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On Cell Cycle of Ascites Tumor

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腹水腫瘍の増殖と細胞周期

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On Cell Cycle of Ascites Tumor

There are many reports on the duration of each phase of the cell cycle and on variation in cell cycle time.1-11

However, as pointed out by Barrett, durations of the phases are generally computed on the hypothesis that they have constant values. He considers that some variability is inevitable in any population of cells. And so he statistically investigated the duration of each phase in subcutaneously transplanted mammary cancer in rats, and found that the thus obtained results agreed well with the experimentally acquired data. Mendelsohn established 3 statistical models of mammary cancer of C3H mouse, and computed the distribution of the generation time (hereafter referred to as T). Authors attempted after Barrett, statistical analysis of the cell cycle phases in Yoshida sarcoma and AH-13 ascites tumor which had often been used in our experiments. The methods and results will be described below.

Experimental Methods:

i) In the previous experiments, 108 cells of Yoshida sarcoma (hereafter referred to as Y.S.) were intraperitoneally transplanted into Wister rats, and on 4 days thereafter, T was computed by autoradiography using 3H-TdR. The results were published in the first report. In this text the above data were used as material of statistical analysis.
ii) On 2 days after intraperitoneal transplantation of $10^6$ cells of AH-13 hepatic ascites cancer (hereafter referred to as AH-13) into Domryu rats, T was computed by autoradiography using 3H-TdR of 100 $\mu$Ci (specific activity, 2.5 Ci/m M), and the data were used for statistical analysis.

Statistical procedure:

The data were dealt with statistically by a Monte Carlo method using an electronic computer. In the program, the time scale was divided into intervals corresponding to 1 hour. The program proceeds as follows.

1. Average m and standard deviation $\sigma$ are given to each phase.
2. The average and the standard deviation for the log-normal distribution are computed from $m$ and $\sigma$ for each phase.
3. According to the log-normal distribution, probability of each phase being found in time period between $t_{i-1}$ and $t_i$ is computed.
4. According to the obtained probability, integer out of 0–999 is assigned to $t_i$ for each phase, that is, integer $N_i$. Corresponding to the time period between $t_{i-1}$ and $t_i$, generated by a computer, time period of a phase should be registered as $t_i$.
5. One of the uniform random numbers of 0–999 is generated, and the duration of $G_2$ phase, $T_{G2}$, is firstly determined by $t$ corresponding to the random number. Then, $T_{G2}$ is obtained by the formula $T_{G2} = t_{G2} - 0.5$.
6. Random number is generated to determine the duration of S phase, $t_s$. Then $T_{G2} = t_{G2} - 0.5 + (t_s - 0.5) + r_{G2}$.
7. 1 is added to each of the channels corresponding to the integers of $T$, which satisfy $T_{G2} < T_i \leq T_{G2} + 1$.
8. Random number is generated to determine the duration of $G_1$ phase, $t_{G1}$. Subsequently is obtained formula $T_{G2} + r = t_{G2} + t_s + t_{G1} - 1.5$.
9. Random number is generated to determine again the duration of $G_2$ phase, $T_{G2}$. Then $T_{G2} + r + r + r = t_{G2} + t_s + t_{G1} + t_{G2} - 2.0$.

The same procedures are repeated until the total 40 hours is produced.
10. The above procedures are repeated usually 1,000 times.
11. In the end, the numerals added to all the channels are read out. Therefore, the sum was obtained of the number of cells now in mitosis that had been in S in any particular hour. The used computer was OKITAC-5090.

Results

1. At 4 days after intraperitoneal transplantation of $10^6$ cells of Y.S. into Wister rats, T and the duration of each phase were determined autoradiographically. The measurement gave 19, 0.35, 12.4, 5.5, and 0.75 hours for T and durations of $G_1$, $S$, $G_2$, and M phases, respectively, whereas the statistical computation gave 18.9, 1.9, 11.0 and 5.9 hours for T, $G_1$, S and $G_2 + M$, respectively. There is good agreement between the two series of the values (Fig. 1).

II. At 2 days after intraperitoneal transplantation of $10^6$ cells of AH-13 into Domryu rats, autoradiographical determination of T and durations of $G_1$, $S$, $G_2$ and M gave 13.0, 0.9, 3.0, 3.5 and 0.6 hours, respectively. On the other hand, the statistical computation gave 13.8, 2.9, 7.5 and 3.5 hours for T,
Fig 1. The Mitotic Cycle of Y.S (4 days after transplantation)

Fig 2. The Mitotic Cycle of AH-13 (2 days after transplantation)

$G_1$, $S$, and $G_2 + M$, respectively. There is good agreement between the two series of values (Fig. 2).

**Discussion**

Many reports have been made by the use of 3H-TdR on the duration of each phase of growth of a population of cells. But the majority of them determined it on the assumption that it is constant in all the cells. Kozuka and More\(^{15}\), who observed HeLa cells during culture cinematographically and autoradiographically, found that, the duration of the same phase varied from cell to cell. Barrett assumed that in any population of cells the duration of each phase would show statistical variation, and on this assumption he theoretically computed percentage labeled mitoses and frequency distribution of cycle time of Marshall tumor cells. He reported that the thus computed values were in good agreement with the experimentally obtained values. In the present experiments authors autoradiographically determined $T$ and the duration of each phase of growth of Y.S. and AH-13, and found that the values obtained agreed well with the results of computation which was performed on the basis of assumption that the duration of each phase would have log-normal distribution. It was subsequently assumed that at least in trans-
planted tumor cells, the duration of each phase would not be the same in all of them, but show statistical variation.

Summary

T and durations of phases G₁, S, G₂ and M of Y.S. and AH-13 were autoradiographically determined by using 3H-TdR, and 19, 0.55, 12.4, 5.5 and 0.75 hours were obtained for Y.S., and 13, 0.9, 8.0, 3.5 and 0.6 hours for AH-13, respectively. Furthermore it was found out that when T and the durations of the phases were statistically computed by giving a definite average and a standard deviation to each on the assumption that each has log-normal distribution, the results were in sufficiently good agreement with the experimentally determined values.

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References