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DSB repair model for mammalian cells in early S and G1 phases of the cell cycle: Application to damage induced by ionizing radiation of different quality

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ABSTRACT

The purpose of this work is to test the hypothesis that kinetics of double strand breaks (DSB) repair is governed by complexity of DSB. To test the hypothesis we used our recent published mechanistic mathematical model of DSB repair for DSB induced by selected protons, deuterons, and helium ions of different energies representing radiations of different qualities. In light of recent advances in experimental and computational techniques, the most appropriate method to study cellular responses in radiation therapy, and exposures to low doses of ionizing radiations is using mechanistic approaches. To this end, we proposed a 'bottom–up' approach to study cellular response that starts with the DNA damage. Monte Carlo track structure method was employed to simulate initial damage induced in the genomic DNA by direct and indirect effects. Among the different types of DNA damage, DSB are known to be induced in simple and complex forms. The DSB repair model in G1 and early S phases of the cell cycle was employed to calculate the repair kinetics. The model considers the repair of simple and complex DSB, and the DSB produced in the heterochromatin. The inverse sampling method was used to calculate the repair kinetics for each individual DSB. The overall repair kinetics for 500 DSB induced by single tracks of the radiation under test were compared with experimental results. The results show that the model is capable of predicting the repair kinetics for the DSB induced by radiations of different qualities within an accepted range of uncertainty.

1. Introduction

Mammalian cells have developed a complex protective pathway to maintain genomic integrity after radiation damage [1,2]. Although recent experiments provide a higher extent of knowledge of the DNA damage response and cell signaling (reviewed in [3–6]), we are still not able to forge a comprehensive mathematical link between DNA damage and final consequences such as cell death. The reason for this shortcoming is that it is not yet possible to provide a mechanistic description of the series of events that lead from initial DNA damage to mutation, chromosome aberration, or cell death. The first step to overcome this problem is to construct a comprehensive model for the repair processes. In this paper, we employ a mechanistic mathematical method to investigate DSB repair kinetics. We use details of repair protein actions at the site of damage to construct a comprehensive model that could explain, within an accepted accuracy, the repair kinetic curves for cells irradiated with radiations of different quality.

The initial cellular responses to radiation damage are DNA repair and cell signaling, which start within a few seconds after damage induction [7]. The cell signaling pathways initiate a series of events including cell cycle arrest to permit more time for repair [8]. If the repair is not successful, the damaged cell might activate cell death pathways to avoid mutation or chromosome aberrations [9]. The repair pathways are specialized for different types of damage. Damage to the DNA includes base damage (BD), single strand breaks (SSB), and double strand breaks (DSB) [10,11]. While repair of the SSB and BD is fairly simple and fast, repair of the DSB is more difficult and may take a long time [12]. The main three DSB repair pathways known to date are nonhomologous end-joining (NHEJ), homologous recombination (HR), and microhomology-mediated end-joining (MMEJ). To these may be added alternative nonhomologous end-joining (Alt-NHEJ) (reviewed in [13–15]). Most of the

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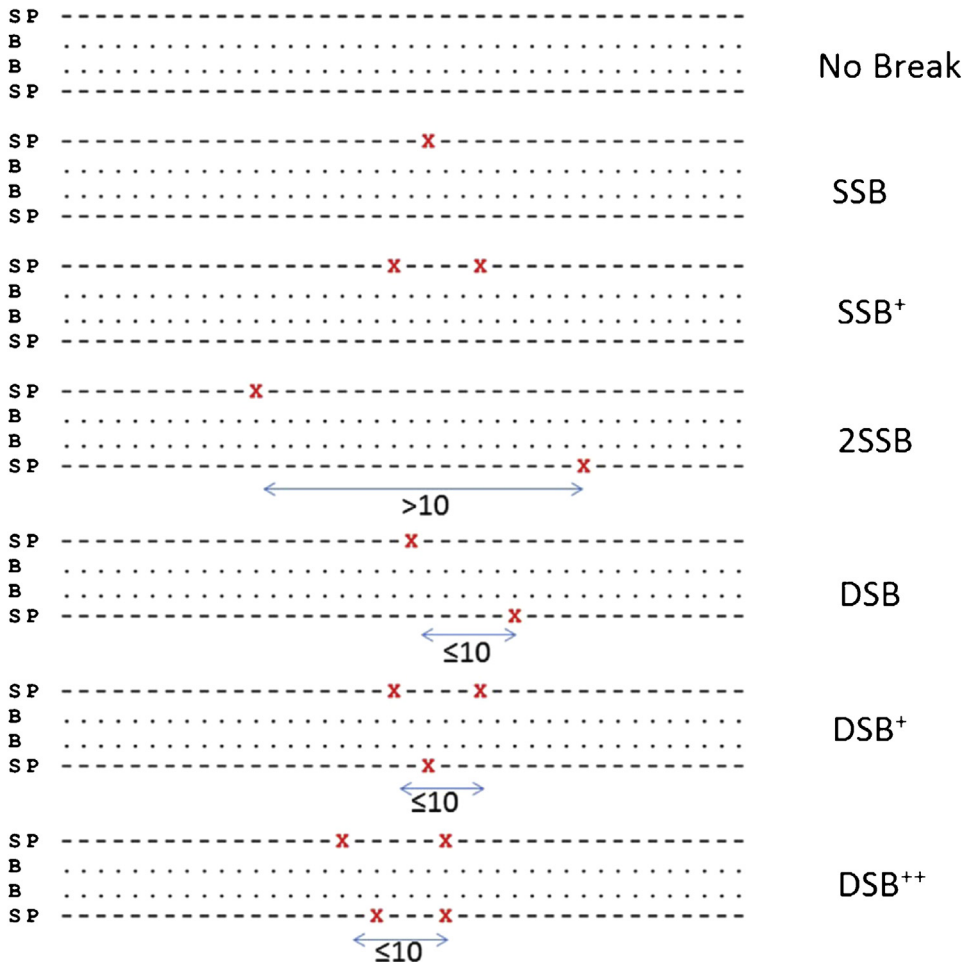

Fig. 1. Model of DNA damage by complexity. The DNA is illustrated in the form of four untwisted helical lines. The top and bottom lines present the sugar-phosphate backbones (SP), and the middle lines show the base pairs (B). The red 'x' shows the damage in the DNA. The damage could result from direct or indirect interactions. According to the definition damage in the sugar-phosphate backbone is a strand break and damage in the base is a base lesion. The DSB is defined as two SSB on the opposite strands separated by ≤10 bp. If a DSB is accompanied by another SSB within 10 bp, it is defined as one kind of complex DSB (DSB_c). If there are two DSB with the confine of 10 bp, it is defined as DSB^{++} which is a more complex DSB. We define complex DSB (DSBC) as the sum of DSB^{+} and DSB^{++}.

DSB in mammalian cells are repaired by NHEJ [16]. On the other hand, it is proposed that HR contributes to the repair of DSB in the late S and G2 phases of the cell cycle [17]. HR is a slow repair process in comparison to NHEJ and requires resection to start the repair [16,17]. Recently, we proposed that resection of the DSB ends is required to repair the complex damage. Because the resection of the DSB ends is performed by HR repair, we proposed HR is the main pathway for the repair of the complex type DSB in late S and G2 phases of the cell cycle [18]. It is proposed that the complex type DSB induced in the G1 and early S phases of the cell cycle are repaired mainly by the Alt-NHEJ repair pathway [13,18]. For the damage that is induced during G1 and early S phases of the cell cycle, we constructed a comprehensive model that explains the function of the known proteins involved in the repair of complex and simple type DSB, as well as the proteins involved in the repair of DSB in the heterochromatin [18]. The number of unknown parameters in the mechanistic repair model is determined by the number of processes that are involved in the mechanism. The repair model consists of 17 repair proteins with 17 unknown rate constants. The initial repair processes are identification of damage and presynaptic processes of the NHEJ repair. The presynaptic processes include Ku70/80 detection of damage and DNA-PKcs recruitment and autophosphorylation [19,20]. The rate constants of the initial processes have been verified by comparison with experimental results [19,21]. The presynaptic processes are required for all types of DSB, while end processing after the synapsis is dependent on the type of damage. Simple type DSB requires relatively fast ligation via NHEJ, whereas simple type DSB in the heterochromatin requires ATM signaling activity that delays the repair [22–25]. Since complex type DSB in the early S and G1 phases of the cell cycle undergo resection, we have proposed that Alt-NHEJ or MMEJ is involved in

Table 1
Rate constants of the DSB repair model in G1 and early S phases of the cell cycle.

Rate constants	Repair model
k_1 (h^{-1})	350
k_2 (h^{-1})	500
k_3 (h^{-1})	50
k_4 (h^{-1})	20
k_5 (h^{-1})	25
k_6 (h^{-1})	18
k_7 (h^{-1})	3
k_8 (h^{-1})	9
k_9 (h^{-1})	2
k_{10} (h^{-1})	0.8
k_{11} (h^{-1})	0.5
k_{12} (h^{-1})	3
k_{13} (h^{-1})	1
k_{14} (h^{-1})	0.7
k_{15} (h^{-1})	0.75
k_{16} (h^{-1})	0.5
k_{17} (h^{-1})	0.15