a direction of regulatory feedback signals of one process to others, numbered from (1) to (5). SC, normal stem cell; EP, early progenitor cells; LP, late progenitor cell; MC, mature cell; SCA, abnormal stem cell; EPA, abnormal early progenitor cell; AP, abnormal progeny. For the definitions of parameter symbols, see the text. Adapted, with permission, from Ganguly and Puri [30].

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