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Report

Stochastic Dynamics of Hematopoietic Tumor Stem Cells

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KEY WORDS

mathematical models, stochastic dynamics, cancer, stem cells, mutation, clonal evolution

ABBREVIATIONS

HSC	hematopoietic stem cell
CSC	cancer stem cell

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ABSTRACT

Many tumors derive from the transformation of normal stem cells into cancer stem cells that retain their self-renewal capacity. This modern view of cancer has provided a natural explanation for the striking parallels which exist between these two different types of self-renewing cells. Here we develop a simple mathematical model to investigate the implications of this concept regarding the evolution of tumors in the hematopoietic system. Our results unequivocally demonstrate that stochastic effects related to the finite size of the active stem cell population have a profound influence on the dynamics of cancer evolution. For input parameters compatible with both the natural history of human cancer and mouse models, our results show how stochastic dynamics alone may lead to both remission in some cases and rapid expansion in others.

INTRODUCTION

Most tissues in complex metazoans undergo continuous cell turnover and contain a rare subset of cells that can both self-renew and give rise to differentiated daughter cells.[1] These so-called stem cells (SC) build tissues during development and are retained in adult life for the maintenance of normal tissue turnover and for tissue repair.[1] Thus, the property of self-renewal in any given tissue is restricted to a rare population of SC. Solid tumors and hematopoietic malignancies such as acute leukemia are not an exception. Indeed, there is a growing consensus[2] that cancer stem cells (CSC) may result from the transformation of normal stem cells or from progenitor cells that reacquire 'stem cell' like properties due to specific mutations, a process whose details are not yet fully understood.[3-8] However, when associated with CSC, self-renewal is a potentially dangerous property, as it allows CSC to replicate in a poorly regulated way since they appear to loose the ability to respond to local microenvironmental cues and acquire abnormal growth characteristics.[9] The result is the tumor that, when significant, induces a lethal burden on the living organism. In other words, the development and spread of cancer are associated with the property of self-renewal and limited potential for differentiation. Both solid tumor[10,11] and leukemia[12] SC have been isolated and shown to exhibit all of the phenotypic characteristics of the whole tumor. Given the increasing evidence that CSC are necessary for both growth and maintenance of tumors, as pointed out by Weissman, CSC should constitute the preferential targets for future therapies.[5]

In the best studied SC model, murine hematopoiesis, long-term self-renewal is restricted to hematopoietic stem cells; all of the downstream oligopotent progenitors lack long-term self-renewal capacity and depend on hematopoietic stem cell input for their maintenance through time[13] (exceptions are the "memory" T and B lymphocytes). In the mammalian hematopoietic system, the SC population residing in the bone-marrow is believed to be roughly constant and comprised of approximately 11,000–22,000 cells.[14] However, only a small fraction of these cells is actively involved in self-renewal and contributes to hematopoiesis at any given time.[3,15] It has been thought that these cells contribute to hematopoiesis for a variable period of time until they are replaced in a process of clonal succession.[16] Recently, two of us have shown that the size of the active SC (N_{SC}) pool scales allometrically with the mass of adult mammals (M) as $N_{SC} \sim M^{3/4}$.[17] For a 70kg adult human, this scaling leads to $N_{SC} \sim 385$. Furthermore, these SC replicate at a rate of approximately once per year[18] and our estimates suggest that they can provide hematopoiesis for the whole lifetime of an adult,[17] in accord with the recent study by McKenzie et al.[19] Hematopoietic stem cells receive input from many sources, including the supporting stroma, circulating growth factors and paracrine cytokines.[20] There is

evidence that hematopoietic stem cells behave in a stochastic fashion with cells responding at random to environmental cues.[13,20-22]

From an evolutionary perspective, the advantage of having a small active population of SC is quite intuitive: In the absence of environmental genotoxic agents, cell division provides the main mechanism for the acquisition of new mutations in DNA. As such it is natural that throughout evolution, SC have developed ways that minimize the risk of accumulating mutations. Indeed, a small and slowly replicating SC compartment combined with immortal strand cosegregation[23] constitute effective means of minimizing such a risk. However, these protection mechanisms are not without risk and a small SC population actually increases the impact of stochastic effects which determine the dynamical coevolution of normal and malignant cells within the SC compartment. Therefore, tissue organization has profound consequences on the evolution of hematopoietic neoplasms.

The evidence that CSC acquire abnormal growth characteristics naturally leads to the view of a CSC as an advantageous mutant in an otherwise monomorphic population of normal SC. Using tools from population genetics, one can describe the dynamics of such a mutant in a finite population in terms of a Markov process. An advantageous mutation confers to such a cell an evolutionary edge over normal cells. Nonetheless, we shall also discuss the possibility that cancer mutations confer either a marginal or even no evolutionary advantage to CSC. This is relevant also from the clinical perspective. It is well known that healthy adults can have clones with the *bcr-abl* fusion gene,[24] the sine qua non for chronic myeloid leukemia[25] and yet they do not develop the disease. It is argued that this observation is evidence that additional mutations are necessary for the development of the disease. However, if animal models are indicative of the human disorder, additional mutations do not seem to be necessary[26-28] and a recent study based on the age specific incidence of this disease in the United States supports the notion that *bcr-abl* alone is sufficient to lead to the disease.[29] In principle, the *bcr-abl* mutation could occur in a progenitor cell rather than in the SC compartment. If this was the case, one would expect relatively frequent elimination of the clone since progenitors have a limited lifetime. Yet, disappearance of these clones has been reported very rarely.[24] Moreover, spontaneous resolution of neoplastic disorders such as transient abnormal myelopoiesis[30] and myelodysplasia[31] have been documented suggesting that stochastic elimination of neoplastic processes, although rare, is not impossible.

Population geneticists have long determined the probability of fixation of a single mutant (in our case a CSC) with an associated relative fitness r, immersed in a homogeneous population of constant size N in which normal SC exhibit fitness 1.[32] With respect to the dynamical evolution of hematopoietic tumor SC however, the relevant question to ask is how long does it take for a single mutant either to reach a given threshold value compatible with the minimum number of CSC necessary to make a positive diagnosis or the induction of a lethal burden on the patient.

In general, one cannot determine a closed formula for these quantities. Furthermore, the stochastic nature of the process means that the time it takes to reach a given state is not associated with a single value but is given by a time probability distribution function. To the extent that this distribution function is sharply peaked, the expected (average) time will provide a reasonably accurate estimate. In the following we investigate in detail the features associated with the stochastic dynamics of stem cells and their association with cancer progression as illustrated in Figure 1. A detailed discussion of the model is provided in the Materials and Methods section.

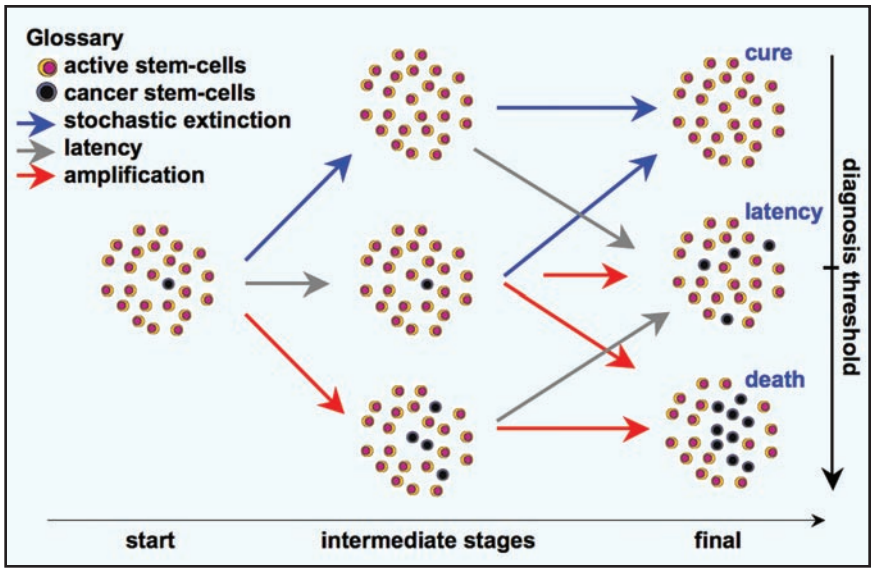

Figure 1. Evolutionary paths of cancer stem cells. A transformation of a normal SC into a CSC leads to the three basic dynamical scenarios attainable at an intermediate stage of cancer evolution. Stochastic tumor extinction (top), quasi-random drift of a single CSC (middle) or proliferation of CSC (bottom) can occur as a result of stochastic evolutionary dynamics. More interestingly, the final stage may be associated either with cure, death of the organism, or with latency that may persist for long periods. Notice that, depending on the relative fitness r of CSC, stochastic extinction of cancer is possible even when the number of CSC surpasses the threshold necessary for diagnosis. Conversely, death of the organism due to accumulation of CSC in the SC compartment may take a long time to occur. The stochastic nature of the process naturally accommodates such different possibilities without the need to explicitly incorporate them in the model.

MATERIALS AND METHODS

We consider a birth-export process starting when one SC is transformed into a CSC at time $t = 0$. We compute analytically the probabilities for CSC to reach levels compatible with the diagnosis of acute leukemia, the probability of invasion of the active SC pool by CSC, as well as the probability for extinction. To this end we consider a homogeneous population of size[17] $N = 385$, where normal SC divide at a rate of once per year, exhibiting a probability of mutation of 5×10^{-7} per replication.[33] In the following we describe our model, our analytical results for the fixation probabilities as well as details of the exact computer simulations which allow us to determine the detailed dynamics of CSC.

Model. The active stem cell pool of size $N_{SC} = 385$ in an adult is responsible for the maintenance of blood cell formation.[17] We assume that these cells are biologically coupled and function as a homogeneous population in the bone-marrow, replicating at a rate of ~1/year. We acknowledge that there is increasing experimental evidence that even within the CSC pool, there is a hierarchical organization.[3,5] Modeling the active SC pool as a homogeneous

population of cells allows us to illustrate the importance of stochastic effects during the evolution of the tumor clone in the regime in which stochastic effects have the smallest impact on the overall population dynamics (homogeneous population).

During replication, cells can acquire mutations at a rate 5 x 10^{-7} per division, which is similar to that of normal cells[33] since it is likely that the initial mutations leading to transformation of normal into tumor cells occur at a normal rate.[34] Normal SC have relative fitness 1 whereas CSC acquire a relative fitness *r*. We simulate the stochastic dynamics of the active stem cell compartment in terms of a birth-export process in which normal SC replicate at the normal rate of ~1/year, whereas CSC replicate at a rate ~ *r*/year. A replicating cell gives birth to two daughter cells and we assume that the cell population remains constant. In other words, every time a replication occurs, one cell from the pool is selected at random for export such that a cell chosen for export cannot be selected again for replication. In this sense, this model provides a simple and intuitive mathematical description of the heterogeneous microenvironmental model of SC self-renewal and differentiation.[35]

The probability that a normal SC mutates into a CSC during replication is μ, while with probability 1-μ no mutation takes place. By iterating the cycle of selection-mutation-replication-export, we map the life history of the active stem cell compartment of an individual. By repeating each of these simulations many times, we determine numerically various probability density functions.

The possible evolutionary paths taking place in the SC compartment are illustrated in Figure 1. Starting from a single CSC in the active stem cell pool, the stochastic dynamics encompasses several possible scenarios, from stochastic extinction to full invasion of the active population. Notice in particular, that stochastic extinction may be possible in spite of the fact that the total fraction of CSC in the population reaches high percentages—for instance, enough to lead to diagnosis—which will sensitively depend on the relative fitness *r* of CSC. We shall come back to this point below.

Our model is similar in spirit to a recent stochastic model developed to describe the kinetics of clonal dominance in myeloproliferative disorders in mice and cats.[22] Similar to ref. 22, we start from a single CSC in a population of otherwise normal SC. However, our model considers only the active stem cell pool (N_{SC} = 385) instead of the total hematopoietic stem cell compartment (N = 11,000). A smaller population size leads to more pronounced stochastic effects. Furthermore, in our model CSC replicate at a rate *r*-times faster than normal SC, unlike in ref. 22 in which both normal and CSC replicate at the same rate. This leads to a markedly different evolutionary dynamics of CSC. In particular, it allows an analytical prediction for the different fixation probabilities of CSC (see below).

An analytical model for the expected probabilities. In the following, we derive simple formulas for the expected values associated with the probability that, starting from a single CSC, a given number of CSC is reached, as well as the expected time it will take to achieve that state.

Given a population of constant size N_{SC}, with M_0 CSC at time $t = 0$, the probability that at *least once* during its evolutionary history, the population will have M_1 CSC is approximately given by (see appendix)

$$p(M_0, M_1) = \frac{1 - r^{-M_0}}{1 - r^{-M_1}}$$

Note that this expression is independent of the size of N_{SC}, apart from the obvious relation $M_1 < N_{SC}$. In general, we start with a single mutant ($M_0 = 1$) whereas M_1 may correspond to the minimum number of mutated SC compatible with a diagnosis (presently stipulated at ≈20% for acute leukemia[36]), or it may define the maximum number of CSC compatible with a living organism.

Exact computer simulations. We carry out exact computer simulations of this model considering a homogeneous population of size N_{SC}. At time $t = 0$, one CSC is present in the population. Normal SC have relative fitness *1*, whereas that of CSC is *r*. Therefore, the replication rate of CSC is *r* times the replication rate of normal SC. We carry out many simulations of the same stochastic dynamical process (3 x 10^6). For each run, we follow the time dependence of the number of CSC in the population. The ratio of the number of simulations when stochastic extinction of the CSC population takes place and the total number of simulations provides the probability of spontaneous remission of the mutant population. Similarly, the ratio between those runs in which the population of CSC becomes extinct after its fraction had surpassed the 20% threshold required for diagnosis gives the conditional probability for extinction, assuming that cancer has been diagnosed.

More interestingly, the extensive computer simulations allow us to plot the probability distribution functions for reaching specific conditions–including the distribution of times until diagnosis, or the distribution of times for invasion of the entire active SC pool by CSC.

RESULTS

Analytical approximation. Initially, we investigated the overall scenario as it emerges from the analytic results that we derived (Fig. 2). In the main panel we plot the probability that, starting with a single CSC, the mutant clone becomes extinct (solid curve), as well as the probability that invasion by CSC occurs (dashed line). Both quantities

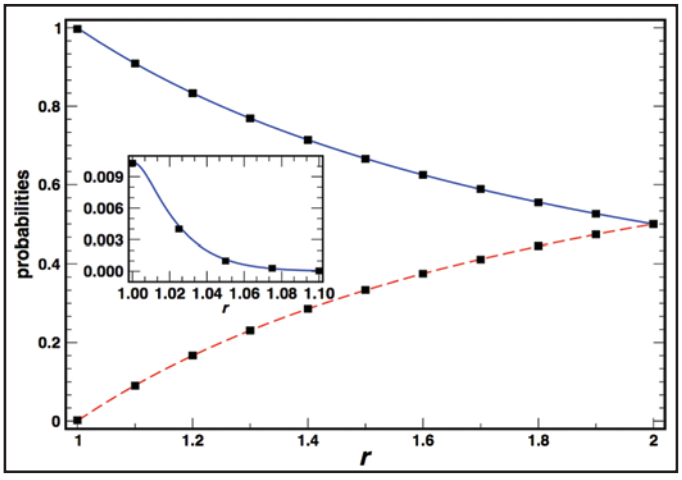

Figure 2. Fixation probabilities. The curves show results of the analytical model for the different fixation probabilities as a function of the relative fitness *r* of CSC; symbols provide the results of exact computer simulations. Main panel: Probability that, starting with a single CSC, the clone becomes extinct (solid curve), as well as the probability that invasion by CSC occurs (dashed line). Inset: Probability that, starting with a single CSC, the population of CSC goes extinct after successfully expand up to or above the 20% threshold for a diagnosis of acute leukemia. In all cases, the agreement between the analytical model and exact computer simulations is excellent, showing that the main role of the (small) mutation rate is to generate the first CSC, its overall role during clonal evolution being negligible.

are plotted as a function of the relative fitness r. We let r assume values between one and two—in other words, we investigate the regime where CSC have a fitness between neutral mutants or twice that of normal SC. In the inset panel, we plot the probability of tumor extinction after CSC successfully expand up to or above the 20% threshold required for diagnosis.[36] In all cases the lines are the result of the analytical model described above, whereas the symbols show the results of the exact stochastic computer simulations. The agreement is excellent for all values of r.

The higher proliferative rate and/or lower apoptosis observed in cancer makes CSC appear as advantageous mutants. When this is the case, expansion of CSC in the SC compartment is efficient and fast, whereas stochastic extinction after diagnosis is rare. Nonetheless, the probability of spontaneous extinction of the CSC lineage is appreciable for all values of r studied. In all cases ($r \leq 2$), a single mutation will always have a probability larger then 50% of not evolving to cancer. Figure 2 conveys a clear cut message: Therapies that are able to reduce the relative fitness of CSC with respect to normal hematopoietic SC, will strongly hinder expansion of the leukemic clone and greatly enhance the probability for cure of the patient. This effect is more evident when we investigate in detail the stochastic dynamics emerging from exact computer simulations, in particular when we examine the time probability distribution functions (see below). Moreover, early diagnosis of SC disorders will also enhance the overall efficiency of therapies aimed at reducing the relative fitness of CSC.

Exact computer simulations. The full symbols in the upper panel of Figure 2 correspond to the results of exact stochastic computer simulations of SC dynamics, and show the accuracy of the analytical approximation in defining the different probabilities. Furthermore, the results also confirm the validity of the assumption made in the analytical model that the mutation rate mostly contributes to the appearance of the first CSC without subsequently affecting the overall dynamics in the active SC compartment. This also holds true for the expected times, although the probability distribution functions depicted in Figure 3 may be wide and are typically skewed, thereby contributing to the significant deviations observed between the expected times and the times at which the probability is maximized. These deviations are more pronounced for smaller values of the relative fitness $r \geq 1$, as shown in Figure 3.

The rapidly (and monotonically) decreasing curves in the upper panel of Figure 3 show the time probability distribution for stochastic extinction of the CSC lineage for different values of the relative fitness r. As expected, the probability of stochastic extinction decreases rapidly with increasing r, which correlates perfectly with the fact that the overall extinction probability decreases with increasing r (Fig. 2). On the other hand, the one-humped curves in the upper panel (notice the logarithmic scale used in plotting the time probability distribution functions) correspond, for different values of r, to the time probability distribution for invasion of the active pool by CSC. The curves exhibit the skewed shape characteristic of this type of processes,[37] their overall width decreasing with increasing r. In the lower panel of Figure 3 we plot the time probability distribution functions for reaching a diagnosis, starting from a single CSC. For a population of this size N_{SC} = 385, we need, on average *77* CSC, according to the current definitions which require >20% blasts in the bone marrow to make a diagnosis of acute leukemia.[36] Here we make the simplifying assumption that the percentage of marrow blasts, normal and malignant, is linearly represented in the normal and malignant SC pool. This threshold is not an absolute, and can

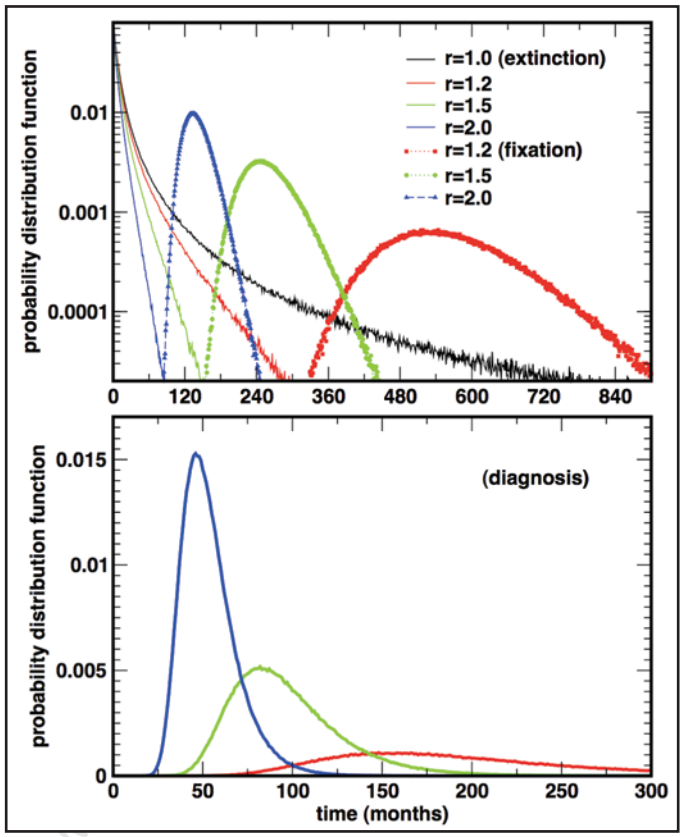

Figure 3. Time probability distribution functions. The different curves show the probability distributions for the time (in months) it takes for a mutant to expand to a specific fraction of the active SC pool, starting from a single CSC for different values of the relative fitness r of CSC: r = 1.0 (black curves), r = 1.2 (red curves), r = 1.5 (green curves), and r = 2.0 (blue curves). Upper panel: We plot the probability distributions for stochastic extinction of CSC (the four curves on the left, monotonically decaying) and the distribution of fixation times (the three remaining curves, one humped). Notice the vertical logarithmic scale. Lower panel: Time probability distributions for reaching 20% occupation of the active SC pool, associated with present convention for a diagnosis of acute leukemia. Overall, the larger the relative fitness of CSC, the faster cancer progression takes place, both for time to diagnosis as well as for marrow failure. Inspection of fixation curves in the upper panel suggest that typical leukemic CSC are expected to have a relative fitness $r \geq 1.5$, since only for such advantageous mutations cancer progression times correlate well with clinical data. Further details are provided in the text.

be further reduced with continuing technological developments. However, the nature of the results and conclusions drawn based on it do not change upon its revision.

DISCUSSION

The general consensus is that multiple genetic events are necessary for the development of cancer.[38-40] However, there is increasing evidence that for some hematopoietic neoplasms, a single mutation may be enough to explain the origin of the disease. Indeed, a mutation at one base (a guanine to thymidine substitution leading to the JAK2V617F mutation) has been recognized in most cases of polycythemia vera (PV)[41,42] as well as a significant proportion of the related myeloproliferative disorders essential thrombocythemia (ET) and myeloid metaplasia with myelofibrosis (MMM).[42,43] Animal

models support the concept that this mutation in a HSC may be enough to initiate both PV[41,44] and MMM.[44] These are all disorders of the hematopoietic stem cell and CSC from patients with PV have been isolated and shown to carry this mutation.[45] Therefore, the model developed here relating to a single mutation is supported by observations.

Hematopoietic stem cells are under the control of numerous signals emanating from neighboring cells, the supporting extracellular matrix, cytokines, growth factors and hormones.[46] Even under physiological conditions, the dynamics at the level of the HSC is thought to be stochastic in nature.[13,21]

Assumptions. Here we utilized a simple model for the origin of the myeloproliferative and other clonal stem cell disorders. Any model and its predictions are dependent on the assumptions on which it is based. We assumed that a limited number of stem cells (~385 in adults) are responsible for the maintenance of hematopoiesis and they replicate once/year. Once a given cell is selected for replication, it may contribute towards blood formation perhaps for the lifetime of the individual. However, these assumptions are supported by experimental evidence[18,19] and references therein.

Model predictions and clinical observations. Our model predicts that mutant cells can expand, exhibit latency or die simply due to stochastic effects, even if the mutation(s) give a selective advantage to the cell. The model also predicts that there may be wide variability in the life-time of the clone, even in the presence of constant external conditions. Moreover, mutant clones that achieve a large size or have a high reproductive fitness may undergo extinction, although this is an unlikely event.

Perhaps the concept of spontaneous tumor extinction may appear as a purely theoretical exercise. This is not necessarily so as our results demonstrate and as discussed elsewhere.[22] Possibly the best example of spontaneous tumor resolution is the disorder known as transient myeloproliferative disorder (TMD) that is seen mainly in children with Down's syndrome. The disorder has all the attributes of an acute leukemia with clonal hematopoiesis and often cytogenetic abnormalities.[30] The neoplastic cells express both myeloid as well as lymphoid markers suggesting that they arise from very primitive cells in the bone marrow. Patients with TMD can have extremely high numbers of circulating blasts, yet in most patients, the disease disappears spontaneously. There has not been any satisfactory explanation for spontaneous resolution of this disease that can sometimes be fatal.[30] However, our stochastic model can accommodate this observation and provide a potential explanation for the behavior of these cells, especially if their relative fitness compared to normal stem cells is only marginally advantageous. In addition, the size N_{SC} in the newborn is small[47] and therefore more susceptible to stochastic fluctuations. Stochastic elimination or latency is also compatible with the observation of healthy people who have hematopoietic stem cells with *bcr-abl* transcripts who never progress to chronic myeloid leukemia or who experience extinction of the clone.[24] The latency predicted by our model is further supported by the recent observation in patients with ET where JAK2V617F positive clones may remain stable for long periods of time without expansion [48]. Whenever proliferation of CSC occurs, the time span of the entire evolutionary process becomes broad, constituting a fingerprint of the role of stochasticity in the evolution of CSC. On the other hand, the negligible probability for spontaneous self-remission for $r \geq 1.1$ (cf. Fig. 2) explains why spontaneous resolution of most tumors is so rare.

Figure 3 also allows us to relate the present model with clinical practice. It is known[49,50] that for many neoplasms the characteristic time elapsed from cancer detection to its ultimately dire consequences is of the order of one decade. However, the survival of individuals who develop a tumor is dependent on the type of tumor and may be very short (even days from diagnosis) to several decades. This again can be seen from the wide time distribution in Figure 3. Inspection of Figure 3 shows that only when the relative fitness of CSC satisfies $r \geq 1.5$ do the results become compatible with this evidence. On the other hand, studies in some patients with myelodysplastic syndromes show that the time necessary for the accumulation of marrow blasts compatible with the diagnosis of acute myeloid leukemia can be of the order of five years.[51] This corresponds, in our model, to a relative fitness of CSC of $r \approx 1.7$. Also, the fact that for $r = 2$ the probability for diagnosis is maximal for $t = 50$ months suggests that, for childhood acute lymphoblastic leukemia, r may be greater than 2. These results correlate well with the inequality above and indicate the overall capacity of the present model to provide consistent estimates despite its simplicity. Furthermore it shows that, in spite of the manifest fitness advantage of CSC with respect to normal SC, stochastic effects are still responsible for the wide variability of the time probability distribution functions exhibited in Figure 3. Indeed, even when $r = 2$, a diagnosis may be made from two to six years after the appearance of the first mutant cell. The tumor may reach a lethal burden sometime between eight to sixteen years after the first mutation took place, that is, six to twelve years after diagnosis which is compatible with evidence from solid tumors[49] as well as disorders such as non-Hodgkin lymphoma and multiple myeloma.[36,50]

In summary, our model shows that if initial steps in the evolution of the neoplastic clone are stochastic, the time for disease progression can vary over a wide range even for identical external conditions. Hence stochastic effects should not be ignored especially if the population at risk, in our case hematopoietic stem cells, is small.

APPENDIX

The general expression for the fixation probability reads

$$p(M_0, M_1) = \frac{\Theta(M_0)}{\Theta(M_1)},$$

in which the common function appearing in the numerator and denominator reads

$$\Theta(X) = 1 + \sum_{p=1}^{X-1} \prod_{k=1}^{p} \frac{T^-(k, N_{SC})}{T^+(k, N_{SC})}.$$

For the birth-export process we are considering, the transition probability $T^+(k, N_{SC})$ that the number of CSC increases from k to $k + 1$ is given by

$$T^+(k, N_{SC}) = \{p_{CSC}(k) + \mu[1 - p_{CSC}(k)]\}\frac{N_{SC} - k}{N_{SC}},$$

where the probability p_{CSC} to select a CSC proportional to its relative fitness r reads

$$p_{CSC}(k) = \frac{kr}{kr + (N - k)}.$$

The meaning of the expression above for the transition probability is clear: The first term is simply the probability that a CSC is chosen for reproduction, whereas the second term gives the probability that a normal cell is chosen for reproduction and mutates (with probability μ). Naturally, both terms have to be multiplied by the probability

that a normal SC is chosen for export, since only in this case will the number of CSC increase.

For $T^{-}(k, N_{SC})$ we have

$$T^{-}(k, N_{SC}) = (1-\mu)[1-p_{CSC}(k)]\frac{k}{N_{SC}}$$

where now a normal SC must be chosen for replication ($1 - p_{CSC}(k)$) and should not mutate ($1 - \mu$), while a CSC should be chosen for export.

As shown in the main text, for small values of the mutation probability μ we can neglect its role during the evolutionary dynamics, since once a normal SC mutates into a CSC, the remaining dynamical process is clearly dominated by selection. Whenever $\mu = 0$, the ratio $T^{-}(k, N_{SC}) / T^{+}(k, N_{SC})$ simply becomes $1/r$, independent of N_{SC}. This leads to the closed formula for the resulting probability

$$p(M_0, M_1) = \frac{1-r^{-M_0}}{1-r^{-M_1}}.$$

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