A compartment size dependent selective threshold limits mutation accumulation in hierarchical tissues

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Cancer is a genetic disease fueled by somatic evolution. Hierarchical tissue organization can slow somatic evolution by two qualitatively different mechanisms: by cell differentiation along the hierarchy "washing out" harmful mutations (Nowak et al. 2003, Werner et al. 2013) and by limiting the number of cell divisions required to maintain a tissue (Derényi and Szöllősi 2017). Here we explore the effects of compartment size on somatic evolution in hierarchical tissues by considering cell number regulation that acts on cell division rates such that the number of cells in the tissue has the tendency to return to its desired homeostatic value. Introducing mutants with a proliferative advantage we demonstrate the existence of a third fundamental mechanism by which hierarchically organized tissues are able to slow down somatic evolution. We show that tissue size regulation leads to the emergence of a threshold proliferative advantage, below which mutants cannot persist. We find that the most significant determinant of the threshold selective advantage is compartment size, with the threshold being higher the smaller the compartment. Our results demonstrate that in sufficiently small compartments even mutations that confer substantial proliferative advantage cannot persist, but are expelled from the tissue by differentiation along the hierarchy. The resulting selective barrier can significantly slow down somatic evolution and reduce the risk of cancer by limiting the accumulation of mutations that increase the proliferation of cells.

Somatic Evolution | Tissue hierarchies | Cancer Evolution | Physics of Cancer

Tumors develop as genetic and epigenetic alterations spread through a population of premalignant cells and some cells accumulate changes over time that enable them and their descendants to persist within tissues (1, 2). From an evolutionary perspective each tumor is an independent realization of a common reproducible evolutionary process involving "adaptive" mutations that are preferentially selected by the tumor environment. This process is clonal, which means that a subset of mutations termed "drivers" confer clonal growth advantage and they are causally implicated in cancer development.

A large body of work (2–5) has focused on understanding clonal evolution of an initially homogeneous populations of identical cells, a subset of which progress toward cancer as they accrue driver mutations. Beerenwinkel et al. (6), for instance, considered the Wright-Fisher process (a homogeneous population of initially identical cells) to explore the basic parameters of this evolutionary process and derive an analytical approximation for the expected waiting time to the cancer phenotype and highlighted the relative importance of selection over both the size of the cell population at risk and the mutation rate.

Self-renewing tissues, which must generate a large number of cells during an individual's lifetime and in which tumors typically arise, are comprised of a hierarchy of progressively differentiated cells and, as a result, are not homogeneous populations of identical cells. There is empirical evidence (7–9) and theoretical rationale (10–12) that such hierarchical tissue architecture has profound effect on neoplastic progression. Theoretical work has demonstrated that hierarchically organized tissues suppress tumor evolution by limiting the accumulation of somatic mutations in two fundamentally different ways, as follows:

As described in a seminal paper by Nowak et al. (11) the linear flow from stem cells to differentiated cells to apoptosis in a spatially explicit, strictly linear organization has the property of canceling out selective differences. Nowak et al. considered a system, where only asymmetric cell divisions are allowed, i.e., after each cell division one of the daughter cells differentiates to the next level of the hierarchy pushing all cells at higher levels further along the hierarchy (see Fig. 1a). In this idealized construction mutations, irrespective of how much they increase division rate, are invariably "washed out" unless they occur in the stem cell at the root of the hierarchy. In a more general setting, where symmetric divisions are allowed, the strength of this "washing out" effect can be quantified by introducing the self-renewal potential of cells. The self-renewal potential is defined as the logarithm of the ratio between the

Significance Statement

Renewed tissues of multicellular organism accumulate mutations that lead to ageing and cancer. To mitigate these effects self-renewing tissues produce cells along differentiation hierarchies, which have been shown to suppress somatic evolution both by limiting the number of cell divisions, and thus reducing mutational load, and by differentiation "washing out" mutations. Our analytical results reveal the existence of a third mechanism: a compartment size dependent threshold in proliferative advantage, below which mutations cannot persist, but are rapidly expelled from the tissue by differentiation. In sufficiently small compartments the resulting selective barrier can greatly slow down somatic evolution and reduce the risk of cancer by preventing the accumulation of mutations even if even they confer substantial proliferative advantage.

ID and GJSz designed the study, DG, ID and GJSz carried out calculations and wrote the paper.

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rate of cell divisions that increase the number of cells at a given level of the hierarchy (division producing two cells at the same level) and the rate of events that result in the reduction at the level (division producing two differentiated cells that move higher up in the hierarchy or cell death). In healthy homeostatic tissues the self-renewal potential of stem cells is zero (corresponding to equal rates of differentiation and self-renewal), while for differentiated cells it is always negative, as these cells have an inherent proliferative disadvantage as a result of which they are eventually "washed out" of the tissue from cells differentiating from lower levels of the hierarchy. In the following, lower (higher) refers to levels closer to (further away from) the stem cell compartment.

More recently, Derényi and Szöllősi (12) showed that in self-renewing tissues hierarchical organization provides a robust and nearly ideal mechanism to limit the divisional load (the number of divisions along cell lineages) of tissues and, as a result, minimize the accumulation of somatic mutations. The theoretical minimum number of cell divisions can be very closely approached: as long as a sufficient number of progressively slower dividing cell types towards the root of the hierarchy are present, optimal self-sustaining differentiation hierarchies can produce N terminally differentiated cells during the course of an organism's lifetime from a single precursor with no more than $\log_2(N)+2$ cell divisions along any lineage.

Here, we examine the effect of compartment size by introducing interaction among cells in the form of cell number regulation, which acts on the cell division rates such that the number of cells at each hierarchical level of the tissue has the tendency to return to its desired homeostatic value. We consider a single (non stem cell) level of the hierarchy that is renewed from below by cell differentiation. We introduce mutants with a proliferative advantage, i.e., mutants with a positive self-renewal potential. As detailed below, using both simulations and an approximation adopted from nonequilibrium statistical physics, we find that under a wide range of parameters a third fundamental mechanism exists by which hierarchically organized tissues can slow down somatic evolution and delay the onset of cancer.

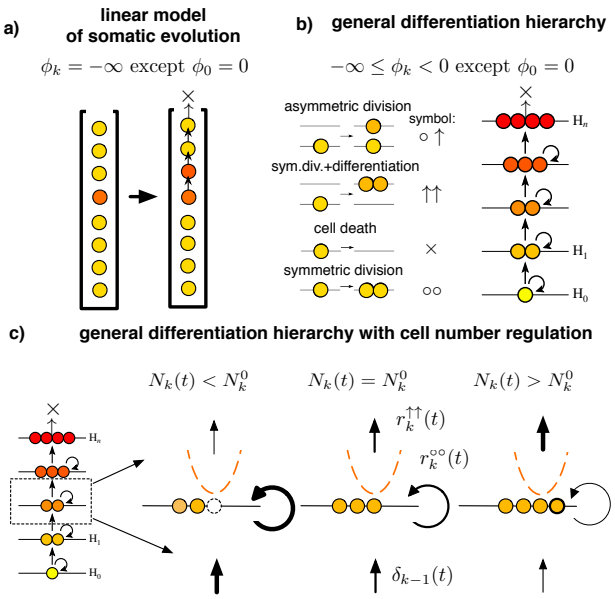

Fig. 1. Self-renewing tissue comprised of a hierarchy of progressively differentiated cells can suppress somatic evolution. a) The linear process of somatic evolution considers a strict linear organization, where after each cell division one of the daughter cells differentiates to the next level pushing all cells above further along and the top most cell is lost from the system. Such an idealized construction, where self-renewal at individual levels of the hierarchy is not allowed has a minimal self-renewal potential $\phi_k = -\infty$, with the exception of the stem cell level at the root of the hierarchy with $\phi_0 = 0$. This has the effect of canceling out selective differences between cells, i.e., any non stem cell, regardless of how large its division rate is, will be "washed out" of the tissue by cell differentiating from below. b) General differentiation hierarchies are characterized by intermediate values of the self-renewal potential with the exception of the stem cell. In such systems, in the absence of cell number regulation, any mutant with a proliferative advantage, i.e., a positive self-renewal potential, will spread exponentially if it does not go extinct stochastically. c) We introduce cell number regulation that changes the rate of different events such that the strength and direction of the regulation depends on the difference between the number of cells present at a given time $N_k(t)$ and the homeostatic number N_k^0 in a manner equivalent to being in a quadratic potential (cf. Eq. (1)). As described in the text, this leads to the emergence of a positive threshold proliferative advantage below which mutants cannot persist.

Results

We consider level $k > 0$ of a general differentiation hierarchy that is renewed by cell differentiation from level $k-1$ below. The tissue dynamics is described by the rates of asymmetric differentiation ($\circ\uparrow$), symmetric division with differentiation ($\uparrow\uparrow$), symmetric division ($\circ\circ$), cell death ($\times$), and the total rate δ_{k-1} of differentiation from below (see Fig. 1 b and c).

To model tissue size regulation at level k we introduce cell number-dependent modifiers of the above rates that act to maintain the tissue's homeostatic size. For simplicity and mathematical convenience we parametrize these density dependent factors by considering the quadratic potential

$$U(N_k) = \frac{1}{2}\beta\frac{\left[N_k(t) - N_k^0\right]^2}{N_k^0}. \qquad [1]$$

Mechanistically $\frac{\beta}{N_k^0}$ can be viewed as a spring constant that multiplies the deviation of the cell number N_k from its homeostatic value N_k^0. The corresponding cell number-dependent rate modifiers for, respectively, events that increase and decrease cell number are defined as

$$\rho^+(N_k) = \mathrm{e}^{-\frac{1}{2}\beta\frac{N_k - N_k^0}{N_k^0}} \quad \text{and} \quad \rho^-(N_k) = \mathrm{e}^{\frac{1}{2}\beta\frac{N_k - N_k^0}{N_k^0}}, \qquad [2]$$

which satisfy the condition of detailed balance

$$\frac{\rho^+(N_k)}{\rho^-(N_k+1)} = \mathrm{e}^{-[U(N_k+1)-U(N_k)]}. \qquad [3]$$

It follows that the variance of the cell number distribution is $\frac{N_k^0}{\beta}$. Biologically such a regulation scheme corresponds to, e.g., the local concentration of a regulatory signal that conveys information on the density of cells in a compartment.

The evolutionary dynamics of level k is determined by the per cell rate $r_k^+ = r_k^{\circ\circ}$ of cell number increase through symmetric cell division ($\circ\circ$), the per cell rate $r_k^- = r_k^{\uparrow\uparrow} + r_k^{\times}$ of cell number decrease through either symmetric division with differentiation ($\uparrow\uparrow$) or cell death ($\times$), and the per level rate $\delta_k^+ = \delta_{k-1}$ of cell number increase through differentiation from below; each multiplied by the corresponding cell number-dependent modifier.

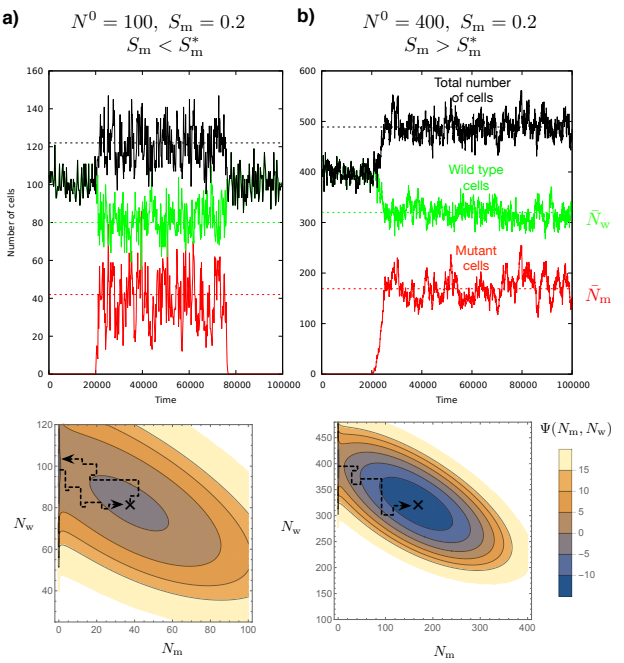

Fig. 2. Mutants go extinct under a threshold proliferation advantage. The continuous lines show the size of the mutant (red) and wild type (green) populations and their combined number (black) during the simulation. The dashed lines correspond to the theoretical mean population sizes in the quasi-stationary state. (**a**) if the proliferation advantage of the mutant is below the threshold the mutant will rapidly escape from the shallow quasi-stationary state and go extinct. On the bottom panels the black $\times$ on the continuous approximation of the potential marks the quasi-stationary state. Parameters: $N^0 = 100$, $\beta = 1$, $r^+ = 0$, $r^- = 1$, and $S_m = 0.2$ is below the threshold $S_m^* = 0.34$. (**b**) Increasing the compartment size to $N^0 = 400$ the potential well becomes deeper and the threshold proliferation advantage correspondingly smaller $S_m^* = 0.17$, allowing a mutant with the same advantage of $S_m = 0.2$ to persist in the tissue during the individual's lifetime.

At homeostasis the rates must satisfy the stationarity condition

$$\left(r_k^- - r_k^+\right) N_k^0 = \delta_k^+. \qquad [4]$$

In the following, we focus on a single (non stem cell) level, and drop index k for brevity. Time is measured in units of the cell production by the symmetric cell differentiation ($\uparrow\uparrow$) from this level, $1/(2r^{\uparrow\uparrow})$. Thus, the lifetime of the tissue T is identical to the number of differentiated cells produced by this level through symmetric cell differentiation during an individuals lifetime. As the asymmetric differentiations ($\circ\uparrow$) do not have any influence on the number of cells of this level, we set its rate $r_k^{\circ\uparrow}$ to zero for convenience.

The self-renewal potential of the cells is defined as

$$\phi = \ln \frac{r^+}{r^-} < 0, \qquad [5]$$

which converges to $-\infty$ as the rate of the ($\circ\circ$) events approach zero.

We introduce mutants with an elevated rate of divisions that increase cell number, r_m^+, such that it exceeds the rate of cell number decrease: $r_m^+ > r^-$. This corresponds to a positive self-renewal potential for mutant cells:

$$\phi_m = \ln \frac{r_m^+}{r^-} > 0. \qquad [6]$$

In the absence of cell number regulation ($\beta = 0$) a single such mutant either goes extinct stochastically, or spreads exponentially with probability

$$S_m = 1 - r^-/r_m^+ = 1 - e^{-\phi_m} \qquad [7]$$

(13). In the following we use S_m to parametrize the selective advantage of mutants. We note that in the absence of differentiation from below (i.e., $\delta^+ = 0$), for fixed population size (i.e., $\beta \to \infty$), for all but extremely small populations or nearly neutral mutations, S_m also corresponds to the probability of fixation of the mutant (14–16).

Denoting the number of wild type cells by N_w and mutant cells by N_m the dynamics is described by the transition rates

$$\begin{aligned}
k_w^+(N_m, N_w) &= \left(N_w r^+ + \delta^+\right) \rho^+(N_m + N_w),\\
k_w^-(N_m, N_w) &= N_w r^- \rho^-(N_m + N_w),\\
k_m^+(N_m, N_w) &= N_m r_m^+ \rho^+(N_m + N_w),\\
k_m^-(N_m, N_w) &= N_m r^- \rho^-(N_m + N_w),
\end{aligned}$$

which can be shown to satisfy detailed balance in the effective potential

$$\begin{aligned}
\Psi(N_m, N_w) = &- N_m \phi_m + \ln N_m - N_w \phi + \ln N_w\\
&+ \ln \frac{(N_w - 1)!}{(\delta^+/r^+ + N_w - 1)!}\\
&+ U\left(N_m + N_w\right), \qquad [8]
\end{aligned}$$

the continuous approximation of which is shown in the bottom panels of Fig. 2 a and b for different parameters.

The presence of size regulation (i.e., $\beta > 0$) leads to a quasi-stationary state in which the mean number of wild type $\bar{N}_w$ and mutant $\bar{N}_m$ cells can be determined to good approximation by solving:

$$\frac{k_w^+(N_m, N_w)}{k_w^-(N_m, N_w)} = \frac{k_m^+(N_m, N_w)}{k_m^-(N_m, N_w)} = 1, \qquad [9]$$

which gives:

$$\bar{N}_w \approx N^0 \left[\frac{1 - S_m}{1 - r^+/r_m^+} \; \frac{\delta^+}{N^0 r^-}\right] \qquad [10]$$

$$\bar{N}_m \approx N^0 \left[\frac{S_m}{1 - r^+/r_m^+} + \frac{\phi_m}{\beta}\right]. \qquad [11]$$

As illustrated in Fig. 2, the behavior of this quasi-stationary state can be divided into two regimes based on the value of the proliferative advantage S_m of the mutant. Below a threshold proliferative advantage S_m^* mutants, even if they initially fix (i.e., avoid early stochastic extinction with probability S_m) will nonetheless rapidly go extinct and, as a result, have vanishing probability to persist in the tissue throughout its lifetime. Above this threshold, however, if a single mutant avoids early stochastic extinction, with probability S_m, a population of its descendants will persist with near certainty in the tissue throughout its lifetime.

The characteristic residence time of a population of mutants that have initially fixed corresponds to the mean exit time τ of escape from the quasi-stationary state described above. Following the approach described by Gardiner (17) and Derényi et al. (18) an analytical approximation can be derived for

τ of the general form (for details of see the Supplementary Information):

$$\tau = \tau_0 \mathrm{e}^{\Delta\Psi}, \qquad [12]$$

where τ_0 is the reciprocal of the attempt frequency and $\Delta\Psi = \Psi(1, N^0) - \Psi(\bar{N}_\mathrm{m}, \bar{N}_\mathrm{w})$ is the height of the potential barrier for the escape from the quasi-stationary state (cf. Fig. 2). $\Delta\Psi$ increases approximately linearly with N^0 (for large N^0), corresponding to and exponential increase in τ. In contrast, τ_0, which depends only on the local geometries of the potential well and barrier, is proportional to $(N^0)^{-3/2}$. In particular, in the limit of strong regulation ($\beta \to \infty$) and strong washing out ($r^+ = 0$, i.e., $\delta^+ = N^0 r^-$) we have

$$\Delta\Psi = N^0(\phi_\mathrm{m} - S_\mathrm{m}) - \ln\left(\frac{N^0 S_\mathrm{m}}{1 - S_\mathrm{m}}\right),$$

and

$$\tau_0 = (N^0)^{-\frac{3}{2}} (2\pi)^{-\frac{1}{2}} \frac{S_\mathrm{m}}{1 - S_\mathrm{m}}. \qquad [13]$$

Using the mean exit time for escape from the quasi stationary sate, the probability P that a single mutant persist for the lifetime of the individual can be expressed as:

$$P = S_\mathrm{m}\, \mathrm{e}^{-T/\tau}. \qquad [14]$$

As show in Fig. 3a the above approximation for the escape time τ is highly accurate, and it depends very sharply on the selective advantage of mutants. This results in a well defined threshold selective advantage (cf. Fig. 3a) below which mutants, even if they avoid early stochastic extinction, will rapidly go extinct, i.e., will be washed out by cells differentiating from below. Furthermore, the threshold value depends only weakly on the value of β for reasonably strong cell number regulation, i.e., for $\beta > 1$ corresponding to the variance (in time) of the cell number being smaller than N^0. Finally, as shown in Fig. S1, even for weak washing out the threshold spreading factor can be large in small compartments.

Discussion

In classical population genetics models of finite populations, a mutation is either fixed in the population or lost from it within a finite length of time. A fundamental result of population genetics theory is that in constant populations mutations with a given selective advantage will avoid early stochastic extinction and fix with a probability independent of population size and proportional to the selective advantage (14–16). As a corollary, in the context of somatic evolution Michor et al. (19) demonstrated that the accumulation of oncogene-activating mutations (i.e., mutations that provide a proliferative advantage) that occur at a constant rate per cell division is faster in large than in small compartments. Consequently, as pointed out by Michor et al. the classical theory of finite populations of constant size implies that the organization of self-renewing tissues into many small compartments, such as the stem cell pools in colonic crypts, from which the tissue is derived, protects against cancer initiation (5). Further work by Beerenwinkel et al. using qualitatively similar models with a single compartment without differentiation from below, found that the average waiting time for the appearance of the tumor is strongly affected by the selective advantage, with the average waiting time decreasing roughly inversely proportional to the selective advantage. The mutation rate and the size of the population at risk in contrast were found to contribute only logarithmically to the waiting time and hence have a weaker impact (6).

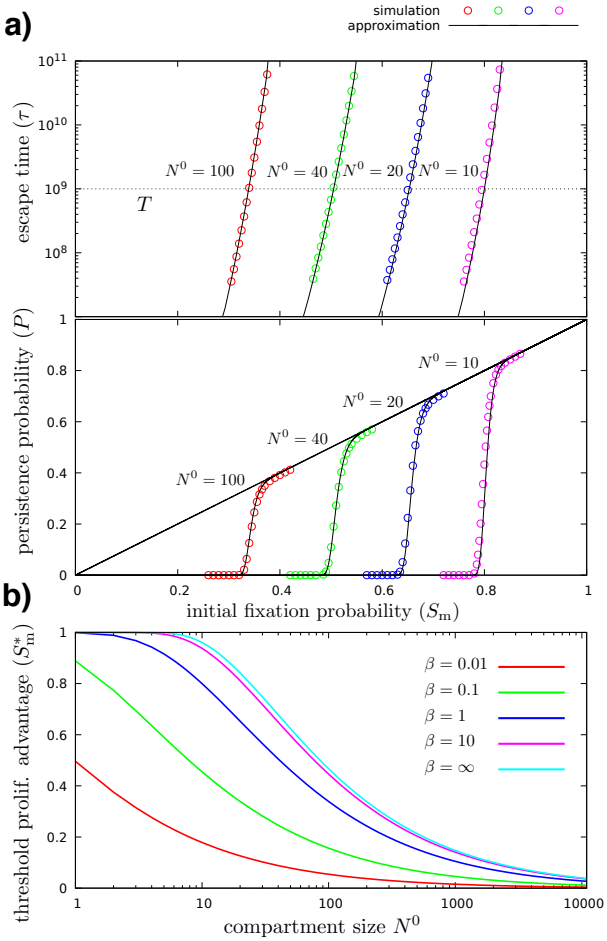

Fig. 3. There is no somatic evolution under the threshold spreading factor. (**a**) In presence of tissue size regulation ($\beta > 0$), below a threshold proliferation advantage S^*_m mutants rapidly go extinct and, as a result, have vanishing probability to persist in the tissue through its lifetime, while above this threshold, if a single mutant avoids early stochastic extinction, which occurs with probability S_m, it will persist with near certainty. The diagonal line corresponds to the initial fixation probability, the colored circles show the results of the simulation, and the black continuous curves show the theoretical approximation, for different compartment sizes (N^0). $\beta = 1$, $r^+ = 0$, $r^- = 1$, and $T = 10^9$ throughout. (**b**) The threshold separates the plot into two distinct regimes: below the curve the persistence probability is zero, mutations cannot accumulate; above the curve the mutants that avoid early stochastic extinction, which occurs with probability S_m, will persist in the tissue during the lifetime of the individual, and mutations can accumulate, leading to neoplastic progression.

In hierarchically organized tissues with finite compartment size the situation is more complicated. A mutant that avoids early stochastic extinction and achieves a sizable seemingly stable population can go extinct as a result of differentiation from below. This results in a qualitatively different and more profound ability of smaller compartment size to limit the accumulation of mutations. Similarly to classical population genetics models, the initial fixation probability of a mutation in a compartment of a hierarchical tissue is proportional to the proliferative advantage S_m and independent of the compartment size. However, as can be seen in Fig. 3a, the probability of the mutation to persist in the tissue exhibits a threshold

that is strongly dependent on compartment size. For small compartments even mutants with a very large selective advantage will only persist for a very short time, e.g., a mutant with a selective advantage of 10%, i.e., $S_{\mathrm{m}} \approx 0.1$, the largest value considered by Beerenwinkel et al., will rapidly go extinct in compartments with up to several hundred cells.

An important exception is constituted by tissue specific stem cell compartments residing at the bottom of the hierarchy, such as the stem cells at the bottom of colonic crypts. As these compartments do not receive an influx of cells from lower levels, their dynamics can be described by the classical population genetics models discussed above, i.e., mutations can accumulate more easily.

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Supplementary Information for

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This PDF file includes:

Supplementary text
Fig. S1
References for SI reference citations

Supporting Information Text

Mean exit time. The derivation of the mean exit time from the effective potential well near the quasi-stationary state $(\bar{N}_\mathrm{w}, \bar{N}_\mathrm{m})$ to the boundary line corresponding to zero mutants ($N_\mathrm{m} = 0$) is outlined below. Exact analytical formula exists either for continuous systems of arbitrary dimensions (subsections 5.2.7 and 9.3.2 of Gardiner (1)), or discrete systems in one dimension (section 7.4 of Gardiner (1) and Derényi et al. (2)). One can, however, generalize the discrete one-dimensional formula to our discrete two-dimensional system in a straightforward manner.

Let us first select any of the shortest paths (with only upward and leftward transitions) form $(\bar{N}_\mathrm{w}, \bar{N}_\mathrm{m})$ through $(1, N^0)$ to $(0, N^0)$. The main contribution to the mean exit time (which, in one dimension, is often referred to as "mean first passage time") along this one-dimensional path comes from the product of all backward transition rates (except for the outermost one from $(0, N^0)$ to $(1, N^0)$) divided by the product of all forward transition rates (including the one from $(1, N^0)$ to $(0, N^0)$). This contribution is independent of the selected path (because the rates correspond to an effective potential, i.e., their product in one direction along a circle is the same as their product in the other direction), and it is proportional to $\exp(\Delta\Psi)$, where $\Delta\Psi = \Psi(1, N^0) - \Psi(\bar{N}_\mathrm{m}, \bar{N}_\mathrm{w})$ is the height of the effective potential barrier.

The mean exit time involves the sum of similar contributions between any pairs of states along the selected path (section 7.4 of Gardiner (1) and Derényi et al. (2)). Only those contributions are significant for which the starting and ending positions are close to the bottom and the top of the effective potential, respectively. The summation for these contributions leads to a correction factor to the main contribution. This correction factor consists of two terms: a sum of the $\exp\{-[\Psi(N_\mathrm{m}, N_\mathrm{w}) - \Psi(\bar{N}_\mathrm{m}, \bar{N}_\mathrm{w})]\}$ Boltzmann weights of the states $(N_\mathrm{m}, N_\mathrm{w})$ along the path near the bottom; and a conceptually similar sum near the top (not detailed here, because its terms cannot be readily expressed by the potential Ψ, but rather only by the products of the ratios of the corresponding transition rates).

Since a typical exit process follows the diagonally oriented potential valley of the state space (see Fig. 2 in the main text), let us restrict the selected path to run along this valley. The correction factor for such a path will depend only on the local "geometry" of the bottom and the top of the effective potential, parallel to the direction of the main valley.

This one-dimensional result can be generalized to two (or any higher) dimensions in analogy to the generalization of the one-dimensional continuous version of the mean exit time (see subsection 9.3.2 of Gardiner (1)): the sum of the above Boltzmann weights should be extended to all states near the bottom of the effective potential; and the result should be divided by the sum of a different type of Boltzmann weights, $\exp\{-[\Psi(1, N_\mathrm{w}) - \Psi(1, N^0)]\}$, for all the states $(1, N_\mathrm{w})$ along the exit line.

The obtained mean exit time, τ, will still be proportional to $\exp(\Delta\Psi)$ and its prefactor, denoted by τ_0, is often referred to as the reciprocal of the attempt frequency.

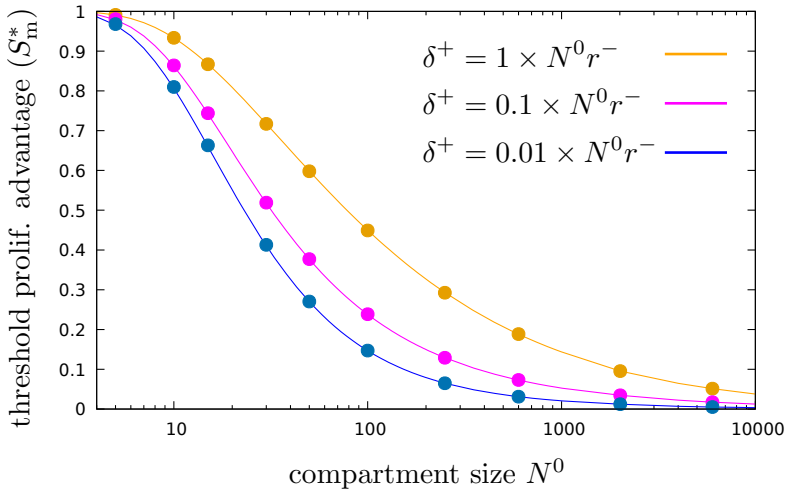

Fig. S1. The threshold spreading factor for varying strength of washing out, corresponding to different self-renewal rates $r^+ = r^- - \delta^+/N^0$, i.e., to 100%, 10%, and 1% of cells being produced by differentiation from below instead of self-renewal or, equivalently, $\phi \approx -\infty, -0.1$, and -0.01, respectively, for $\beta = 10$, $r^- = 1$, and $T = 10^9$. Similarly to Fig. 3b in the main text the threshold spreading factor separates the plot into two distinct regimes: below the curve the persistence probability is close to zero, mutations cannot accumulate; while above the curve mutants that avoid early stochastic extinction, which occurs with probability S_{m}, will persist in the tissue during the lifetime of the individual, and can accumulate further mutations leading to neoplastic progression. Continuous lines are theoretical estimates based on the mean exit time approximation, while points indicate explicit numerical simulations.

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