SINGLE CELL AGAINST MULTICELL HYPOTHESES OF TUMOR FORMATION

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Certain passages of the preceding paper by Linder [2] suggest the question whether tumors such as leiomyomas always emerge from one single cell or whether they may have their origin in several cells. On the face of it, the evidence presented strongly supports the single cell hypothesis. It is not my intention to dispute this; it may be interesting, however, to see that a phenomenon like the one described by Linder could also be explained by a chance mechanism. The point is that even if every tumor starts with *both* kinds of cells present, the chance mechanism that we describe would imply that large tumors containing both types of cells would be very rare.

A model frequently used to describe the growth of a population of cells is that of a birth and death process. Here the number of cells present at time t is a random variable $X(t)$. Given $X(t) = n$, the following changes may occur within a subsequent short time interval of length τ:

(i) a birth, that is, $X(t + \tau) = n + 1$, with probability $\lambda_n\tau + o(\tau)$,
(ii) a death, that is, $X(t + \tau) = n - 1$, with probability $\mu_n\tau + o(\tau)$,
(iii) other changes, with probability $o(\tau)$,

where λ_n, μ_n are nonnegative numbers and where $o(\tau)/\tau$ tends to zero as $\tau \to 0$. A birth and death process will be called linear if $\lambda_n = \lambda n$ and $\mu_n = \mu n$.

This model has been extended by Reuter [5] to describe the simultaneous development of two populations allowing for interaction, for example, competition, between the different populations. For the present purpose, however, a very particular case of his general scheme will be sufficient.

Thus, let us assume that two populations develop independently, each one according to a linear birth and death process. Denote their sizes by $A(t)$ and $B(t)$. Then we want to study the conditional probability

$$P\{A(t) > 0, B(t) > 0 | A(t) + B(t) \geqq N\}, \tag{1}$$

the condition $A(t) + B(t) \geqq N$ reflecting the fact that we consider only tumors large enough to be detected and included in the study. Since, apparently, either one of the two cell types can be detected only if it is present in at least a certain proportion, say α, (according to [2] α is between 0.05 and 0.15), we may consider instead

$$P\{A^*(t) \geqq \alpha, B^*(t) \geqq \alpha | A(t) + B(t) \geqq N\}, \tag{2}$$

where $A^*(t) = A(t)/[A(t) + B(t)]$ and $B^*(t) = B(t)/[A(t) + B(t)]$.

Under these assumptions the following results hold. Their proofs will be published elsewhere [1].

THEOREM 1. *Let $A(t)$ and $B(t)$ be two independent linear birth and death processes with birth rates λ_A, λ_B and death rates μ_A, μ_B. Then, if $\lambda_A < \mu_A$ and $\lambda_B < \mu_B$, whatever $N \geqq 1$ and whatever the fixed or random initial population sizes $A(0)$ and $B(0)$ may be,*

$$\lim_{t\to\infty} P\{A(t) > 0, B(t) > 0 | A(t) + B(t) \geqq N\} = 0. \tag{3}$$

THEOREM 2. *Let $A(t)$ and $B(t)$ be two independent linear birth and death processes both with the same birth rate λ and the same death rate μ. Then, if $\lambda > \mu$, and if $A(0) = B(0) = 1$, for any α with $0 \leqq \alpha \leqq 1/2$,*

$$\lim_{t\to\infty} P\{A^*(t) > \alpha, B^*(t) > \alpha | A(t) + B(t) \geqq N\} = (1 - 2\alpha)\frac{1 - \mu/\lambda}{1 + \mu/\lambda}. \tag{4}$$

Since leiomyomas are benign tumors, one may tend to think in terms of subcritical birth and death processes, that is, those with $\lambda < \mu$. Then, theorem 1 would simply say that after a long time it would be very unlikely to find both types of cells in a tumor, no matter from how many cells of each kind the tumor originated.

However, it seems that at least the early stages of growth, which we may consider the most important for our question, are quite supercritical so that we should look at theorem 2 instead. An estimate of λ can be obtained from studies using tritiated thymidine as a marker of cells in DNA synthesis [3], [4]; also $\lambda - \mu$ can be estimated from the sizes and ages of the tumors under study. Combining these estimates we find that μ/λ may be of the order of 0.95; together with $\alpha = 0.1$. This combination would make the limit in (4) of the order of two per cent.

Thus, even if all tumors had started with one cell of each type, under the present model we would not expect to find more than three or four tumors with two bands among all the 122 leiomyomas studied. The presence of real selection forces would further decrease the probability of finding tumors containing both types of cells. In conclusion we may say that although there seems to be strong evidence for a single cell origin of leiomyomas, the possibility that this evidence was brought about by a chance mechanism including some competition like forces cannot be excluded.

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