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ORIGINAL PAPER

Stochastic model of the formation of cancer metastases via cancer stem cells

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Abstract The author presents Monte Carlo simulations of the temporal kinetics of the formation of cancer metastases with emphasis on cancer stem cells. The model used implies the existence of premetastatic niches. The population of cancer stem cells located outside tumors and inducing the formation of new tumors in niches is considered to be heterogeneous. If the niches are equivalent with respect to the formation of metastases, the kinetics are predicted to exhibit an induction period and then rapid growth of the number of metastases. If the niches are heterogeneous, the kinetics are found to be more gradual.

Keywords Cancer · Metastases · Cancer stem and progenitor cells · Premetastatic niches · Proliferation, differentiation and death of cells · Mean-field kinetic equations · Monte Carlo simulations

Introduction

To some extent, our life is reduced to a multitude of biochemical processes occurring on very different scales. Such processes are often inherently stochastic. In our cells, for example, most genes exist at single or low copy numbers, the number of mRNA and regulatory proteins is often low, and accordingly the gene-transcription kinetics frequently exhibit stochastic features (Paulsson 2004; Kaern et al. 2005). Another important example of the stochasticity occurring on a larger scale is the formation of cancer metastases. The analysis of such stochastic processes is obviously of high interest from very different perspectives.

Concerning cancer, it is appropriate to recall that in the developed countries this is one of the major causes of premature deaths. For this reason, cancer has long attracted attention of the research community. The understanding of the mechanistic details of cancer is however still far form complete, because the disease occurs on very different time and length scales (from a single cell to macroscopic tumors) and includes the interplay of a multitude of factors. The treatments of cancer are known to fail often. One of the key problems here is that the growth of a primary cancer tumor is usually accompanied by the formation of metastases already at the early stages, so that approximately 90% of all cancer deaths arise from the metastatic spread of primary tumors (Christofori 2006).

The uncertainty in the basic knowledge of the molecular biology of cancer is manifested in the debate about the specific features of the cells initiating tumors (Abbott 2006; Moore and Lemischka 2006; Morrison and Kimble 2006). Traditionally, the population of cancer cells was and is still often considered to be uniform so that each cancer cell may cause the formation of a metastasis. Numerous clinical observations that the structure of mature tumors is heterogeneous and that particular tumor types metastasize preferably in particular organs are indicative that the cancer cells are actually heterogeneous. In the mid-1990s, this issue was addressed quantitatively by seeding leukemia or tumor growth in mice by transplantation of human-leukemia cells [see the studies by Lapidot et al. (1994) and Bonnet and Dick (1997), a review by Lobo et al. (2007), and recent debates by Kelly et al. (2007), Kennedy et al. (2007), and

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Adams et al. (2007)]. Such experiments showed that tumors are initiated by only a minute proportion [from 10^{-7} to 10^{-4}; however, see Kelly et al. (2007)] of the cancer cells. These tumor-initiating cells are able to self-renew and to spawn many different kinds of cancer cells. Basically, the latter feature is typical of stem cells. For this reason, the tumor-initiating cells are usually classified as *cancer stem cells*.

Studies of cancer stem cells responsible for leukemia are numerous (Krivtsov et al. 2006; Lobo et al. 2007). More recently, cancer stem cells have been identified in a variety of human tumors [see general reviews by Ailles and Weissman (2007), Barnhart and Simon (2007), Giordano et al. (2007), Hill and Perris (2007), Keith and Simon (2007), and Lee and Herlyn (2007)] including those in breast (Al-Hajj et al. 2003; Sleeman and Cremers 2007; Stingl and Caldas 2007), brain (Singh et al. 2004; Clark et al. 2007), colon (Shibata 2008), prostate (Nikitin et al. 2007), and skin (Schatton et al. 2008; Schatton and Frank 2008). Within a given tumor, the fraction of cancer stem cells is typically less than 1% (Ailles and Weissman 2007; Lee and Herlyn 2007) and they have hundreds of genes expresed distinctly (Ailles and Weissman 2007).

The normal stem cells typically function in niches (Moore and Lemischka 2006; Scadden 2006). Physically, stem cell niches represent microscopic compartments formed of environmental cells that nurture stem cells and enable them to maintain tissue homeostasis. The cancer stem cells seem to function in niches or, more specifically, in premetastatic niches as well. The available experimental studies indicate that the cancer stem cells may use the niches of conventional stem cells (Ailles and Weissman 2007). Alternatively, tumors seem to be able to produce factors that induce the formation of premetastatic niches in organs where metastases will ultimately develop [see the reports by Kaplan et al. (2005), Hiratsuka et al. (2006) and reviews by Li et al. (2007), Sleeman and Cremers (2007), and Yilmaz et al. (2007)].

The conventional stem cells and their malignant counterparts share many intrinsic and extrinsic factors to regulate self-renewal, differentiation and proliferation pathways (Giordano et al. 2007). In analogy with conventional stem cells, the cancer stem cells exhibit higher resistance to various chemotherapeutic approaches (Lagasse 2008) and to radiation (Rich 2007). For new treatment options related to the concept of cancer stem cells, see, e.g., a recent report by Dieguez-Acuna et al. (2007).

Kinetic models describing various aspects of cancer are numerous [see a comprehensive review by Araujo and McElwain (2004) and more recent reviews by Byrne et al. (2006), van Leeuwen et al. (2006), Sanga et al. (2006), Bellomo and Maini (2007), Sanga et al. (2007), and Roose et al. (2007)]. The bulk of the models is focused on the growth of a primary tumor. The models of the formation of metastases are available as well [see the already mentioned review by Araujo and McElwain (2004) and recent original articles by Iwata et al. (2000), Peter and Semmler (2004), Hanin et al. 2006, Hochedlinger and Jaenisch (2006), and Fedotov and Iomin (2007)]. This process is usually described by employing the phenomenological temporal mean-field (MF) integral equations (Iwata et al. 2000), phenomenological temporal stochastic equations (Hanin et al. 2006), temporal MF models including compartments (Peter and Semmler 2004), and spatio-temporal Monte Carlo (MC) simulations (Peter and Semmler 2004; Fedotov and Iomin 2007). In all these models, the population of the cells, proliferating and initiating metastases, is considered to be uniform and the cancer stem cell issue is not addressed.

In recent literature, one can find a few temporal models taking into account cancer stem cells (Michor et al. 2005; Ganguly and Puri 2006, 2007; Dingli et al. 2007;Komarova 2007) and an 1D spatio-temporal model (Komarova 2007). In these models, the formation of cancer metastases is not analyzed.

Our introduction above indicates that now it is timely to explicitly incorporate the specifics of cancer stem cells into the analysis of the stochastic kinetics of formation of cancer metastases. In this article, we follow this line.

Model

According to the standard hierarchy (Hochedlinger and Jaenisch 2006), the adult mammalian cells can be subdivided into three groups including (1) multipotent stem cells, (2) progenitor cells, and (3) terminally differentiated cells. In practice, the difference between the cells of the first two categories is often vague. This means that basically these cells represent a heterogeneous population. In our model, the cancer stem and progenitor cells are considered to be of N types.

The proliferation and differentiation of cancer stem cells and formation of primary and secondary tumors are considered to take place in the premetastatic niches. Specifically, the model implies the existence of $\mathcal{N}$ niches. As noted in the introduction, the cancer stem cells may use the niches of conventional stem cells or, alternatively, tumors may produce factors that induce the formation of new niches. In the latter case, the number of premetastatic niches may depend on time. In our present simulations, we assume that during the formation of metastases $\mathcal{N}$ is constant. This assumption is of course not always reasonable and if necessary should be relaxed.

To some extent, the concept of "premetastatic niches" is similar to that of "compartments". In the available models (see, e.g., Peter and Semmler (2004) and references therein), the compartments are however considered to be

macroscopic so that there is reversible exchange of cells between them. In contrast, the niches for stem cells typically contain only a few cells. Thus, the role of premetastatic niches is reduced to initiation of the formation of tumors. For this reason, the way we use below to describe niches is different compared to that employed usually for compartments.

In general, the approximations used to describe tumors and the cancer stem and progenitor cells, located outside tumors and inducing the formation of new tumors, depend on the relationship between the time scales of various processes. The time scale of formation of metastases is often longer than that characterizing diffusion of cells in a body. For this reason, we consider that the cancer stem and progenitor cells are well mixed and do not explicitly analyze diffusion of cells. Thus, our attention is focused on temporal kinetics.

With the specification above, the MF equation for the probability of the metastasis formation in niche $i(1 \leq i \leq \mathcal{N})$ is as follows

$$dP_i/dt = \sum_j \kappa_{ij} N_j (1 - P_i), \tag{1}$$

where j ($1 \leq i \leq N$) is the subscript characterizing the type of cells, N_j is the number of the cancer stem and progenitor cells located outside tumors, $(1-P_i)$ is the probability that niche i does not contain cancer cells, and κ_{ij} is the rate constant of the matastasis formation in niche i due to its interaction with cells j. Initially (at $t = 0$), the cancer is considered to be associated with the niche with $i = 1$. Thus, the initial condition for Eq. (1) is $P_i = 1$ for $i = 1$ and $P_i = 0$ for $1 < i \leq \mathcal{N}$.

For the cell population located outside tumors, we use

$$dN_j/dt = \sum_k f_{kj} \mu_k P_k - r_j N_j, \tag{2}$$

where μ_k is the rate of cell generation by the tumor associated with niche k, f_{kj} is the distribution of the newly generated cells defined for each tumor so that $\sum_j f_{kj} = 1$, and r_j is the rate constant of cell death. In addition, the equation for N_j may contain the terms describing reduction of N_j due to the formation of metastases and the interaction of cells with tumors. The use of Eq. (2) implies that the rates of the latter two processes are low compared to the rate of cell death, and accordingly the corresponding terms are neglected. Usually, this approximation is fairly robust. The number of tumors, for example, is much smaller that the number of the cancer cells located outside tumors. This means that the contribution of the reduction of N_j due to the formation of metastases to the balance of cells is negligible.

In general, the rate constant μ_k and distribution f_{kj} depend on the time interval after the formation of metastasis k. Although this effect can easily be incorporated into the model, we consider that μ_k and f_{kj} are independent of time in order to keep the presentation compact.

The death rate constants r_j are partly associated with the interplay between cancer and the immune system. At the late stages of cancer, the immune system deteriorates and accordingly r_j decrease. We are interested in the initial stages of the formation of metastases. In this case, it makes sense to keep r_j constant.

The time scale of the formation of metastases is usually longer than that characterizing the generation and death of cancer cells located outside tumors. For this reason, we can use the steady-state approximation in order to solve Eq. (2). This approximation yields

$$N_j = \sum_k f_{kj} \mu_k P_k / r_j. \tag{3}$$

Substituting this expression into Eq. (1), we obtain

$$dP_i/dt = \sum_{jk} \kappa_{ij} f_{kj} \mu_k P_k (1 - P_i)/r_j. \tag{4}$$

The equations introduced and derived above form a mathematical basis for our simulations.

Algorithm of simulations

Equation (4) can be integrated numerically. This procedure corresponds to the MF approximation, because it ignores fluctuations. The initial stages of the formation of metastases are however inherently stochastic, because the number of metastases is small. For this reason, we perform stochastic MC simulations of the formation of metastases. Specifically, we use a hybrid MC algorithm based on the MF steady-state approximation for cells [such algorithms are often employed to simulate the systems containing subsystems with small and high numbers of particles (Zhdanov 2007)]. This approximation resulting in expression (3) is accurate, because the number of cells is large, and accordingly it can be combined with the conventional MC technique for metastases. Using expression (3), we should perform MC simulations corresponding to Eq. (4). To realize the latter procedure, we employ the standard MC algorithm based on the calculation of the total rate of rate processes under consideration (Gillespie 1977; Landau and Binder 2000).

To run MC simulations, we introduce the discrete variables n_i, defined for niches so that $n_i = 0$ and 1 correspond to the situations before and after the formation of a tumor in niche i. If niche i is healthy (i.e., $n_i = 0$), the corresponding rate of the metastasis formation is given by [cf. Eq. (4)]

$$w_i = \sum_{jk} \kappa_{ij} f_{kj} \mu_k n_k / r_j. \quad (5)$$

The total rate of the metastasis formation is

$$w_{\text{tot}} = \sum_i w_i, \quad (6)$$

where the summation is considered to take into account the niches with $n_i = 0$.

With the specification described, the MC algorithm consists of sequential trials of the formation of new metastases. For each MC trial, we calculate w_{tot}, choose one of the healthy niches with probability w_i / w_{tot}, and switch n_i from 0 to 1. After a trial, time is incremented by $|\ln(\rho)|/w_{\text{tot}}$, where ρ $(0 < \rho \leq 1)$ is a random number. The initial condition for each MC run is $n_i = 1$ for $i = 1$ and $n_i = 0$ for $i > 1$.

Results of simulations

Although our model is conceptually simple, it contains a lot of parameters and makes it possible to illustrate the role of various factors in the kinetics of the formation of metastases. In this study, we focus attention on the role of the heterogeneity of premetastatic niches with respect to the formation of tumors. Specifically, we show typical kinetics predicted for two very different distributions of κ_{ij}. The other model parameters are chosen and fixed so that the time scale of the formation of metastases is physically reasonable.

To introduce the parameter values, we first note that in general the number of premetastatic niches is large. Due to the heterogeneity of niches, the initial stages of the formation of metastases are expected to be related to a limited number of niches. At present, it is not quite clear how high this number is. To be specific, we use $\mathcal{N} = 20$. The heterogeneity of cells is assumed to be minimal, i.e., we consider that there are only one type of cancer stem cells and one type of progenitor cells. This means than $N = 2$ and j is either 1 or 2 (these values of j correspond to stem and progenitor cells, respectively). The distribution f_{kj} is assumed to be the same for all the niches. In particular, the probabilities of generation of stem and progenitor cells are considered to be $f_{k1} = 0.1$ and $f_{k2} = 0.9$. The ratio of the rate constants of cell generation and death is fixed as $\mu_k/r_j = 100$.

The first set of simulations was performed for the case when all the premetastatic niches are equivalent with respect to the formation of metastases. Specifically, the rate constants of the metastasis formation were fixed as $\kappa_{i1} = 5 \times 10^{-4}$ mon^{-1} (mon $\equiv$ month) and $\kappa_{i2} = 0.01\ \kappa_{i1}$. The corresponding kinetics (Fig. 1) exhibit an induction period (about 15 months) and then rapid growth of the number of metastases. The transition from slow growth to rapid growth is related to the positive feedback between the rates of the formation of metastases and the generation of cancer cells located outside tumors.

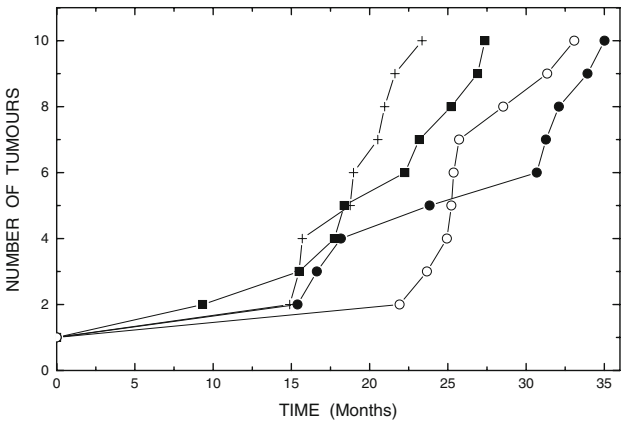

Fig. 1 Typical kinetics (four MC runs) of the formation of first ten tumors in the case when the premetastatic niches are equivalent with respect to the formation of metastases. The corresponding rate constants are $\kappa_{i1} = 5 \times 10^{-4}$ mon^{-1} and $\kappa_{i2} = 0.01\ \kappa_{i1}$

The second set of simulations was executed for the case when the premetastatic niches are strongly heterogeneous with respect to the formation of metastases. Specifically, the rate constants of the metastasis formation were chosen as $\kappa_{i1} = 10^{-3}\ \xi_i$ mon^{-1} and $\kappa_{i2} = 0.01\ \kappa_{i1}$, where $\xi_i (0 < \xi_i \leq 1)$ are random numbers. The corresponding kinetics presented in Fig. 2 are typically much more gradual compared to those shown in Fig. 1, because now in the course of the disease the positive feedback between the rates of the formation of metastases and the generation of cancer cells, located outside the tumors, is partly compensated by the decrease of the rate constants κ_{ij} of the remaining healthy

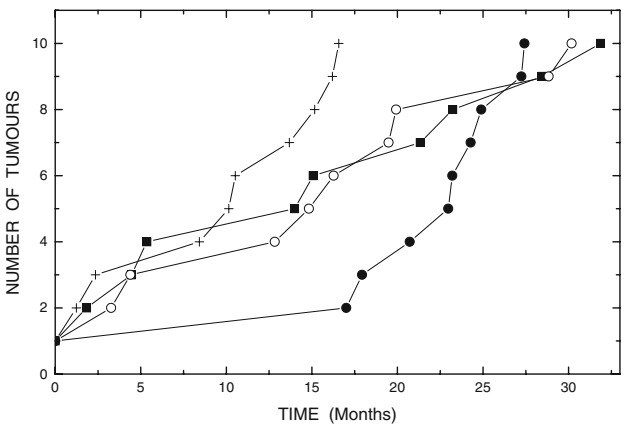

Fig. 2 As Fig. 1 for the case when the premetastatic niches are heterogeneous with respect to the formation of metastases: $\kappa_{i1} = 10^{-3}\ \xi_i$ mon^{-1} and $\kappa_{i2} = 0.01\ \kappa_{i1}$. Each MC run was performed with its own set of the random numbers $\xi_i (0 < \xi_i \leq 1)$

niches (note that the formation of metastases is more likely in niches with high values of κ_{ij}).

Conclusion

In summary, we have proposed a generic kinetic model of the initial stages of the formation of cancer metastases with emphasis on cancer stem cells. The model implies the existence of premetastatic niches and the heterogeneity of the population of cancer stem cells, located outside tumors and inducing the formation of new tumors in niches. Employing a hybrid MC algorithm, we have illustrated the likely kinetics of the formation of metastases.

At present the accurate experimental data on the kinetics of the formation of the first metastases are still lacking, because the reliable identification of such metastases is far from trivial. For this reason, we do not try to explicitly interpret specific experiments. Our article is rather suitable for general readership. In other words, our simulations are complementary to the available experimental studies (see the introduction) indicating that the cells inducing cancer metastases can be classified as cancer stem cells.

Finally, it is appropriate to articulate that although the simulations presented (Figs. 1, 2) are focused on the dependence of the kinetics on the heterogeneity of premetastatic niches with respect to the formation of tumors, our model makes it possible to scrutinize the role of many other factors as well. Introducing the model, we noted that some of the assumptions used do not always hold. For this reason, our article also opens up ways of modifications of the model proposed and/or constructing alternative models of the formation of cancer metastases induced by cancer stem cells. The ultimate goal of such models should be the suitability for analysis and interpretation of clinical data and the ability to make quantitative predictions. At present, we are obviously far from this goal because the understanding of the role of cancer stem cell in the formation of metastases is far from complete and the quantitative experimental data for validation of the model parameters are nearly lacking. Our model is just the first step towards the ultimate goal.

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