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A Model for Radiation Injury (5)
— On the Target Theory —

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放射線障害の模型 (5)
— 標的説について —

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細胞レベルでの生存率曲線の分析に標的説を用いる際に生ずる理論的問題について考察を行った.細胞系が種々の観点から均質と考えられない場合にも,理論的には均質の場合と同じような生存率曲線が得られることが知られた. multi-target model で hitness number の違う細胞が混在する場合,又は均質系ではあるが細胞死には hitness number の違ういくつかの死の mode がある場合の生存率曲線を計算した.この生存率曲線は単純で均質な細胞系が示す生存率曲線と類似なものとなるため, 実験的に観察される extrapolation number や target volum eは微細構造を持つ可能性が常に存在する.すなわち観察された extrapolation number はいくつかの機構の hitness number の積又は荷重平均である可能性がある.又一方観察された target volume についてもいくつかの機構に対応する target volume の和である可能性がある. colony count の生存率曲線を mulit-target model で計算すると,平均 colony size が漸次減少するので生存細胞が hit から完全に回復しても生存率曲線は同じ形にはならない.細胞系内の吸収線量の不均一も生存率曲線に重大な影響を与える.

I. INTRODUCTION

Recently the target theory appears so often in the analysis of survival curves in cellular levels. In such cases careful caution must be taken for the applicability of the target theory. Also the target theory gives a group of survival curves but any experimental survival curves may be explained in many ways including the target theory. Within the target theory, it will be shown in this paper that some complicated systems have the same appearance as that of simple homogeneous systems. A few generalizations of the target theory have already been done by Pollard et al[1]., Zirkle et al[2]. and Quastler[3].

Pollard et al. have proposed the following equation,

$$P=e^{-S\,(1-e^{-Jt})\,B} \tag{1}$$

where S: cross section of the target

J: primary ion pairs/unit path length

t: thickness of the target

B: flux, number of particle/unit area.

In the above equation, the conventional target volume will be expressed as follows,

$$V=S\ (1-e^{-Jt}) \tag{2}$$

The Poisson distribution is used twice in equation (1), namely, the first in e^{-Jt} and the second in e^{-VB}. This formula is a more generalized one than the usual single hit theroy in the sense that the latter is deduced from the former as the case $Jt \ll$ small.

In the same way, giving a fine structure in the target volume, single hit formula can be written as follows,

$$P=e^{-(V_1+V_2+\cdots\cdots+V_n)D} \tag{3}$$

where Vi: target volume for the i-th effect. Zirkle-Tobias Diffusion Model gives two target volumes, one for the direct effect and the other for the indirect effect which is calculated from the diffusion theory of ions.

Another generalization of the target theory has been done by Quastler. Consider the organization having n_1 components where functioning of at least one component suffices for survival. The group of these n_1 components is also one component of the second-order system as shown in Fig. 1. In all these systems,

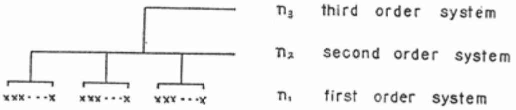

Fig. 1 Hierarchy of the system

the multi-target model is assumed to be applicable.

For given dose of radiation, the probability, Pi, of the component in the i-th order to survive will be written as follows,

$$\begin{aligned} P_2&=1-(1-P_1)^{n_1} \\ P_3&=1-(1-P_2)^{n_2} \\ &\vdots \\ P_i&=1-(1-P_{i-1})^{n_{i-1}} \end{aligned} \tag{4}$$

In equations (4), assuming

$P_i \ll$ small for any i,

P_i has the following form approximately,

$$P_i=1-e^{-n_{i-1}n_{i-2}\cdots n_1P_1} \tag{5}$$

In this paper some other applications of the multi-target model will be discussed, and also the effect of non-uniformity of dose distribution on the survival curve will be given.

II. RESULTS

1) Heterogeneous system of cells having several hitness numbers and mean lethal doses

Consider a cell population where several different types of cells co-exist in regard to hitness number n_i and to mean lethal dose D_{oi}. Let P_i the fraction of the i-th type of cells, then the survival is given by the following equation,

$$S=\sum_i P_i[1-(1-e^{-D/D_{oi}})^{n_i}] \tag{6}$$

The slope of the survival curve will be given as follows,

$$\frac{d\ (\ln S)}{dD}=\frac{-\sum_i P_i n_i \frac{1}{D_{oi}}\ (1-e^{-D/D_{oi}})^{n_i-1}\, e^{-D/D_{oi}}}{\sum_i P_i\,[1-(1-e^{-D/D_{oi}})^{n_i}]} \tag{7}$$

If $n_i > 1$ for any i,

$$\left(\frac{d\ (\ln S)}{dD}\right)_{D=0}=0 \tag{8}$$

If $n_j=1$, $n_i>1$ for $i \neq j$,

$$\left(\frac{d\ (\ln S)}{dD}\right)_{D=0}=-\frac{P_j}{D_{oj}} \tag{9}$$

Asymptotic form for $D \gg$ large is as follows,

$$S \fallingdotseq \sum_i P_i\ n_i\ e^{-D/D_{oi}} \tag{10}$$

Then in this heterogeneous system of cells the slope at $D=0$ is equal to zero as far as there is no component of single hit. If the mean lethal dose is the same for any component, the extrapolation number is the weighted mean of each extrapolation number.

2) Homogeneous system of cells having several modes of death.

Consider a cell population where cell death may occur by several modes of death. Let the i-th mode has hitness number n_i and mean lethal dose Doi, then the survival will be given as follows,

$$S=\prod_i\,[1-(1-e^{-D/D_{oi}})^{n_i}] \tag{11}$$

The slope of the survival curve is

$$\frac{d\ (\ln S)}{dD}=\sum_i\frac{\left(-\frac{n_i}{D_{oi}}\right)\left(1-e^{-D/D_{oi}}\right)^{n_i-1}\ e^{-D/D_{oi}}}{[1-(1-e^{-D/D_{oi}})^{n_i}]} \tag{12}$$

If $n_i>1$ for any i,

$$\left(\frac{d\ (\ln S)}{dD}\right)_{D=0}=0 \tag{13}$$

If $n_i=1$, $n_i>1$ for $i \neq j$,

$$\left(\frac{d\ (\ln S)}{dD}\right)_{D=0}=-\frac{1}{D_{oj}} \tag{14}$$

Asymptotic form for $D \gg$ large is as follows,

$$S \fallingdotseq n_1 n_2 \cdots n_m\, e^{-D\left(\frac{1}{D_{o1}}+\frac{1}{D_{o2}}+\cdots+\frac{1}{D_{om}}\right)} \tag{15}$$

where m is the number of modes of death. Then in this system the slope at $D=0$ is equal to zero as far as

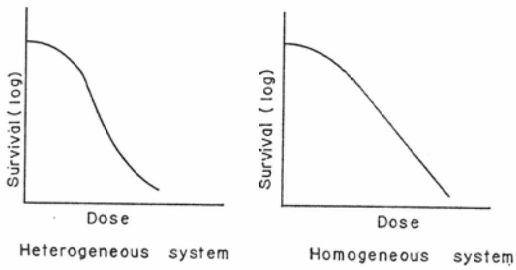

Fig. 2 The survival curves of the two systems

there is no mode of single hit. The extrapolation number is $\prod_i n_i$ and the target volume is the sum of each target volume. In Fig. 2 two types of survival curves corresponding to the above two populations are shown in general form.

3) Survival curve for colony count.

A detailed discussion for the survival curve and the recovery in divided exposures has been done by Elkind et al[4]. If a survival curve is given in colony count instead of individual cell numbers, the survival curves in divided exposures must be modified in extrapolation number. Let P the probability of survival in each cell, then the probability with which the colony of size N survives as the colony of size r ($r \leqq N$) is given as follows,

$$P(N \rightarrow r) = {}_N C_r P^r (1-P)^{N-r}$$

Let $\bar{N}_0$ the mean colony size before the irradiation, $\bar{N}$ the mean colony size after the irradiation, C the total number of colonies, C_N the fraction of colonies of size N and C'_N the number of colonies of size N. Then the whole number of colonies changing from size N to size r is given as follows,

$$C'_N P(N \rightarrow r) = C'_N {}_N C_r P^r (1-P)^{N-r}$$

The number of survivals having colony size r after irradiation is

$$\sum_{N \geq r} C'_N {}_N C_r P^r (1-P)^{N-r}$$

Also the whole number of survival colonies is as follows,

$$C_\sigma = C \sum_N C_N [1-(1-P)^N]$$

Then the mean colony size after the irradiation is as follows,

$$\bar{N} = \frac{\sum_r r \sum_N C\, C_N {}_N C_r P^r (1-P)^{N-r}}{C \sum_N C_N [1-(1-P)^N]} \tag{16}$$

This value is not in general the same as $\bar{N}_i$ given below.

$$\bar{N}_i = \sum_r C_r \cdot r \tag{17}$$

An example of this calculation is given below. Consider the homogeneous colony population of

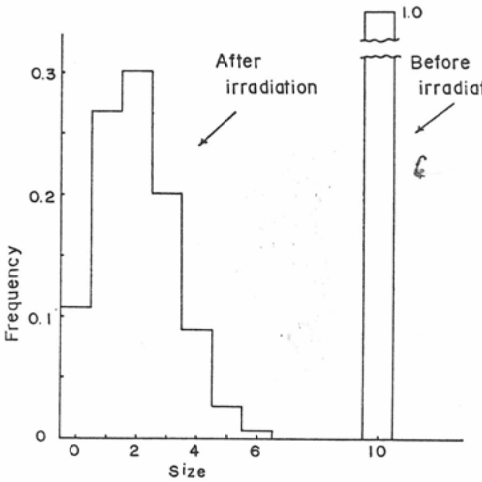

Fig. 3. The distribution of colony size

size 10. If the population is irradiated with a dose corresponding to P=0.2, the distribution of colony size in survival is shown in Fig. 3.

In this example survival of colony is 89% and the mean colony size after the irradiatin is 2. Then the survival curves in divided exposures in the region of the full recovery in the sense of Elkind et al.'s analysis are given in Fig. 4.

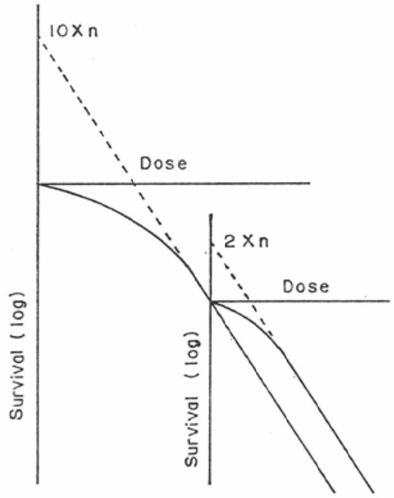

Fig. 4 The recurrence of survival curves

Namely in the recurrence of the survival curves given by divided exposures the extrapolation number continues to decrease owing to the decrease of colony size. In the Appendix appears the proof that the ratio of survival of divided exposures to that of single exposure of the same dose is maximum in the exponential region and is equal to the extrapolation number[4].

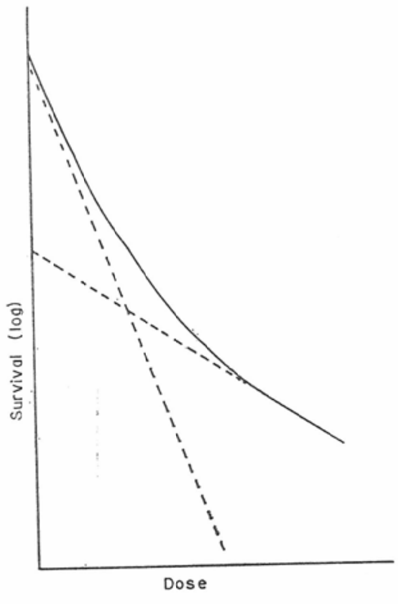

Fig. 5 Survival curves for two groups

4) The effect of non-uniformity of dose distribution on the survival curve

In case one has a concave survival curve, one may suppose that there would be two components (See Fig. 5)

Consider a simple case where accidentally dose distribution is not uniform in the population. For simplicity sake, we assume that there are two groups of dose, D_1 and D_2. In single hit theory each survival is given as follows,

$$N_1 = N_{10}\, e^{-bD_1}$$

$$N_2 = N_{20}\, e^{-bD_2}$$

In practice both are observed in the same time and the observed survival is

$$\frac{N_1+N_2}{N_{10}+N_{20}} = \frac{1}{N_{10}+N_{20}} \left(N_{10}\, e^{-bD_1} + N_{20}\, e^{-bD_2}\right)$$

Using $a = D_2/D_1$,

$$\frac{N_1+N_2}{N_{10}+N_{20}} = \frac{N_{10}}{N_{10}+N_{20}}\, e^{-bD_1} + \frac{N_{20}}{N_{10}+N_{20}}\, e^{-abD_1} \tag{18}$$

In appearance the survival curve is the same as that of two components having target volumes b and ab. In general, the survival of the population receiving non-uniform irradiation is given as follows,

$$S = \frac{1}{\sum_i N_{io}} \left\{ \sum_i N_{io}\, e^{-bD_{io}} \right\} \tag{19}$$

III. DISCUSSIONS

In the heterogeneous system if the lethal dose Doi is the same for any component, the survival curve in asymptotic form becomes the same as that of homogeneous population having extrapolation number $\sum_i P_i n_i$. In the homogeneous system having multiple modes of death, the survival curve in asymptotic form gives the same one as that of single mode of death. Accordingly the observed extrapolation numbers or observed target volumes may have the possibility that these parameters have fine structure. In the analysis of colony count, the sensitivity independence is assumed twice, namely once in the independence in each hit and the second, the independence of sensitivity from colony size. Particularly the latter assumption is desired to be examied experimentally. The dose distribution in the population is also an important factor for the shape of the survival curves. In addition to the above discussions, there is an experimental difficulty of the discrimination between multi-target model and multi-hit model. The individual fluctuation of the cells in radiosensitivity is left for further studies.

SUMMARY

The multi-target model is applied in some complicated systems of cells and the survival curves are calculated. In the heterogeneous system, the survival curves have in general no exponential region and no extrapolation number. The survival curves from the cells having multiple modes of death are the same as those of single mode of death. The survival curves on colony count never regenerate with divided exposure in the full recovery of the cells due to the decrease of the mean colony size. Non-uniformity of the dose distribution gives rise to a concave survival curve even in single hit model.

Reference

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2) Hutchinson F. and Pollard, E.: Mechanisms in Radiobiology Vol. 1 (ed. Maurice Errera et al.), 71—92, 1961.

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APPENDIX

A proof that the ratio of survival of divided exposures to that of single exposure of the same dose is maximum in the exponential region and is equal to the extrapolation number is given below.

1) In the exponential region

The survival probabilities of doses D_1, D_2, and D_3 are, respectively, P_1, P_2, and P_3 when each dose is given by single exposure (See Fig. 6).

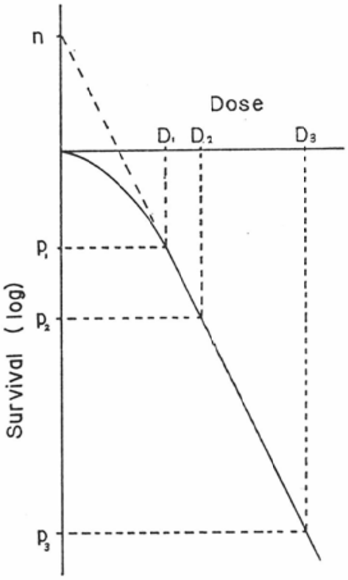

Fig. 6 Exponential region

And $D_1+D_2=D_3$. The following equations hold.

$$\frac{\ln n-\ln P_1}{\ln n-\ln P_3}=\frac{D_1}{D_3}$$

$$\frac{\ln n-\ln P_2}{\ln n-\ln P_3}=\frac{D_2}{D_3}$$

Adding the above both equations,

$$\frac{2\ln n-\ln P_1P_2}{\ln n-\ln P_3}=\frac{D_1+D_2}{D_3}=1$$

$$\ln\frac{n^2}{P_1P_2}\Big/\ln\frac{n}{P_3}=1$$

$$\therefore\frac{P_1P_2}{P_3}=n \qquad (20)$$

where $P_1\times P_2$ is the survival probability of divided exposures in the full recovery.

2) In the threshold region

Using the same notations as above (See Fig. 7),

$$\frac{\ln a-\ln P_1}{\ln a-\ln P_3}>\frac{D_1}{D_3}$$

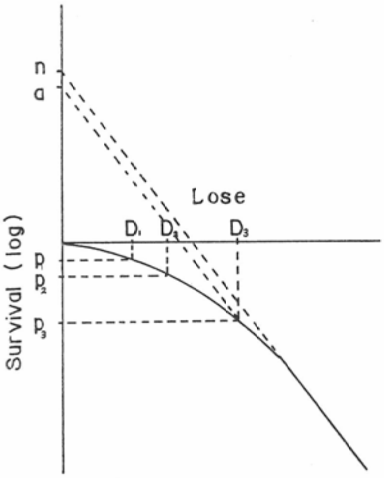

Fig. 7 Threshold region

$$\frac{\ln a - \ln P_2}{\ln a - \ln P_3} > \frac{D_2}{D_3}$$

where a is the intercept at D=0 of the line drawn from the point (D_3, P_3) parallel to the extrapolation of the exponential region. Adding the above both equations,

$$\frac{2\ln a - \ln P_1P_2}{\ln a - \ln P_3} > 1$$

$$\frac{\frac{a^2}{P_1P_2}}{\frac{a}{P_3}} > 1$$

$$\therefore \frac{P_1P_2}{P_3} < a < n \qquad (21)$$