On the Relation between Recovery from Potential Lethal and Sublethal Radiation Lesions of Yeast Cells

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Summary. Tetraploid yeast cells were used to study the time course of recovery from potential lethal lesions by delayed plating after a single dose of gamma-radiation and recovery from sublethal lesions by using two fraction dose technique. The mean lifetime of potential lethal and sublethal lesions in comparable conditions are the same. The elimination of lethals in the first steps of recovery process is accompanied by transition of lethally damaged cells into sublethally damaged ones.

Sublethals are in principle completely reversible. As potential lethals consist of sublethals the number of which are critical the former immediately after irradiation also are complete reversible in principle. In a time course a definite fraction of potential lethals is fixed into true irreversible lethals. This pattern is in close agreement with the common model of formation of two-hit chromosome aberration.

Introduction

Two different methods of study of the process of postirradiation recovery are known in cellular radiobiology. They are:

1. the use of dose fractionation technique and
2. variation of postirradiation conditions.

The influence of dose fractionation on cell survival primary was shown for mammalian cells by Elkind (Elkind and Sutton, 1959; Elkind and Sinclair, 1965) and on this basis the concept of recovery from sublethal lesions has been formulated. The increase of cell survival by variation of environmental conditions during postirradiation period was observed by many authors and particularly by Korogodin for yeast cells (Korogodin, 1966). In the latter case it is common to describe the experimental results in terms of cell recovery from potential lethal lesions.

As a rule the recovery from potential lethal and sublethal lesions are investigated as completely independent. The relationship between both kinds of recovery is discussed only in a few recent papers. The study of time course of postirradiation effect of Actinomycin D on sublethals and lethals leads to the conclusion that both kinds of lesions differ only quantitatively (Elkind et al., 1967). The work performed on yeast cells with the study of time course of recovery from lethals and sublethals leads to the opposite conclusion that both kinds of recovery are different and independent processes (Bacchetti et al., 1966).

It is known that the use of two dose fractions of X- or γ-rays with proper time intervals may lead to complete additivity of effects of separate dose fractions. In the opposite way to this a population of cells irradiated by a single dose never returns to a 100% survival under any conditions. These lethal lesions, which cannot be eliminated, are usually described as irreversible (Korogodin, 1966).
In our previous papers [Barsukow et al., 1966 (1, 2)] it was shown that the number of so-called irreversible lesions is reduced by dose fractionation up to the simple additivity of separate dose fraction effects. In terms of both sublethal and lethal recovery concepts this means that so-called irreversible lesions are the results of interaction of sublethals, which are reversible in principle. Therefore there is no reason to consider the recovery from potential lethal and sublethal lesions to be completely different processes.

Theoretical Considerations

In the common case for any sigmoid dose-survival curve inequality (1) is correct:

\[ S_D < S_{d_1} \cdot S_{d_2} \]  

where \( D; d_1; d_2 \) are doses of radiation \( (D = d_1 + d_2) \) and \( S_D; S_{d_1}; S_{d_2} \) are the survivals after the treatment with the doses \( D, d_1 \) and \( d_2 \). It is quite possible to convert the inequality (1) to the equality (2) by introducing the coefficient \( S_{int} (S_{int} < 1) \):

\[ S_D = S_{d_1} \cdot S_{d_2} \cdot S_{int} \]  

or

\[ \ln S_D = \ln S_{d_1} + \ln S_{d_2} + \ln S_{int} \]  

where \( S_{int} \) is the fraction in reducing the survival due to the fact that the doses \( d_1 \) and \( d_2 \) are used simultaneously and give an additional effect by interaction of lesions, decreasing with separate dose fractions. The employment of survival logarithm is not only more convenient to express availability or absence of additivity of single dose fraction effects but survival logarithm can also have quite valuable sense taking account of the mean number of lethal events per cell. Indeed, according to the hit principle, one can assume that a number of lethal events, each of which is enough for a lethal effect, may arise independently within the limits of one cell. For example, this occurs on the formation of point and chromosomal mutations. If lethal events arise independently of one another, their distribution over the cells will conform Poisson's law (at least over some range of doses). Then, the probability of a cell to survive will be:

\[ S = e^{-m} \quad \text{or} \quad -\ln S = m \]

where \( S \) is the survival and \( m \) the mean number of lethal events per cell independently of hitness of the lethal event itself. The dependence of the mean number of lethal events on the dose \( m = f(D) \) may be any.

Independently of validity of this interpretation the employment of survival logarithm as a measure of radiation cell damage must not cause principle objections similarly, for instance, to the traditional use of semilogarithmic scale for dose effect curves.

If the doses \( d_1 \) and \( d_2 \) are separated by a time interval the survival can increase up to the additivity of effects of each dose fraction. In order to express the effect of gradual dose fractionating it is reasonable to introduce the new coefficient \( q \), which is dependent on the time interval between two dose fractions \( (t) \):

\[ \ln S_D (t) = \ln S_{d_1} + \ln S_{d_2} + q \cdot \ln S_{int} \]  

(4)