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Somatic selection for and against cancer

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Abstract

In multicellular organisms, cells cooperate within a well-defined developmental program. Cancer is a breakdown of such cooperation: cells mutate to phenotypes of uncoordinated proliferation. We study basic principles of the architecture of solid tissues that influence the rate of cancer initiation. In particular, we explore how somatic selection acts to prevent or to promote cancer. Cells with mutations in oncogenes or tumor suppressor genes often have increased proliferation rates. Somatic selection increases their abundance and thus enhances the risk of cancer. Many potentially harmful mutations, however, increase the probability of triggering apoptosis and, hence, initially lead to cells with reduced net proliferation rates. Such cells are eliminated by somatic selection, which therefore also works to reduce the risk of cancer. We show that a tissue organization into small compartments avoids the rapid spread of mutations in oncogenes and tumor suppressor genes, but promotes genetic instability. In small compartments, genetic instability, which confers a selective disadvantage for the cell, can spread by random drift. If both deleterious and advantageous mutations participate in tumor initiation, then we find an intermediate optimum for the compartment size.
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1. Introduction

Somatic mutations accumulate during the lifetime of an individual. For functional purposes, let us define somatic mutations as any kind of modification of the genetic material of a cell that is passed on to the daughter cell. Hence 'mutation' includes point mutations, chromosomal rearrangements, unequal crossing over, loss of heterozygosity, modification of DNA methylation, etc. Such mutations are caused by intrinsic errors of DNA replication and repair as well as by external factors such as exposure to mutagenic substances or radiation. Many somatic mutations are neutral: they do not change the phenotype of a cell. Some somatic mutations lead to cells that reproduce more slowly than their neighbors. These mutations are 'disadvantageous' with respect to somatic selection. A small proportion of mutations lead to cells that reproduce faster than their neighbors. These mutations are 'advantageous' with respect to somatic selection. All types of somatic mutations can increase the risk of developing cancer.

The activation of an oncogene is normally thought to confer a growth advantage to the cell, and hence is an advantageous mutation (Stehelin et al., 1976; Kinzler and Vogelstein, 1998; Meier et al., 2000). Inactivation of the first copy of a tumor suppressor (TSP) gene is normally a (nearly) neutral mutation, while inactivation of the second copy of a TSP is normally an advantageous mutation (Knudson, 1971; Moolgavkar and Knudson, 1981; Friend et al., 1986). We can also envisage mutations in oncogenes or TSP genes as initially conferring a selective disadvantage (for example by triggering apoptosis) to the cell. The selective advantage might only emerge at a later stage of tumor formation following additional mutations.

Mutations in genes that induce genetic instability (Loeb et al., 1974; Tomlinson et al., 1996; Lengauer

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et al., 1997; Loeb, 1998; Tomlinson and Bodmer, 1999; Sen, 2000) could be selectively neutral, advantageous or disadvantageous. They are advantageous if in addition to increasing mutation rates they also increase the rate of cellular proliferation. The presence of certain carcinogens could provide direct selection pressure for genetic instability mutations (Breivik and Gaudernack, 1999a, b; Bardelli et al., 2001). Normally, however, one would consider genetic instability mutations to be disadvantageous: they induce many mutations which might trigger apoptosis. Hence, there is a cost for genetic instability. The discussion concerning the importance of genetic instability in driving tumorigenesis requires a calculation whether or not the cost of genetic instability is balanced by accelerating the rate of accumulation of advantageous mutations (Komarova et al., 2002, 2003; Nowak et al., 2002).

The majority of human cancers arises in epithelial tissues. These tissues are organized into small compartments of cells (Mintz, 1971, 1977; Kovacs and Potten, 1973; Bach et al., 2000). Apoptosis plays a major role in normal development and in regulating cell numbers in compartments (Jacobson et al., 1997). In addition, apoptosis has a protective function against cancer (Levine, 1993, 1997). Cells have internal sensors to detect DNA damage or oncogene expression. These sensors feed into complex gene regulation networks that can trigger apoptosis. In this context, the role of apoptosis is to ensure that many somatic mutations have a selective disadvantage and are, therefore, prevented from spreading in a tissue.

Hence, somatic selection plays a dual role in the war against cancer that is waging within every multicellular individual. On one hand, somatic selection favors those cells that have an unwanted replicative advantage due to mutations in genes like oncogenes or TSP genes. In this context, somatic selection works for cancer. On the other hand, somatic selection leads to the elimination of cells with mutations that reduce the net proliferation rate of cells, possibly by triggering apoptosis. In this context, somatic selection works against cancer, because it prevents the accumulation of somatic mutations. We study this tension between somatic selection for and against cancer (Cairns, 1975).

2. Spatial somatic selection

Consider a tissue containing Z cells that are at risk of acquiring mutations that provide a step towards tumor formation. Suppose the tissue is organized into M compartments, each containing N cells. We have $Z = MN$. Homeostasis, that is constancy in cell number, is achieved by density regulation within each compartment and by maintaining a constant number of compartments. Tumor formation is escape from homeostatic regulation: a clone of mutant cells increases in abundance beyond compartment boundaries.

More generally, we can interpret the compartment size, N, as denoting the spatial scale of density regulation within a solid tissue. If N is large, then many cells of the tissue contribute to maintaining homeostasis at a particular location. If N is small, then only a few cells contribute to maintaining homeostasis at a particular location.

Note that we do not consider all cells of a solid tissue, but only those that can receive mutations that might lead to cancer. For example, the human colon is organized into about 10^7 crypts each containing approximately 10^3–10^4 cells. Each crypt is maintained by a small number of stem cells (possibly 1–10) (Bach et al., 2000; Yatabe et al., 2001). If only the stem cells are at risk of mutating into cells that can give rise to neoplasia and later to cancer, then the compartment size of our model would be $N \approx 1$–10 (Michor et al., 2003a). Thus, in the context of our analysis, N is the effective number of cells per compartment that can in principle receive mutations that lead to cancer. Furthermore, a specific spatial structure within a compartment and asymmetric cell divisions can also reduce the effective population size (Michor et al., 2003c).

3. One mutation

Let us first consider the dynamics of a mutation in a particular gene. Denote by u the probability that this mutation occurs per cell division. Denote by r the relative growth rate of the mutant cell compared to a wild-type cell. If $r > 1$, the mutant cell has a selective advantage. If $r = 1$, the mutation is neutral. If $r < 1$, the mutant cell has a selective disadvantage.

Denote by $x_0(t)$ the probability that a compartment contains only wild-type cells at time t. Denote by $x_1(t)$ the probability that a compartment contains only mutant cells at time t. If $u \ll 1/N$, we can neglect compartments that contain a mixed population. In this case, we have $x_0(t) + x_1(t) = 1$. The rate at which mutant cells are being produced in a single compartment is given by Nu. The probability that a single mutant cell takes over the compartment is given by $\rho = (1 - 1/r)/(1 - 1/r^N)$. This is the exact fixation probability for the Moran Process (Komarova et al., 2003). It holds both for strong and weak selection. It holds for $r > 1$ and $r < 1$. In the limit $r \to 1$, we obtain $\rho = 1/N$. Kimura derived a similar equation for the Wright Fisher Model using diffusion approximation which holds in the limit of weak selection (Ewans, 1969).

Assume cells divide every τ days. Let t measure time in units of τ. If $ut \ll 1$, we obtain $x_1(t) = Nu\rho t$. The expected total number of mutant cells at time t is

given by

$$Z_m(t) = ZNu\rho t. \quad (1)$$

The crucial question is the following: given a fixed number of cells, Z, what is the optimum number of cells per compartment, N, to minimize the rate of accumulation of mutated cells? In other words, what is the optimum way to compartmentalize a tissue with respect to homeostatic regulation in order to provide maximum stability against tumor initiation? Minimizing $Z_m(t)$ as a function of N means minimizing $N\rho$. To protect against advantageous mutations we find that compartments should be as small as possible: for $r > 1$, $N\rho$ increases with N. Hence, the best protection against advantageous mutations is a tissue organization into many small compartments. Once such a mutation arises, there is a high probability that it will take over the compartment, but subsequently the number of mutated cells is kept low, because the compartment is small. To protect against disadvantageous mutations, however, we find that compartments should be as large as possible: for $r<1$, $N\rho$ decreases with N. For neutral mutations, we have $N\rho = 1$ and the compartment size does not affect the rate of accumulation of mutated cells (Fig. 1). These results are obvious from the perspective of population genetics, but worth noting for understanding the somatic evolution of cancer.

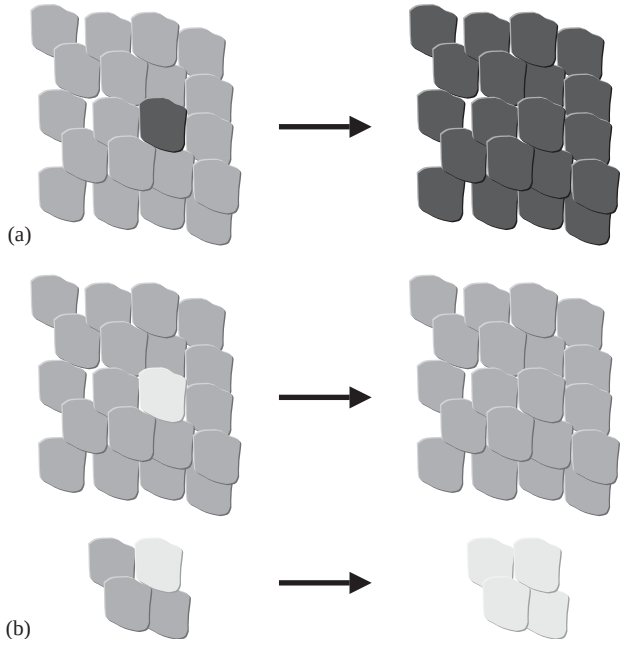

Fig. 1. Somatic selection and the architecture of tissue compartmentalization determine the abundance of different types of mutations. (a) Mutations in oncogenes or TSP genes normally confer a growth advantage to the respective cell (black). Such cells have a high probability to take over both small and large compartments. After the takeover, there are fewer mutated cells in small compartments than in large compartments, which reduces the risk of further tumor progression. Here we suppose the mutation is contained within the boundaries of the compartment. Hence, small compartments are more effective in containing the accumulation of cells with mutations in TSP genes. (b) Mutations that induce genetic instability and/or trigger apoptosis can lead to a growth disadvantage of the respective cell (light gray). Since random drift is important in small compartments, there is still a certain probability that such cells will be fixed. In large compartments, this probability is negligible. Hence, large compartments are ideal for limiting the accumulation of chromosomally unstable cells. A tissue design that delays mutations in oncogenes or TSP genes increases the incidence of genetic instability.

4. Several mutations

Suppose that in a particular tissue, mutations in several different genes can lead to cells that are phenotypically modified toward neoplasia and cancer. Assume there are n such mutations; mutation i occurs at rate u_i and leads to a relative growth rate r_i. The probability of fixation of mutation i in a compartment of size N is given by $\rho_i = (1 - 1/r_i)/(1 - 1/r_i^N)$. The total number of mutated cells at time t is given by

$$Z_m(t) = ZN \sum_{i=1}^{n} u_i \rho_i t. \quad (2)$$

Again we want to find the optimum compartment size, N, that minimizes the number of mutated cells, $Z_m(t)$.

There exists an intermediate optimum if at least one mutation is advantageous and $\sum_i u_i(1 - 1/r_i) < 0$. Let $u = \sum_i u_i$ denote the total mutation rate. We can define the harmonic mean of the phenotypic consequence of mutation as $H = [\sum_i (u_i/u)(1/r_i)]^{-1}$. Then an intermediate optimum exists if at least one mutation is advantageous and $H < 1$.

Another possibility to express the crucial condition is

$$\sum_{i\,:\,r_i>1} u_i \left(1 - \frac{1}{r_i}\right) < \sum_{i\,:\,r_i<1} u_i \left(\frac{1}{r_i} - 1\right). \quad (3)$$

Hence, the rate of generating advantageous mutations multiplied by a factor that measures how much they deviate from neutrality has to be less than the rate of generating disadvantageous mutations multiplied by the same factor. If this condition holds, then there exists an intermediate optimum N which minimizes the rate of accumulation of mutated cells.

The optimum compartment size, N, is given by the solution of the equation $\sum_i u_i(1 - 1/r_i) g(r_i^N) = 0$, where $g(x) = x(x - 1 - \ln x)(x - 1)^{-2}$. From this we can see that nearly neutral mutations ($r_i \approx 1$) and very deleterious mutations ($r_i \approx 0$) have no effect on the optimum compartment size. Those mutations that are advantageous and intermediately deleterious shape the optimum compartment size (Fig. 2).

4.1. Two mutations

As a specific example, let us calculate how mutations in two genes shape the optimum compartment size.

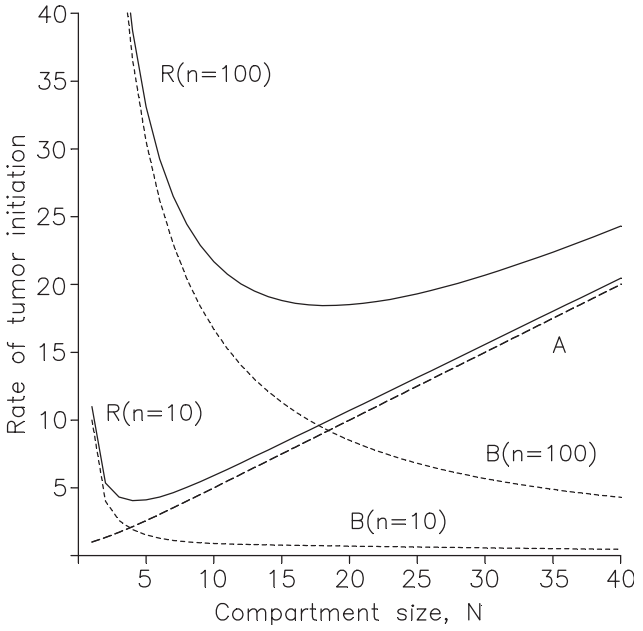

Fig. 2. Computing the optimum selective scenario that minimizes the rate of accumulation of dangerous mutations. Consider a cell type where mutation in one gene causes a growth advantage ($r_0 = 2$), while mutations in $i = 1, \ldots, n$ genes lead to a reduction in the reproductive ratio (we take the r_i values from a uniform random distribution between 0 and 1). We show two examples: $n = 10$ and $n = 100$. The solid lines show the total rate $R = A + B$. The broken lines show the contributions that come from advantageous mutations ($A = N\rho_0$) or deleterious mutations ($B = N\sum_{i=1}^{n}\rho_i$). The more the number of advantageous mutations exceeds the number of deleterious mutations, the smaller the optimum compartment size becomes. For $n = 10$, the optimum is $N = 4$, whereas for $n = 100$, the optimum is $N = 18$.

Assume that mutations in gene 1 occur with mutation rate u_1 and lead to cells with a selective advantage $r_1 > 1$, whereas mutation in gene 2 occur with mutation rate u_2 and lead to cells with a selective disadvantage, $r_2 < 1$. We can also include relative weights k_1 and k_2 that determine how dangerous mutations in the corresponding genes are with respect to the further somatic evolution of cancer. We have $\rho_1 = (1 - 1/r_1)/(1 - 1/r_1^N)\rho_2 = (1 - 1/r_2)/(1 - 1/r_2^N)$. We want to minimize the function $f(N) = N(u_1k_1\rho_1 + u_2k_2\rho_2)$. This can be rewritten as

$$f(N) = N\left(\frac{a}{1 - e^{-bN}} + \frac{c}{e^{dN} - 1}\right). \quad (4)$$

Here $a = u_1k_1(r_1 - 1)/r_1$, $b = \log r_1$, $c = u_2k_2(1 - r_2)/r_2$ and $d = -\log r_2$. This function has a minimum for positive N provided $c > a$. The minimum is given by the solution of the equation

$$a\frac{[1 - e^{-bN}(1 + bN)]}{[1 - e^{-bN}]^2} = c\frac{[(dN - 1) + e^{-dN}]e^{-dN}}{[1 - e^{-dN}]^2}. \quad (5)$$

We can derive two approximations for the optimum compartment size that minimizes the risk. One approximation works for small N, the other one for large N. For small N, that is $N < 1/b$ and $N < 1/d$, we have

$$N^* \approx 3\frac{c - a}{ab + cd}. \quad (6)$$

For large N, that is $N \gg 1/b$ and $N \gg 1/d$, Eq. (5) becomes $dN = \log h + \log(dN)$, where $h = c/a$. This can be solved by iteration $N_1 = (1/d)\log h$ and $N_{i+1} = (1/d)[\log h + \log(dN_i)]$. We obtain solutions of increasing accuracy:

$$N_1^* \approx \frac{1}{d}\log h, \quad N_2^* \approx \frac{1}{d}\log(h\log h),$$

$$N_3^* \approx \frac{1}{d}\log(h\log(h\log h)), \ldots \quad (7)$$

5. Mutations that ignore compartment boundaries

So far we have considered mutations that are at least initially constrained by the boundaries of the compartment in which they arise. Let us now consider advantageous mutations that immediately give rise to cellular proliferation that exceeds the compartment boundary. Specifically, let us consider a particular mutation with a somatic fitness advantage, $r > 1$, that gives rise to neoplasia of 'size' K with probability $\rho = (1 - 1/r)/(1 - 1/r^N)$ (see Fig. 3). The parameter K can denote the average number of cells of the neoplasia weighted with some risk factor of further tumorigenesis. In general, K could be independent of N or some function of N. If K is independent of N, then the compartment size has no effect on the size of the initial neoplasia. If larger compartments allow larger neoplasias, then K is an increasing function of N. These are the two reasonable possibilities that we have to investigate.

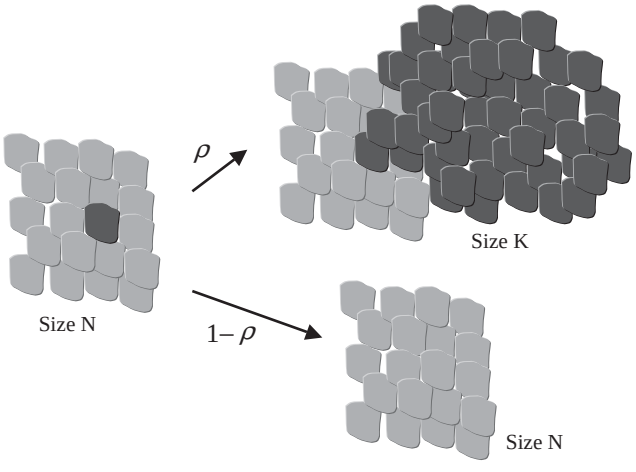

Fig. 3. Mutations that ignore compartment boundaries. Cells bearing advantageous mutations can immediately give rise to cellular proliferation that exceeds the compartments boundaries. Denote by ρ the probability that the advantageous mutation breaks through the boundaries of the compartment and gives rise to a neoplasia of size K.

The total number of mutated cells (or more generally, the risk of cancer) can be written as

$$Z_m(t) = ZK(N)\rho ut. \quad (8)$$

If K is a constant, then larger compartment sizes are more effective in delaying the onset of cancer. Note that ρ is a decreasing function of N. If K depends on N, then the crucial question is if $K(N)\rho$ is an increasing or decreasing function of N or has an intermediate minimum. Denote by $K'(N)$ the first derivative, $dK(N)/dN$. $K(N)\rho$ is an increasing function of N if $K'(N)/K(N) > r^{-N}\log r$. In this case, the smallest possible compartment size is most effective in delaying the onset of cancer. As a generic example, consider $K(N) = N^{\alpha}$. For $\alpha > 0$, the optimum compartment size is a finite value of N. For $\alpha > \ln(r)/(r-1)$, the optimum compartment size is $N = 1$.

6. Discussion

Somatic selection plays a dual role in affecting the emergence of cancer in multicellular organisms. Somatic selection works in favor of cancer by increasing the abundance of cells that have mutations in TSP genes and oncogenes. Somatic selection works against cancer by eliminating cells that bear potentially harmful mutations which, however, increase the chance of triggering apoptosis. Thus, apoptosis as a defense mechanism against cancer exerts somatic selection.

The optimum selective scenario that maximally delays the onset of cancer depends on the types and relative frequencies of mutations that can occur. Mutations that increase the net proliferation rate are best controlled by small compartments, while mutations that reduce the net proliferation rate are best controlled by large compartments. If both types of mutations occur in a particular cell type and if the harmonic mean of the phenotypic effect of mutation is less than one, then there is an intermediate optimum compartment size. Large compartments augment selection, while small compartments emphasize random drift and minimize the consequences of selective differences.

Mutations in genes that confer genetic instability are considered to reduce the net reproductive success of cells when they first arise. Genetic instability increases the chance of inactivating housekeeper genes, introducing lethal mutations, and hereby triggering apoptosis. This selective disadvantage can be counterbalanced by an increased chance of generating advantageous mutations such as the inactivation of TSP genes. The per se deleterious mutation causing genetic instability might, in the absence of recombination, hitch-hike on advantageous mutations (Giraud et al., 2001; De Visser, 2002). Here, however, we are interested in the first step toward cancer and neglect the probably advantageous consequences of initially deleterious mutations giving rise to genetic instability. Hence, the small compartment sizes that may have evolved in order to contain mutations in oncogenes and TSP genes make the organism vulnerable to cancer initiation via genetic instability (Michor et al., 2003b).

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