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## Generalized Concept of the LET-RBE Relationship of Radiation-induced Chromosome Aberration and Cell Death

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### Radiation/LET/RBE/Chromosome aberration/Cell killing

The frequency of chromosome aberrations per traversal of a nucleus by a charged particle at the low dose limit increases proportionally to the square of the linear energy transfer (LET), peaks at about 100 keV/ $\mu\text{m}$  and then decreases with further increase of LET. This has long been interpreted as an excessive energy deposition over the necessary energy required to produce a biologically effective event. Here, we present an alternative interpretation. Cell traversed by a charged particle has certain probability to receive lethal damage leading to direct death. Such events may increase with an increase of LET and the number of charged particles traversing the cell. Assuming that the lethal damage is distributed according to a Poisson distribution, the probability that a cell has no such damage is expressed by  $e^{-cLx}$ , where  $c$  is a constant,  $L$  is LET, and  $x$  is the number of charged particles traversing the cell. From these assumptions, the frequency of chromosome aberration in surviving cells can be described by  $Y = \alpha SD + \beta S^2 D^2$  with the empirical relation  $Y = \alpha D + \beta D^2$  in the low LET region, where  $S = e^{-cL}$ ,  $\alpha$  is a value proportional to LET,  $\beta$  is a constant, and  $D$  is the absorbed dose. This model readily explains the empirically established relationship between LET and relative biological effectiveness (RBE). The model can also be applied to clonogenic survival. If cells can survive and they have neither unstable chromosome aberrations nor other lethal damage, the LET-RBE relationship for clonogenic survival forms a humped curve. The relationship between LET and inactivation cross-section becomes proportional to the square of LET in the low LET region when the frequency of a directly lethal events is sufficiently smaller than unity, and the inactivation cross-section saturates to the cell nucleus cross-sectional area with an increase in LET in the high LET region.

### INTRODUCTION

The lethal effect of charged particles and the induction of chromosome aberrations in living cells depend largely on LET of the charged particles, and the dependence is usually expressed by

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RBE. Many studies indicate that the LET-RBE curve is convex upwards with a maximum at around 100 keV/ $\mu\text{m}$ . An increase in the RBE for the low LET region forms the major basis of the "Theory of Dual Radiation Action" of Kellerer and Rossi<sup>1,2)</sup>. However Goodhead *et al.* proposed an alternative explanation, assuming a difference in the quality of the damage caused by low and high LET radiation<sup>3,4)</sup>. A decrease in the RBE in the high LET region has been generally accepted as a saturation effect, resulting from waste of the destructive energy, termed "overkilling".

Empirically, a clear LET-RBE relationship has been recognized in the low LET region while its theoretical bases is not solid, and much is remained to be solved for LET-RBE relationship in the high LET region. Recently, Sato and Soga<sup>5)</sup> reported that the survival of Chinese hamster V79 cells irradiated with high energy heavy ions was best expressed by

$$S_F(n, L) = \exp[-n\{1 - \exp[-(L/L_1)^2]\}], \quad (1)$$

where  $n$  is average number of hits to cell nucleus,  $L$  is LET, and  $L_1$  is a constant. This formula is equivalent to the expression of saturation effect in the modeling of Kellerer and Rossi<sup>1)</sup> that was adopted from the formulation proposed by Powers *et al.*<sup>6)</sup>. Since the constant  $L_1$  is empirical parameters fitted to the cell survival data, the formulation does not provide the basis of chromosome aberration formation with its associated cell killing. Here, we present more generalized concept for the LET-RBE relationship of chromosome aberration formation and cell death.

## LET DEPENDENCE OF CHROMOSOME ABERRATION

A dicentric is a type of chromosome aberration that is readily distinguishable and provides a useful measure for the quantitative analysis of the genetic effects of radiation. The frequency of dicentrics per cell induced by charged particles may be expressed as:

$$Y = \alpha D + \beta D^2, \quad (2)$$

where  $D$  is the dose absorbed  $\alpha$  and  $\beta$  are constants depending on the kinds of charged particles, their kinetic energy and cell. Many studies report that  $\beta$  is not largely dependent on the quality of radiation, in contrast to the wide variation in the value of  $\alpha$ <sup>7-10)</sup>.

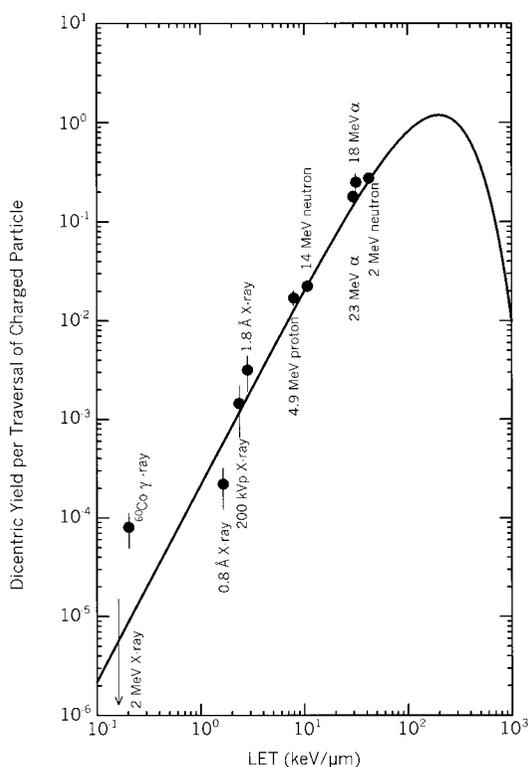
The fluence of charged particles is proportional to the absorbed dose and can be expressed as:

$$\Phi = \frac{k}{L} D, \quad (3)$$

where  $L$  is LET and  $k$  is a constant determined by the density of the substance. When the density of the substance is 1 g/cm<sup>3</sup>,  $k$  is 6.241 when the units of  $\Phi$ ,  $L$  and  $D$  are  $\mu\text{m}^{-2}$ , keV/ $\mu\text{m}$  and Gy, respectively. Therefore, Eq. 2 can be transformed as:

$$Y = aL^2\Phi + bL^2\Phi^2, \quad (4)$$

where  $a = \frac{\alpha}{Lk}$  and  $b = \frac{\beta}{k^2}$ . The LET dependence of dicentric aberrations in human peripheral blood lymphocytes irradiated *in vitro* was tested in the experimental data obtained in our laboratory<sup>11-14</sup>). In this case, the LET of X- and  $\gamma$ -ray is expressed as LET of recoil- or photo-electrons. As shown in Fig. 1, the frequency of dicentrics per single traversal of a charged particle at the low dose limit in the low LET region is roughly proportional to the square of LET.  $\beta$  is not largely dependent on LET and can be assumed to be constant. Therefore,  $a$  and  $b$  may be considered to be constants independent of LET in the low LET region. Eq. 2 can be represented as:



**Fig. 1.** The relationship between LET and the dicentric yield per traversal of the cell nucleus by a charged particle at the low dose limit. For X- and  $\gamma$ -ray, the charged particle is a recoil- or photo-electron induced by the photon. Dots show the experimental value. The bar on each dot represents the standard error. The line is the theoretical value according to Eq.18 when  $a_A = 2.2 \mu\text{m}^2/\text{keV}^2$  and  $c = 1 \times 10^{-2} \text{keV}^{-1}$ .

$$Y = kLaD + k^2bD^2. \quad (5)$$

Eq. 4 and Eq. 5 will hold in the relatively low LET region. Although  $a$  and  $b$  may change slightly depending on the type of charged particle because of different track structures, slight differences do not significantly alter the concept of our model.

### PROBABILITY OF DIRECT DEATH OF CELLS TRAVERSED BY CHARGED PARTICLES

When cells are irradiated by radiation, a proportion of these cells may be killed before cell division as the direct result of radiation (interphase death including apoptotic death) or fail to reach cell division because of cell cycle delay. In this paper, we use the term 'direct death' to include both cell death and division delay which might affect the study population of cells with the biological endpoint of interest. Edwards *et al.*<sup>15)</sup> estimated the probability of the direct death of human lymphocytes irradiated by 4.9 MeV alpha particles (track average LET is 140 keV/ $\mu\text{m}$ ) to be 0.66 per traversal (or  $S = 0.34$ ). Direct death is one of the significant factors that modify the dose-effect relationship for high LET radiation<sup>13,16)</sup>.

As a general expression, the probability of the direct death of cells in which the cell nucleus is traversed by  $x$  charged particles can be denoted as:

$$S_d(x) = \exp(-\{a_1x + a_2x(x-1) + a_3x(x-1)(x-2) + \dots + a_nx(x-1)(x-2)\dots(x-n+1)\}). \quad (6)$$

Choosing appropriate values of  $a_1, a_2, a_3, \dots, a_n$ , any value between 0 and 1 can be given to  $S_d(x)$  for every  $x$ . However,  $a_3, \dots, a_n$  may be negligible, since the dose-effect relationship of cell inactivation can be generally given with sufficient accuracy by:

$$S(D) = \exp(-\alpha D + \beta D^2). \quad (7)$$

We also assume that  $a_2$  is negligible, since influence of  $a_2$  seems unimportant for biological doses unless we are interested in the supra-lethal doses.

Defining  $S_1 = \exp(-a_1)$ , Eq. 6 may be approximated by:

$$S_d(x) = \exp(-(a_1x)), \text{ or} \quad (8)$$

$$S_d(x) = S_1^x,$$

where  $S_1$  is the probability of surviving direct death when one charged particle traverses the cell nucleus.

### DOSE-EFFECT RELATIONSHIP OF CHROMOSOME ABERRATIONS UNDER THE INFLUENCE OF DIRECT DEATH

The number of charged particles traversing the cell nucleus may follow a Poisson distribution:

$$p(x) = \frac{\lambda^x}{x!} \exp(-\lambda), \quad (9)$$

where  $x$  is the number of charged particles traversing the cell nucleus with an average number  $\lambda$ . The distribution of  $x$  for cells escaped from the direct death can be expressed as:

$$p(x) = \frac{\frac{\lambda^x}{x!} \exp(-\lambda) S_1^x}{\sum_{i=0}^{\infty} \frac{\lambda^i}{i!} \exp(-\lambda) S_1^i} \quad (10)$$

The numerator expresses the probability that  $x$  charged particles traverse a cell nucleus that escaped from the direct death. The denominator expresses the probability that a cell can escape from the direct death regardless of the number of charged particles traversing it, that is:

$$\sum_{i=0}^{\infty} \frac{\lambda^i}{i!} \exp(-\lambda) S_1^i = \sum_{i=0}^{\infty} \frac{(\lambda S_1)^i}{i!} \exp(-\lambda) = \exp(\lambda S_1) \exp(-\lambda) \quad (11)$$

Substituting Eq. 11, Eq. 10 is expressed as:

$$p(x) = \frac{(\lambda S_1)^x}{x!} \exp(-\lambda S_1) \quad (12)$$

The expression is a Poisson distribution with a mean of  $\lambda S_1$ . Therefore, the effective fluence of charged particles to cells escaping direct death is  $S_1$  times the actual fluence. Therefore, Eq. 2 may be modified in the following manner:

$$Y = \alpha S_1 D + \beta S_1^2 D^2, \quad (13)$$

and Eq. 4 as:

$$Y = aL^2 S_1 \Phi + bL^2 S_1^2 \Phi^2. \quad (14)$$

### LET DEPENDENCE OF DIRECT DEATH

Ionization occurs at a rate approximately proportional to the absorbed dose, regardless of the kind of charged particle. Therefore, it is likely that damage causing direct death is approximately proportional to the absorbed dose. If so, the average number of events that cause direct death per charged particle must be proportional to LET, and may be expressed as  $cL$ , where  $L$  is LET and  $c$  is some constant. Assuming the events follow a Poisson distribution,  $S_1$  in Eq. 8 can be expressed as:

$$S_1 = \exp(-cL). \quad (15)$$

When  $S_1 = 0.34$  and  $L = 140 \text{ keV}/\mu\text{m}$ ,  $c$  is  $7.7 \times 10^{-3} \mu\text{m}/\text{keV}^{15}$ . The  $S_1$  of 23 MeV alpha particles (LET is  $29.6 \text{ keV}/\mu\text{m}$ ) is estimated to be about 0.73 times of that of 4.9 MeV protons (LET is  $7.9 \text{ keV}/\mu\text{m}^{13}$ ), which gives  $c = -\log(0.73) / (29.6 - 7.9) = 1.06 \times 10^{-2} \mu\text{m}/\text{keV}$ . Thus,  $c$  is expected to

be close to  $1 \times 10^{-2} \mu\text{m}/\text{keV}$  for human peripheral blood lymphocytes. Substituting Eq. 15, Eq. 14 may be expressed as:

$$Y = aL^2 \exp(-cL)\Phi + bL^2 \exp(-2cL)\Phi^2. \quad (16)$$

Let  $A$  be the cross-sectional area of a cell nucleus. Then, the average number of charged particles traversing is:

$$m_A = A\Phi. \quad (17)$$

Finally, Eq. 16 may be expressed as:

$$Y = a_A L^2 \exp(-cL) m_A + b_A L^2 \exp(-2cL) m_A^2, \quad (18)$$

where  $a_A = \frac{a}{A}$  and  $b_A = \frac{b}{A^2}$ . The coefficient of  $m_A$  of Eq. 18 when  $a_A = 2.2 \mu\text{m}^2/\text{keV}^2$  is plotted in Fig. 1.

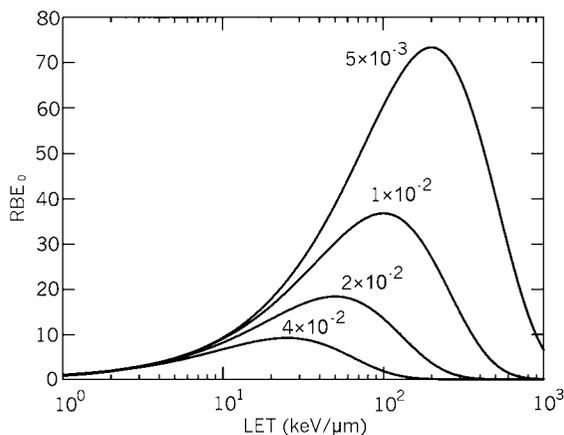
### LIMITING RBE AT LOW DOSE EXPOSURES

From Eq. 3 and Eq. 16, the dose-effect relationship is given by:

$$Y = akL \exp(-cL) D + bk^2 \exp(-2cL) D^2. \quad (19)$$

From this expression, the limiting RBE at low dose is expected to be:

$$RBE_0 = L \exp(-cL). \quad (20)$$



**Fig. 2.**  $RBE_0$  given by Eq. 20 plotted against LET. The parameters attached to the curves are values of  $c$  in  $\mu\text{m}/\text{keV}$ .

In Fig. 2,  $RBE_0$  is plotted against  $L$  for varying values of  $c$ .

### CELL KILLING

We assume that reproductive death occurs as a result of direct death and the formation of unstable chromosome aberrations in which dicentric formation plays a major role. According to Takatsuji *et al.*<sup>12)</sup>, the distribution of chromosome aberrations between cells can be expressed by an  $N$ -fold convolution ( $N = 100$ ) of distribution:

$$p(x) = \sum_{k=0}^{\infty} \frac{m_1^k}{k!} \exp(-m_1) \frac{\{a_1 k + b_1 k(k-1)\}^x}{x!} \exp[-\{a_1 k + b_1 k(k-1)\}], \quad (21)$$

where  $m_1$  is the mean number of charged particles crossing one  $N^{\text{th}}$  subsection of a cell nucleus cross-section, and  $a_1$  and  $b_1$  are constants dependent on radiation quality. The mean of  $x$  follows the distribution  $a_1 m_1 + b_1 m_1^2$ . Moreover,  $a_1 \propto L^2$ , and  $b_1 \propto L^2$  are apparent from Eq. 4. The  $N$ -fold convolution of Eq. 21 has the mean value of:

$$Y = Na_1 m_1 + Nb_1 m_1^2. \quad (22)$$

From Eq. 21, the probability that neither chromosome aberration nor damage causing direct death is induced in one subsection is:

$$p_{\text{alive}} = \sum_{k=1}^{\infty} \frac{m_1^k S_1^k}{k!} \exp(-m_1) \exp[-\{a_1 k + b_1 k(k-1)\}]. \quad (23)$$

The Taylor expansion of  $-\log(p_{\text{alive}})$  for  $m_1$  is:

$$-\log(p_{\text{alive}}) = \{1 - S_1 \exp(-a_1)\} m_1 + \frac{1}{2} \exp(-2a_1) \{1 - \exp(-2b_1)\} S_1^2 m_1^2 + \dots \quad (24)$$

The surviving fraction is  $S = p_{\text{alive}}^N$  and therefore,

$$-\log(S) = \{1 - S_1 \exp(-a_1)\} N m_1 + \frac{1}{2} \exp(-2a_1) \{1 - \exp(-2b_1)\} S_1^2 N m_1^2 + \dots \quad (25)$$

Replacing  $a_1$  by  $a_A L^2$ ,  $b_1$  by  $N b_A L^2$ ,  $m_1$  by  $\frac{m_A}{N}$ , and  $S_1$  by  $\exp(-cL)$  in order to transform the expression from particles per section to particles per nucleus and to make the LET dependence clear, Eq. 25 can be expressed in the following approximation function:

$$\begin{aligned} -\log(S) &= \{1 - \exp(-a_A L^2 - cL)\} m_A \\ &+ \frac{1}{2N} \exp(-2a_A L^2) \{1 - \exp(-2N b_A L^2)\} \exp(-2cL) m_A^2. \end{aligned} \quad (26)$$

Here,  $a_A$  and  $b_A$  can be shown to be the same as in Eq. 18 by replacing  $a_1$  by  $a_A L^2$ ,  $b_1$  by  $N b_A L^2$ ,

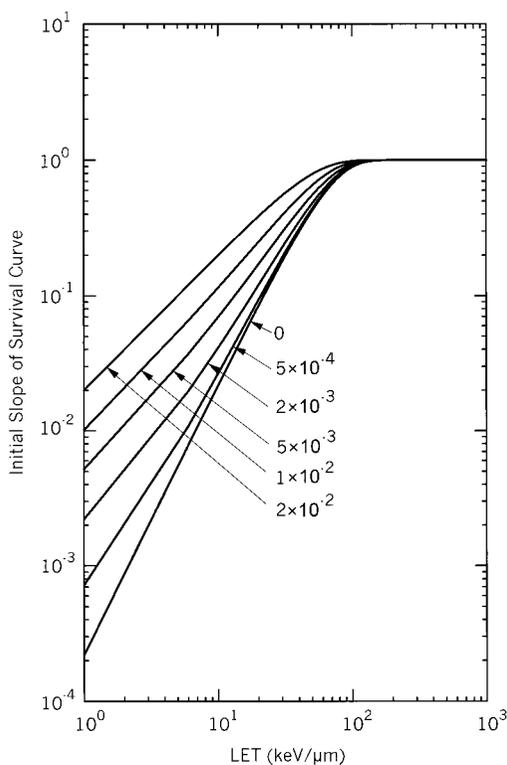
and  $m_1$  by  $\frac{m_A}{N}$  in Eq. 22. When  $c = 0$  and  $b_A = 0$ , Eq. 26 is found the same as Eq. 1 and that the high degree terms ignored in Eq. 26 are zeros. From Eq. 26, we also obtain,

$$\lim_{L \rightarrow \infty} S = \exp(-m_A). \quad (27)$$

This equation gives the probability that no charged particle traverses the nucleus, and it means that all the cells traversed by a charged particle must be killed at the high LET limit. Expanding the exponential functions of Eq. 26 to polynomials, when  $L$  is small the surviving fraction can be approximated by:

$$S = \exp\left(-\left[\left\{\left(a_A - \frac{1}{2}c^2\right)L^2 + cL\right\}m_A + b_AL^2m_A^2\right]\right). \quad (28)$$

From Fig. 1,  $a_A$  for dicentrics is estimated to be about  $2.2 \times 10^{-4} \mu\text{m}^2/\text{keV}^2$ , therefore  $a_A$  for all unstable chromosome aberrations must be larger. In Fig. 3, the initial slope of the survival curve derived from Eq. 26,  $1 - \exp(-a_AL^2 - cL)$ , is plotted against  $L$  for varying values of  $c$ .

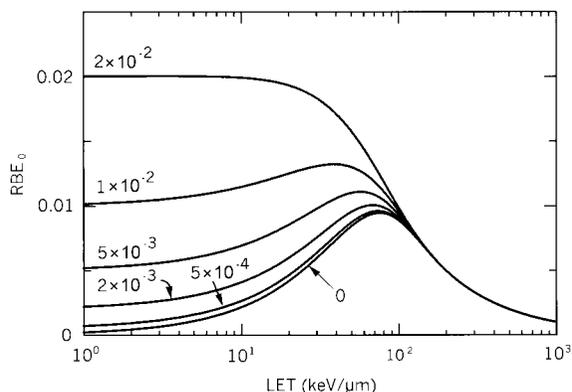


**Fig. 3.** The initial slope of the survival curve according to Eq. 26,  $1 - \exp(-a_AL^2 - cL)$ , plotted against  $L$ . The parameters attached to the curves are values of  $c$  in  $\mu\text{m}/\text{keV}$ .  $a_A$  is assumed to be  $2.2 \times 10^{-4} \mu\text{m}^2/\text{keV}^2$ .

From Eq. 26, Eq. 3, and Eq. 17, the limiting RBE at low dose is expected to be:

$$RBE_0 = \frac{1 - \exp(-a_A L^2 - cL)}{L}. \quad (29)$$

Figure 4 plots the  $RBE_0$  against  $L$  for varying values of  $c$ .



**Fig. 4.**  $RBE_0$  given by Eq. 29 plotted against LET. The parameters attached to the curves are values of  $c$  in  $\mu\text{m}/\text{keV}$ .  $a_A$  is assumed to be  $2.2 \times 10^{-4} \mu\text{m}^2/\text{keV}^2$ .

When the surviving fraction expressed in Eq. 26 is transformed to a function of the radiation dose,  $S(D) = \exp(-(\alpha D + \beta D^2))$ ,  $\beta$  can be expressed as:

$$\beta = \frac{A^2 k^2}{2NL^2} \exp(-2a_A L^2) \{1 - \exp(-2Nb_A L^2)\} \exp(-2cL) \quad (30)$$

from Eq. 17 and Eq. 3.

$\beta$  is a monotonously decreasing function of LET.  $\beta$  is expected to be almost zero for high LET radiation.

## DISCUSSION

Neary<sup>17)</sup> developed a theory of LET dependency for the induction of chromosome aberrations. Based on his theory, the decrease of the  $\alpha$  term in Eq. 2 in the high LET region comes from limited numbers of sites in the cell nucleus. If the sites are very small and the number is extremely large, or the nucleus can be regarded as a homogenous puck of chromosomal DNA, a decrease in RBE may not be expected.

Edwards *et al.*<sup>8)</sup> assumed that the probability of direct death is expressed as:

$$S_1 = \exp(-cL^2) \quad (31)$$

and that it may follow the theory of dual radiation action. However, it seems that there is no reason to follow the theory, because the mechanism of direct death and the induction of dicentric chromosomes seems to be independent events, and physical and chemical reactions that occur in response to radiation seem to occur in rough proportion to the absorbed dose. Moreover, the dependency of Eq. 31 appears steeper than in reality, because the  $S_1$  of 23 MeV alpha particles (LET = 29.6 keV/ $\mu\text{m}$ ) is estimated to be about 0.95 when deduced from the  $S_1$  value of 0.34 for 4.9 MeV alpha particles (140 keV/ $\mu\text{m}$ )<sup>15)</sup>. The  $S_1$  for 23 MeV alpha particles has been estimated to be smaller than 0.73 by Takatsuji and Sasaki<sup>13)</sup>. Therefore, Eq. 15 seems more realistic than Eq. 31.

We have assumed that cell death is the consequence of direct death and the formation of unstable chromosome aberrations. As seen in Fig. 3, if the probability of direct death is small, the LET dependence of the initial slope of the survival curve becomes nearly proportional to the square of LET, and if the probability is large, the LET dependence becomes nearly proportional to LET in the low LET region. At intermediate probabilities, the curves bend near the point of 10 keV/ $\mu\text{m}$ . Goodhead *et al.*<sup>3)</sup> indicated that the LET dependence of cell killing is roughly proportional to the square of LET in Fig. 1 of their paper. Their results may imply that the cultured cells referred to therein have a small probability of direct death.

Here, we present a generalized concept for the LET dependence of RBE in chromosome aberration formation and reproductive death. According to this concept, the decrease of RBE in chromosome aberration formation in the high LET region can readily be explained by direct killing that is directly dependent on the absorbed energy. The decrease of RBE in cell killing is initially self-evident from the geometrical condition. However, the state of the decrease is expected to depend largely on the probability of direct death per single pass of a charged particle.

The concept we presented here may not necessarily be straightforwardly connected to the biological mechanism of radiation action in living cells, but it clearly shows that the physical parameters strongly restrict the gain of biological endpoints. This concept may provide a useful framework in interpreting the experimental data on the effects of radiations on living cells.

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