

Numerical Simulations of Structural Chromosomal Instability

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The origin of dose-response curves for radiation-induced chromosomal instability (CI) is studied using the mechanistic CI model. The model takes into account DNA damage generation and repair in the progeny of irradiated cells and cell passage through mitotic cycle. We consider the formation of DNA double-strand breaks (DSBs) *de novo* in the S phase, where predominantly chromatid-type aberrations are formed. Among them sister chromatid exchanges of the “isochromatid deletion” type, or “chromatid dicentrics” are of primary interest. When the cell enters mitosis, the fate of chromosomal aberrations depends on their types. Chromosomal and chromatid fragments, having entered mitosis, either are transmitted into one of the daughter cells, or are lost. A chromatid dicentric in mitosis forms an anaphase bridge. These mechanistic assumptions were used to demonstrate that the dose-response curves are closely related to the dynamic curves for CI. The principles underlying this relationship are analyzed.

Keywords: chromosomal instability, ionizing radiation, delayed chromosomal damage, prediction, dose response.

Introduction

Chromosomal instability (CI) is defined as the increased frequency of chromosomal rearrangements (chromosomal aberrations) in offspring of irradiated cells [1]. As a theoretical basis, the theory of targets is not applicable here [2]. The first attempts at computer simulation of CI brought about promising results [3, 4], but led to a multitude of questions. Some of these issues are resolved in this paper. The influence of various factors on the main characteristics of gamma-induced CI dose-response and dynamic curves are analyzed. The delayed aberrations in the form of dicentrics are modeled here as an end-point of radiation-induced CI. The sensitivity of dose-response curves for dicentrics to the variation of the parameters of the CI model is analyzed.

1. Modeling

The mechanistic model of CI following ionizing radiation exposure incorporates DNA / chromosome damage interaction pathways determining outcomes of factors involved in genome destabilization. The modeling technique described previously [4] is used here with some modifications. The main points of the model are as follows.

DNA double-strand breaks (DSBs) can be formed in both irradiated cells and their progeny in the G1 phase, as well as in the S phase. The DSB formation in the G2 phase upon irradiation is neglected. For most cell types, when the asynchronous population is irradiated, the fraction of G2 cells is small, 10–15%. Besides, irradiation of G2-phase cells does not lead to the formation of dicentrics. In addition to DSBs, DNA single-strand breaks (SSBs) and oxidative base damage (BD), as well as complex lesions (SSB + BD) are also induced. They are repaired by BER pathway. Unrepaired SSBs + BDs alone do not lead to the formation of aberrations, but can turn into DSBs either due to nuclease attack of opposite DNA chain in G1 or during replication. The

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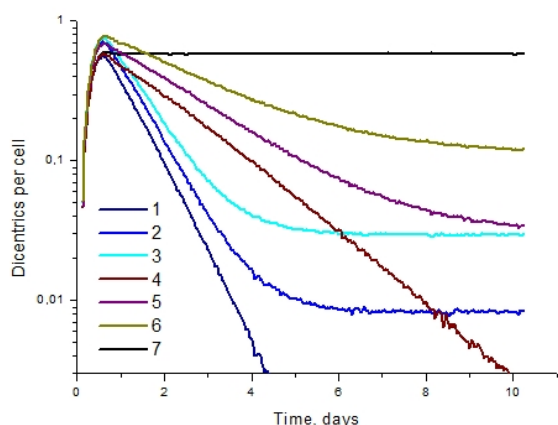
DSBs can be repaired by NHEJ or HR pathways, misrepaired with the formation of aberration of chromosome or chromatid type depending on the phase of the cell cycle, or lose their reactivity, forming a blunt-end aberration, or fragment. In the progeny of irradiated cells, as in [4], we consider the formation of DSBs *de novo* in the S phase, where predominantly chromatid-type aberrations are formed, of which sister chromatid exchanges of the “isochromatid deletion” type, or “chromatid dicentrics” are of primary interest. When the cell enters mitosis, the fate of CAs depends on their types. Chromosomal and chromatid fragments, having entered mitosis, either are transmitted into one of the daughter cells, or are lost. A chromatid dicentric in mitosis forms an anaphase bridge. Since both kinetochores in this aberration belong to the same chromatid, it cannot segregate normally. The mitotic spindle pulls it to opposite poles. An anaphase bridge either leads to cell death, or breaks (part of the so called “BFB cycle” [4]), and each of the daughter cells gets a centric chromosomal fragment with a sticky end. The chromosomal dicentric, in contrast to the chromatid dicentric, has four kinetochores, two on each chromatid, and therefore can either segregate normally, or form a double anaphase bridge. With normal segregation, each of the daughter cells receives a dicentric, and with the formation of a double bridge, the same outcomes are possible as in the case of a single bridge: the death and bridge breakage as part of the BFB cycle. As a result of breakage of anaphase bridges, in G1 centric fragments with sticky ends appear: single or double, depending on the type of the bridge that is broken. The reactive ends can interact with each other as well as with the DSBs generated in the S phase to form dicentrics and other types of aberrations. The cycle of formation, breakage and fusion of anaphase bridges is called BFB (Breakage and Fusion of Bridges [4]).

DSBs of non-radiation nature in the progeny are formed through three channels, $N_{dsb} = N_1 + N_2 + N_3$. N_1 is an autonomous channel, i.e. these DSBs are formed in each cell regardless of external factors (intercellular signals). N_2 is a non-autonomous channel, determined by intercellular interactions through gap junctions. It depends on the density of the cells, both having and not having DNA damage. N_3 is also a non-autonomous channel, it is determined by intercellular interactions through soluble factors in the medium. For simplicity, DSBs of all three types are considered structurally indistinguishable. The cell passage through cell cycle is taken into account in the same way as in [4].

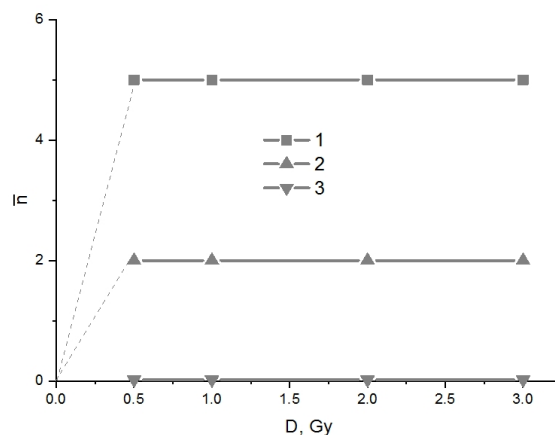
2. Results and Discussion

We studied the impact of the parameters of spontaneous DSB generation in the progeny of irradiated cells, as well as the parameters of the breakage-fusion of the anaphase bridge (BFB cycle) on the shape of the dynamic and dose-response curves of radiation-induced CI. Figure 1a shows dynamic CI curves, i.e. dependence of dicentric frequency on time after irradiation (3 Gy) for different probabilities of anaphase bridge breakage, p , and different levels of DSB generation in the S phase, \bar{n} . Corresponding dose dependencies of DSB generation \bar{n} are shown in Fig. 1b. Figure 1c shows the set of dynamic curves for different doses with parameters corresponding to Fig. 1a, curve 2. The resulting dose dependence at 10 days is presented in Fig. 1d.

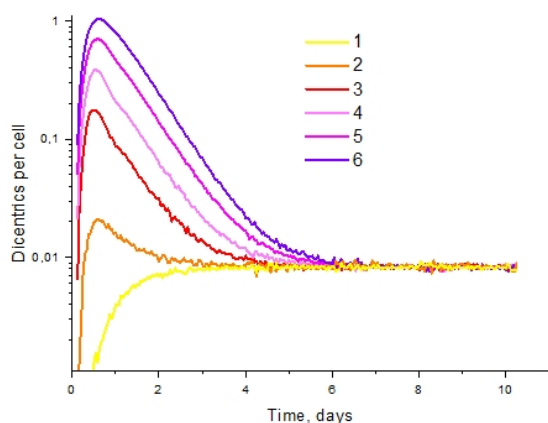
Figure 1 and Fig. 2 demonstrate that, depending on the combination of parameters, two main types of dynamic curves for chromosomal aberrations in offspring of irradiated cells can be distinguished: with (Fig. 1c) and without the plateau (Fig. 2a). All curves are observed for the rate of DSB generation independent of the dose in the range of medium and large doses (Fig. 1b).



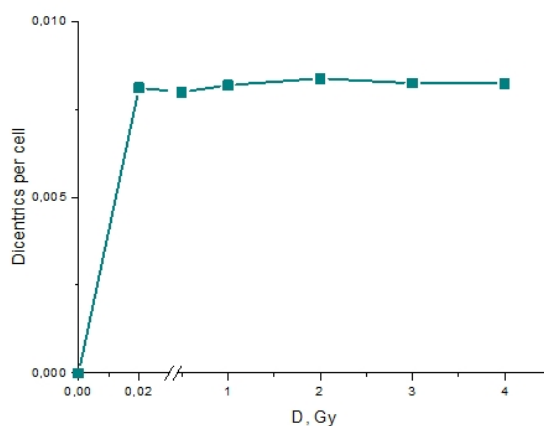
(a) dynamic CI curves for different model parameters. 1-3 - $p=0.6$; 4-6 - $p=0.3$; 7 - $p=1.0$. 1,4,7 - $\bar{n}=0$; 2,5 - $\bar{n}=2$; 3,6 - $\bar{n}=5$



(b) dose dependence of \bar{n} . 1 - for curves 3 and 6 in (a); 2 - for curves 2 and 5 in (a); 3 - for curves 1, 4 and 7 in (a)



(c) dynamic curves for different doses (curves 1-6: $D=0.02, 0.5, 1, 2, 3, 4$ Gy)



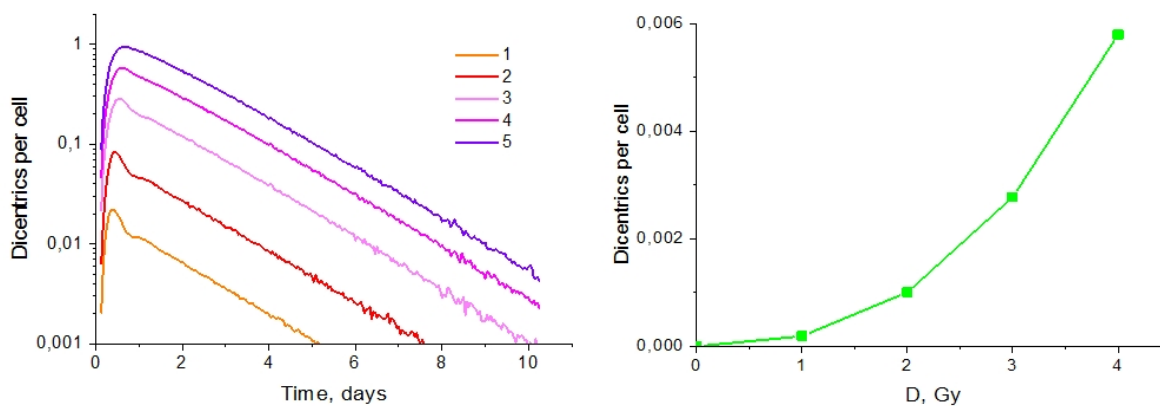
(d) dose curves at $t=10$ days, corresponding to the dynamic curves in (c)

Figure 1. Impact of the DSB generation and BFB parameters on the shape of CI dynamic and dose-response curves

These two types of CI dynamic curves are manifested in two different types of dose-response curves, plateau in a broad dose range (Fig. 1d) and pronounced dose dependence (Fig. 2b).

Conclusions

In conclusion, the basic properties of the developed model of radiation induced CI can be formulated as follows: (*) persistent induction of DNA DSBs and their repair impact the dynamic and dose characteristics of CI; (**) the shape of dose dependence of CI is determined by the quantitative relationships between accumulation and elimination of chromosomal aberrations at any time after irradiation of dividing cell population. Thus, the phenomenon of CI dose dependence-independence is of dynamic origin.



(a) dynamic curves for different doses with parameters corresponding to curve 4 in Fig. 1a (curves 1–5: $D=0.5, 1, 2, 3, 4$ Gy)

(b) the dose curve at $t = 10$ days corresponding to the dynamic curves in panel (a)

Figure 2. dose dependence of CI arises from the shape of dynamic curves at late times

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