Kinetics of the formation of cancer metastases via induced premetastatic cancer-stem-cell niches

Vladimir P. Zhdanov*

Department of Applied Physics, Division of Biological Physics, Chalmers University of Technology, S-41296 Göteborg, Sweden and Boreskov Institute of Catalysis, Russian Academy of Sciences, Novosibirsk 630090, Russia

(Received 16 January 2009; revised manuscript received 15 March 2009; published 10 June 2009)

The author presents a kinetic model describing the formation of new metastases by cancer stem cells in premetastatic stem-cell niches induced by the factors produced by a primary tumor and already formed metastases. The corresponding kinetics is analyzed by employing mean-field kinetic equations and Monte Carlo simulations. In agreement with observations, the model predicts a long latent period with low rate of the metastase growth followed by explosive increase in the number of metastases. The duration of the latent period is found to depend on a multitude of rate constants characterizing various processes.

DOI: 10.1103/PhysRevE.79.061913 PACS number(s): 87.18.Hf, 05.40.−a

I. INTRODUCTION

The understanding of the mechanistic details of cancer in general and the formation of cancer metastases in particular is still far from 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. Often, the population of cancer cells is considered to be uniform so that each cancer cell may cause the formation of a metastasis. Recent experimental studies of human cancer tumors in brain [1,2], colon [3], prostate [4], and skin [5,6] indicate however that metastases are formed by a small fraction of cancer cells which, due to their properties, can be qualified as cancer stem cells (see reviews [7–9]).

In analogy with normal stem cells [10,11], cancer stem cells seem to function in niches. Physically, the 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 may use niches of conventional stem cells [12], or alternatively, tumors seem to be able to produce factors that induce the formation of premetastatic niches in organs where metastases will ultimately develop [7–9]. For example, tumor cells can generate premetastatic niches by recruiting hematopoietic progenitor cells to home to tumor-specific premetastatic sites and to form cellular clusters before the arrival of tumor cells [13]. In another example, the primary tumors have been found to induce expression of the inflammatory chemoattractants by lung endothelium and myeloid cells, which in turn facilitates cancer cell colonization of premetastatic sites within the lung [14].

Numerous kinetic models describing various aspects of cancer are focused mainly on the growth of a primary tumor (see reviews [15–21]). The models of the formation of metastases are available as well (see a brief review in Ref. [22]), but the cancer-stem-cell issue is usually not addressed there. The formation of metastases via cancer stem cells has recently been simulated in our work [22] implying the existence of preformed premetastatic niches. In our present study, we formulate a generic kinetic model describing the formation of new metastases in premetastatic stem-cell niches induced by the factors produced by a primary tumor and already formed metastases.

II. MODEL

In our model, as already noted, the premetastatic stem-cell niches, $\mathcal{N}$, are considered to be formed via interaction of the species (e.g., hematopoietic progenitor cells [13]), $\mathcal{P}$, recruited and/or emitted by a primary tumor and already formed metastases, $\mathcal{M}$ ($\mathcal{M}$ includes the primary tumor). The rate of this process is proportional to the number of sites, where the $\mathcal{N}$ formation is possible. In addition, this rate should be dependent on the $\mathcal{P}$ concentration, c. We assume that each $\mathcal{P}$ can induce the $\mathcal{N}$ formation, i.e., this process can formally be represented as

$$\mathcal{P} \rightarrow \mathcal{N}, \tag{1}$$

and its rate is proportional to c.

Each $\mathcal{N}$ can be converted into $\mathcal{M}$. This process is considered to be initiated by a single cancer stem cell ($\mathcal{S}$),

$$\mathcal{N} + \mathcal{S} \rightarrow \mathcal{M}, \tag{2}$$

and its rate is proportional to the $\mathcal{S}$ concentration, C, outside the primary tumor and metastases.

$\mathcal{P}$ and $\mathcal{S}$ are emitted by $\mathcal{M}$,

$$\mathcal{M} \rightarrow \mathcal{M} + \mathcal{P}, \tag{3}$$

$$\mathcal{M} \rightarrow \mathcal{M} + \mathcal{S}. \tag{4}$$

In addition, we have degradation of $\mathcal{P}$, $\mathcal{S}$, and $\mathcal{N}$,

$$\mathcal{P} \rightarrow \varnothing, \tag{5}$$

$$\mathcal{S} \rightarrow \varnothing, \tag{6}$$

$$\mathcal{N} \rightarrow \varnothing. \tag{7}$$

The $\mathcal{M}$ degradation is neglected.

According to the scheme above, the $\mathcal{N}$ balance is determined by steps (1), (2), and (7), and the equation for the number of $\mathcal{N}$ is represented as

*zhdanov@catalysis.ru

$$dn/dt = k_p c - k_m nC - k_d n, \tag{8}$$

where k_p and k_m are the rate constants of the formation of $\mathcal{N}$ and $\mathcal{M}$ [steps (1) and (2)], respectively, and k_d is the rate constant of $\mathcal{N}$ degradation [step (7)]. In reality, the $\mathcal{N}$-formation rate is proportional to the number of sites, where this process is possible. In our model, this number is included to k_p. This can be done provided that the number is large and its reduction due to the formation of metastases is negligible.

The equation for the number of $\mathcal{M}$ is given by

$$dN/dt = k_m nC. \tag{9}$$

This number is defined so that $N=1$ corresponds to the primary tumor.

To operate with Eqs. (8) and (9), we need the kinetic equations for c and C. These concentrations are determined primarily by the interplay of the $\mathcal{P}$ and $\mathcal{S}$ emission (by $\mathcal{M}$) and degradation [steps (3)–(6)] because these processes are much more frequent than steps (1) and (2). Neglecting the latter steps, we obtain

$$dc/dt = r_e N - r_d c, \tag{10}$$

$$dC/dt = \kappa_e N - \kappa_d C, \tag{11}$$

where r_e, r_d, κ_e, and κ_d are the corresponding rate constants.

The time scale of the metastase formation is from one year to a few years. On this time scale, the emission and degradation processes described by Eqs. (10) and (11) are rapid, and accordingly these equations can accurately be solved by using the steady-state approximation as

$$c = r_e N/r_d \text{ and } C = \kappa_e N/\kappa_d. \tag{12}$$

Substituting these expressions into Eqs. (8) and (9) yields

$$dn/dt = k_1 N - k_2 n - k_3 nN, \tag{13}$$

$$dN/dt = k_3 nN, \tag{14}$$

where

$$k_1 \equiv k_p r_e/r_d, \quad k_2 \equiv k_d, \text{ and } k_3 \equiv k_m \kappa_e/\kappa_d. \tag{15}$$

In combination with the initial conditions,

$$n(0) = 0 \text{ and } N(0) = 1, \tag{16}$$

Eqs. (13) and (14) form a mathematical basis of our model.

III. ANALYSIS

Equations (13) and (14) can easily be integrated numerically. From the tutorial point of view, it is instructive to note that for biologically reasonable parameters Eq. (13) can be solved using the steady-state approximation as

$$n = k_1 N/(k_2 + k_3 N). \tag{17}$$

Substituting this expression into Eq. (14) results in

$$\frac{dN}{dt} = \frac{k_1 k_3 N^2}{k_2 + k_3 N}. \tag{18}$$

Integrating the latter equation, we obtain an approximate analytical expression for the kinetics under consideration

$$\frac{k_2}{k_1 k_3}\left(1 - \frac{1}{N}\right) + \frac{1}{k_1}\ln(N) = t. \tag{19}$$

Equation (18) [or Eq. (19)] indicates that in general the model predicts two qualitatively different regimes of explosive kinetics. The first regime occurs if $k_3 N > k_2$ (note that $N \geq 1$, and accordingly this condition is fulfilled if $k_3 > k_2$). In this case, one can neglect k_2 in the denominator of Eq. (18) and get

$$dN/dt \simeq k_1 N \text{ or } N \simeq \exp(k_1 t).$$

This exponential kinetics does not exhibit a latent period and accordingly is not of interest in our context.

The second regime takes place when $k_3 N \ll k_2$ (this condition is fulfilled during the initial stage if $k_3 \ll k_2$). In this case, one can neglect $k_3 N$ in the denominator of Eq. (18) and obtain

$$\frac{dN}{dt} \simeq \frac{k_1 k_3 N^2}{k_2} \text{ or } N = \frac{k_2}{k_2 - k_1 k_3 t}.$$

This kinetics exhibits a latent period followed by a collapse ($N \to \infty$) at

$$t \to t_* \equiv k_2/(k_1 k_3). \tag{20}$$

With increasing N, the condition $k_3 N \ll k_2$ does not however hold, one cannot neglect $k_3 N$ in the denominator of Eq. (18), and eventually (at $t > t_*$) the growth will be exponential. Thus, t_* can be considered as an estimate of the duration of the latent period.

If $k_3 \ll k_2$ and we use Eqs. (13) and (14) or Eq. (18), the model predicts (see below) in agreement with our analysis above that the latent period (at $t < t_*$) is followed by exponential growth at $t > t_*$.

Using expression (15) for k_1, k_2, and k_3, we can represent t_* as

$$t_* = \frac{k_d r_d \kappa_d}{k_p r_e k_m \kappa_e}. \tag{21}$$

This expression shows that the duration of the latent period depends on the ratio of a multitude of rate constants characterizing various processes and that the change in each rate constant results in increase or decrease in this period.

One may ask: is there any chance that for some of the parameters metastases can be inhibited? Formally, according to our model, the response to this interesting question is "no" because asymptotically (at $t \to \infty$) the model always predicts $N \to \infty$. In reality, however, the situation is not so hopeless even if we are limited by the framework of our assumptions because, as already noted above, t_* depends on a multitude of rate constants and there are chances to increase it appreciably.

IV. EXAMPLES

In our model, the dependence of n and N on t is determined by Eqs. (13) and (14). To show the typical kinetics predicted by these equations, we should choose biologically reasonable values of the rate constants k_1, k_2, and k_3. As

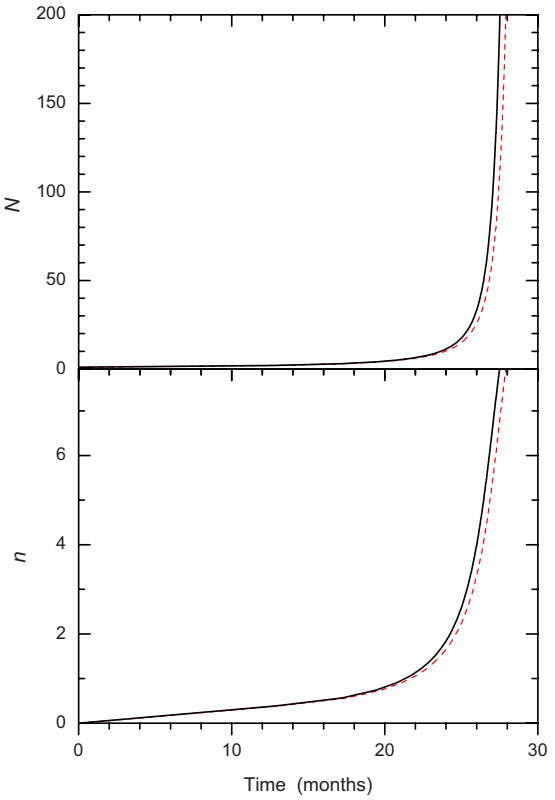

FIG. 1. (Color online) Deterministic kinetics of the formation of metastases according to Eqs. (13) and (14) (solid lines) and Eqs. (17) and (19) (dashed lines).

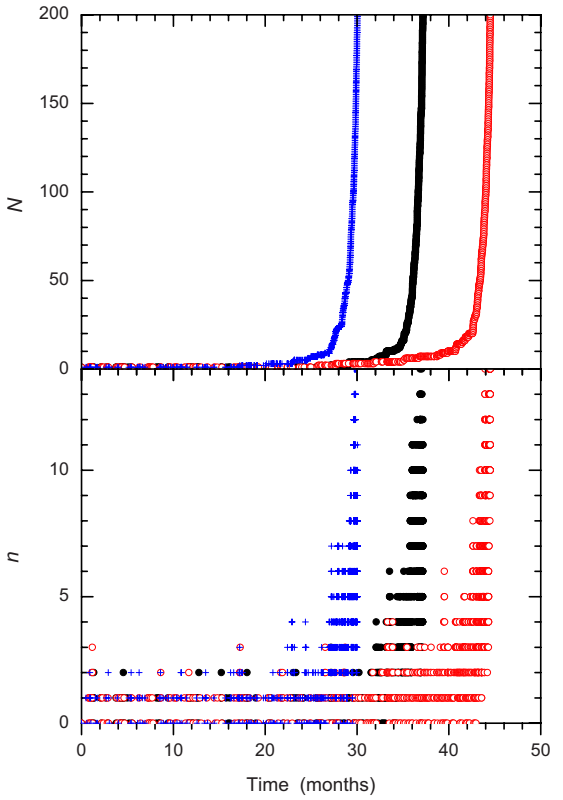

FIG. 2. (Color online) Three MC runs of the stochastic kinetics of the formation of metastases. The data points are shown after each change in N and/or n.

already noted, the time scale of the metastase formation is about one year or longer. This means that k_3 should be about 0.2 mon^{-1} (mon≡month) or lower. For example, we use $k_3=0.2$ mon^{-1}. The formation and degradation of premetastatic niches are expected to occur faster, and we choose $k_1=2$ mon^{-1} and $k_2=10$ mon^{-1}. The results of integration of Eqs. (13) and (14) with these parameters are shown in Fig. 1 by solid lines. The model is seen to predict a long latent period with very low rate of the metastase growth followed by explosive increase in the number of metastases. The duration of the latent period is about 25 months. This value is in perfect agreement with expression (20).

Kinetics (17) and (19), derived using the steady-state approximation (17) for n, are presented in Fig. 1 as well (dashed lines) for comparison. The corresponding curves are very close to those predicted by Eqs. (13) and (14). This means that the steady-state approximation for n is very good (for c and C [expression (12)], the situation is similar).

In addition to deterministic calculations (Fig. 1), we have performed Monte Carlo (MC) simulations of the kinetics corresponding to Eqs. (13) and (14) by using the standard Gillespie algorithm. The stochastic kinetics (Fig. 2) is found to be similar to the deterministic ones. The only new feature in the MC runs is that there is a relatively broad distribution of the duration of the latent period as shown in Fig. 3. Note that the most probable value of the latent period, 26 months, is close to the value, 25 months, predicted by expression (20). The distribution is however asymmetric, and the average MC value of the latent period, 44 months, is longer than the most probable one by a factor of 1.7.

V. CONCLUSION

In summary, we have proposed a kinetic model describing the formation of new metastases by cancer stem cells in premetastatic stem-cell niches induced by the factors produced by a primary tumor and already formed metastases. Despite its simplicity, the model predicts biologically reasonable kinetics of the metastase formation (Figs. 1 and 2) including a long latent period followed by explosive increase in the number of metastases. These basic kinetic features are

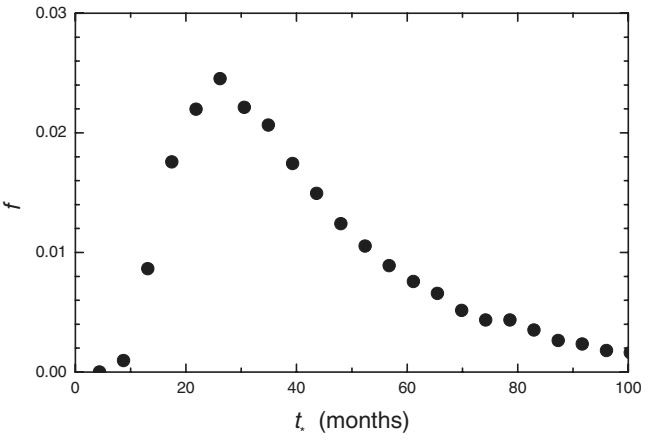

FIG. 3. Distribution of the duration of the latent period obtained using 10^4 MC runs. The duration of the latent period was defined as the time when N becomes to be equal to 200.

much more realistic compared to those obtained with our earlier model [22].

Some other more specific features predicted by our model help to understand what may happen in the cancer scenario under consideration. For example, our analysis shows that the duration of the latent period [Eq. (21)] depends on a multitude of rate constants characterizing various processes. This indicates that experimental identification of all the corresponding factors may be far from trivial.

Finally, it is appropriate to note that in order to articulate the key ingredients of our present model we have deliberately omitted many less important details. In reality, for example, the sites, where the niche formation is possible, are expected to be heterogeneous; the rate of emission of species by metastases depends on the metastase size, etc. Many such details missing in our present treatment can easily be incorporated into the model (some of them were included in our earlier model [22]). Our analysis (not shown) indicates that usually it does not change our conclusions above. This means that as a rule there is a broad range of biologically reasonable parameters where our conclusions hold. Of course, the latter does not exclude finding new kinetic features with introducing additional details.

[1] S. K. Singh *et al.*, Nature (London) **432**, 396 (2004).
[2] P. A. Clark, D. M. Treisman, J. Ebben, and J. S. Kuo, Dev. Dyn. **236**, 3297 (2007).
[3] D. Shibata, Curr. Opin. Gastroenterol. **24**, 59 (2008).
[4] A. Y. Nikitin, A. Matoso, and P. Roy-Burman, Histol. Histopathol **22**, 1043 (2007).
[5] T. Schatton, G. F. Murphy, N. Y. Frank *et al.*, Nature (London) **451**, 345 (2008).
[6] T. Schatton and M. H. Frank, Pigm. Cell. Melan. Res. **21**, 39 (2008).
[7] J. P. Sleeman and N. Cremers, Clin. Exp. Metastasis **24**, 707 (2007).
[8] M. Yilmaz, G. Christofori, and F. Lehembre, Trends Mol. Med. **13**, 535 (2007).
[9] J. E. Visvader and G. Lindeman, Nat. Rev. Cancer **8**, 755 (2008).
[10] K. A. Moore and I. R. Lemischka, Science **311**, 1880 (2006).
[11] D. T. Scadden, Nature (London) **441**, 1075 (2006).
[12] L. E. Ailles and I. L. Weissman, Curr. Opin. Biotechnol. **18**, 460 (2007).
[13] R. N. Kaplan *et al.*, Nature (London) **438**, 820 (2005).
[14] S. Hiratsuka, A. Watanabe, H. Aburatani, and Y. Maru, Nat. Cell Biol. **8**, 1369 (2006).
[15] R. P. Araujo and D. L. S. McElwain, Bull. Math. Biol. **66**, 1039 (2004).
[16] H. M. Byrne, T. Alarcon, M. R. Owen, S. D. Webb, and P. K. Maini, Philos. Trans. R. Soc. London, Ser. A **364**, 1563 (2006).
[17] I. M. M. van Leeuwen, H. M. Byrne, O. E. Jense, and J. R. King, Cell Prolif **39**, 157 (2006).
[18] S. Sanga, H. B. Frieboes, X. M. Zheng, R. Gatenby, E. L. Bearer, and V. Cristini, Neuroimage **37**, S120 (2007).
[19] N. Bellomo and P. K. Maini, Math. Models Meth. Appl. Sci. **17**, 1641 (2007).
[20] S. Sanga, J. P. Sinek, H. B. Frieboes, M. Ferrari, J. P. Fruehauf, and V. Cristini, Expert Rev. Anticancer Ther. **6**, 1361 (2006).
[21] T. Roose, S. J. Chapman, and P. K. Maini, SIAM Rev. **49**, 179 (2007).
[22] V. P. Zhdanov, Eur. Biophys. J. **37**, 1329 (2008).