

like running kinetics^{9–12} and to understand why elephants avoid using an aerial phase.

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Cell biology

Developmental predisposition to cancer

Many human cancers occur in renewing epithelial tissues, in which cellular lineages typically go through two distinct phases: early in life, cell populations expand exponentially to form the tissue, and for the remainder of life, the tissue is renewed by stem cells dividing to create an almost linear cellular history¹. Here we use a simple mathematical model to show that mutations that arise during the exponential phase probably seed tissues with stem cells carrying mutations that may predispose to cancer. Susceptibility to late-life cancers, such as those of the skin and colon, may therefore be influenced by somatic mutations that occur during early development.

Mutations accumulate during exponential cellular growth according to the Luria–Delbrück distribution². Let u_e be the mutation probability per cell division during exponential growth, and N the number of stem cells produced during development to seed the tissue. Starting with one cell, the number of cell divisions required to produce N cells is $N-1$, and the total number of mutation events during the cellular history is $M = u_e(N-1) \approx u_e N$. (The phases of cellular growth are shown in Fig. 1a.)

Figure 1b shows the probability distribution for the number of stem cells that carry mutations. These are the mutations that arise during exponential growth, before further division of the stem lineages to renew the local tissue. The average frequency of stem cells with mutations is $\bar{x} \approx u_e \ln(N)$ (ref. 2).

Although the frequency of stem cells that initially contain a mutation may be small, those mutations can contribute substantially to the total risk, R_T , of cancer. Suppose that k rate-limiting mutations are needed for cancer to develop^{3,4}, then the total risk is $R_T = N(1-x)R_k + NxR_{k-1}$, where x is the frequency of stem cells that start with one mutation, and R_k is the risk that a particular stem-cell lineage acquires k mutations during

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Supplementary information accompanies this communication on Nature's website.

Competing financial interests: declared none.

the phase of linear division and tissue renewal. The risk, R_k , is given roughly by the gamma distribution, which describes the probability of the occurrence of the k th event over a particular time interval. From the gamma distribution, $R_k \approx (u_e \tau)^k / k!$, where u_e is the mutation rate per stem-cell division, and τ is the total number of stem-cell divisions.

The expected fractional increase in cancer risk arising from stem cells that begin with one mutation can be calculated as $F = \bar{x} R_{k-1} / R_k \approx u_e \ln(N) k / u_e \tau$. The next step is to assign approximate magnitudes to these quantities. We can take $k \approx 5$ for the number of rate-limiting mutations required to cause epithelial cancer in humans^{3,4}, $\ln(N) \approx 20$, and τ to range from 100–1,000. This gives the fractional increase in cancer risk, F , ranging from $u_e / 10 u_e$ to u_e / u_e .

If mutations accumulate with the same probability per cell division during exponential growth and linear stem-cell division ($u_e = u_l$), then the increase in risk from mutations arising in development ranges from 10–100%. If, as has been claimed⁵, mutation rates in stem cells are much lower than those during exponential growth, ($u_e \ll u_l$), then almost all cancer arises from predisposed stem-cell lineages that were mutated during development.

The risk of cancer from somatic mutations during development could be quantified by studying inbred rodents. The number of predisposing mutations per individual will vary according to the Luria–Delbrück distribution (Fig. 1b). Individuals with many predisposing mutations are likely to develop multiple independent tumours relatively early in life, whereas those with few predisposing mutations should develop few tumours relatively late in life. Controlled experiments have shown variability in cancer susceptibility among inbred rodents⁶, but the causes of this variability have not been determined.

Mutations during development seed a young individual with a small fraction of mutated stem cells. Those relatively few mutated lineages may therefore be responsible for a substantial proportion of the

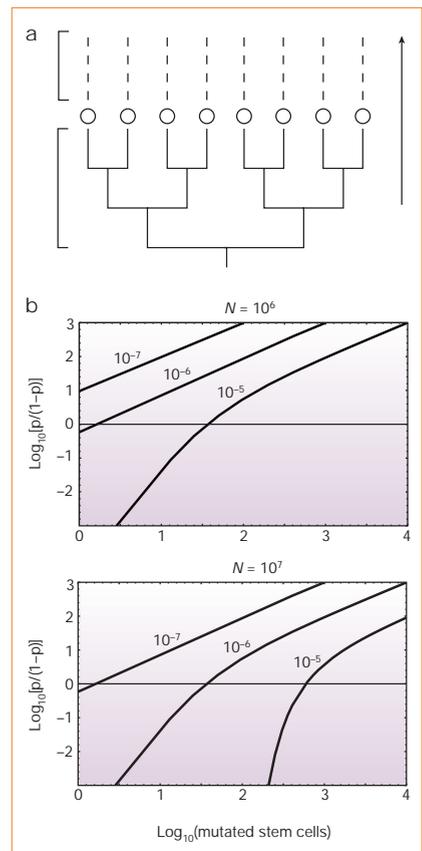


Figure 1 The role of tissue architecture in the accumulation of mutations during development. **a**, The phases of cellular growth in epithelial tissues. Cell populations increase exponentially during development, shown by a branching phase of division; at the end of development, stem cells differentiate in each tissue compartment (circles); stem cells renew each compartment by dividing to form a nearly linear cellular history (dashed lines) — each stem-cell division gives rise to one daughter stem cell that continues to renew the tissue and to one daughter transit cell that divides rapidly to produce a short-lived lineage that fills the tissue. **b**, The cumulative probability, p , for the number of stem cells mutated during development. By plotting $\log_{10}[p/(1-p)]$, the zero line gives the median of the distribution. N , number of stem cells produced during exponential growth. The number above each line is u_e , the mutation probability per cell added to the population during exponential growth. For a single gene, u_e is probably of the order of 10^{-7} ; thus, if there are 100 genes for which initial mutations can influence the progression to cancer, then u_e is roughly of the order of 10^{-5} . The Luria–Delbrück distribution plotted here was calculated using equation (8) of ref. 7.

cancers that develop later in life.

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Competing financial interests: declared none.