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Track structure based modelling of chromosome aberrations after photon and alpha-particle irradiation

Werner Friedland*, Pavel Kundrát

Helmholtz Zentrum München – German Research Center for Environmental Health, Institute of Radiation Protection, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

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ABSTRACT

A computational model of radiation-induced chromosome aberrations in human cells within the PARTRAC Monte Carlo simulation framework is presented. The model starts from radiation-induced DNA damage assessed by overlapping radiation track structures with multi-scale DNA and chromatin models, ranging from DNA double-helix in atomic resolution to chromatin fibre loops, heterochromatic and euchromatic regions, and chromosome territories. The repair of DNA double-strand breaks via non-homologous end-joining is followed. Initial spatial distribution and complexity, diffusive motion, enzymatic processing, synapsis and ligation of individual DNA ends from the breaks are simulated. To enable scoring of different chromosome aberration types resulting from improper joining of DNA fragments, the repair module has been complemented by tracking the chromosome origin of the ligated fragments and the positions of centromeres. The modelled motion of DNA ends has sub-diffusive characteristics and corresponds to measured chromatin mobility within time-scales of a few hours. The calculated formation of dicentrics after photon and α-particle irradiation in human fibroblasts is compared to experimental data (Cornforth et al., 2002, Radiat Res 158, 43). The predicted yields of dicentrics overestimate the measurements by factors of five for γ-rays and two for α-particle irradiation. Nevertheless, the observed relative dependence on radiation dose is correctly reproduced. Calculated yields and size distributions of other aberration types are discussed. The present work represents a first mechanistic approach to chromosome aberrations and their kinetics, combining full track structure simulations with detailed models of chromatin and accounting for the kinetics of DNA repair.

1. Introduction

Ionizing radiation is capable of inducing various types of damage to cellular DNA, of which the most critical ones are DNA double-strand breaks (DSB). To preserve chromosome and genome integrity, cells are equipped with dedicated repair pathways. The dominant pathway of DSB repair in eukaryotic cells is non-homologous end-joining (NHEJ), active throughout the cell cycle [1]. Homologous recombination (HR) contributes in the S/G2 phases when a sister chromatid is available as a repair template [1]. Incorrect repair may lead to the formation of chromosome aberrations [2–4], which have been implicated in radiation-induced cell killing [5–9] as well as in carcinogenesis [10,11].

Several alternative theories on the origin of chromosome aberrations (CA) have been proposed, reviewed in [7,12–14]: In the one-hit (or damage–nondamage interaction) theory, a single radiation-induced DSB is sufficient to initiate a reaction with undamaged DNA that may lead to CA, resembling the mechanism involved in HR repair of DSB. In the exchange theory, the initial chromosome lesions are unstable and decay with time but may also interact with another lesion and produce a CA. In the breakage-and-reunion theory, CA follow from incorrect joining of a chromosome free end with another end, resembling the NHEJ pathway of DSB repair. The breakage-and-reunion theory is nowadays the favoured theory of CA origin for cells in the G0/G1 phase on which this paper is focused; the one-hit mechanism likely contributes in the S/G2 phase [12,13].

Mathematical modelling represents a valuable tool complementing experimental research. It helps obtain quantitative insights and test alternative hypotheses on mechanisms underlying the studied phenomena. Modelling also provides the means to extrapolate the experimental results to conditions that can hardly be assessed directly, e.g. measured CA yields to low and very low doses that are of particular interest for risk assessments.

Motivated by these aims, a number of models for radiation-induced CA have been proposed. They differ in the level of details considered on the structures of radiation tracks, DNA and chromatin, and correspond to diverse CA origin theories. Instead of

* Corresponding author. Tel.: +49 89 3187 2767; fax: +49 89 3187 3363.
E-mail address: friedland@helmholtz-muenchen.de (W. Friedland).

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following the course of break processing and mobility (chromatin dynamics), only their final outcome in terms of joining correct or incorrect chromatin fragments is considered, with diverse assumptions on the distance-dependence of the misrejoining probability between chromosome break ends. Edwards et al. [6,15] considered DSB distributed randomly over the nucleus, for high-LET radiation taking into account radial distributions of ionization events. The misrejoining probability decreased with the DSB distance according to an inverse power law; an option to include a time-dependent factor as in the exchange theory of CA was discussed, too. Sachs et al. used a semi-analytical approach and presented considerations on chromatin dynamics governing the distance-dependent misrejoining [17]. Later, Sachs et al. [18] simulated chromosome territories as cylinders in which DSB induced by low-LET radiation were distributed randomly; the misrejoining probability exponentially decreased with the DSB distance. Cucinotta et al. [19] studied, in addition to the pairwise interaction, also the one-hit mechanism in which enzymatic processing of a single break may lead to simple exchanges. Ballarini et al. [7,8,20,21] modelled interphase chromosomes by a random walk of 200 nm boxes. Chromosome free ends resulted from complex DSB ('cluster lesions'), whose yield was taken from track structure simulations or treated as an adjustable parameter. For low-LET radiation the lesions were distributed randomly, whereas a track core and penumbra model was used for high-LET radiation. The interaction probability was uniform up to an adjustable maximal distance of chromosome ends. Holley et al. [22] modelled chromosomes as random polymers inside spherical territories. DSB were assessed by track structure simulations accounting for both direct and indirect (water radical-mediated) effects. A fraction of DSB was allowed to undergo pairwise misrejoining, with a Gaussian distance-dependence. Kreth et al. [23] constructed chromosome territories by a sequence of spherical chromatin domains, distributed DSB for low-LET radiation randomly, and described the DSB interaction probability by an inverse power law. A similar spherical domain model of chromatin structure was employed by Eidelman et al. [24]. In their approach, CA formation required a contact of two DSB-containing domains, assessed by their dynamic chromatin model, and subsequent DSB interaction, described by an adjustable contact-exchange probability. Alternatively, each DSB produced a chromosome break, and breaks interacted throughout the whole nucleus independently of their distance. Ponomarev et al. [25] used a random walk polymer representation of chromosomes, distributed DSB according to amorphous radiation track structures, and assumed a Gaussian distance-dependent misrejoining probability.

Although differing in the particular assumptions on the distance-dependent misrejoining probability, the existing CA models have in common that they employ only a phenomenological description of repair outcome. Despite the connection between improper DSB repair by NHEJ and aberration induction in G0/G1 cells [26], the CA models lack a detailed link to chromatin dynamics and DSB repair.

On the other hand, NHEJ models have been proposed recently [27–30] that exploit the tremendous amount of experimental knowledge accumulated in the last two or three decades on the underlying processes of the NHEJ pathway: Following DSB induction, rapid local chromatin decondensation occurs which leads to activation of ATM and further chromatin remodelling with histone removal and nucleosome repositioning [1,31,32]. The Ku70/80 heterodimer, a rather small protein with a ring structure, is commonly considered to be the first major player in NHEJ. Ku is a highly abundant protein that binds to most ends as they become accessible [1]. When the nucleosomes surrounding the damage site are released, the DNA end with attached Ku recruits DNA-PKcs [1]. The synapsis of two DNA ends proceeds via dimerization of DNA-PKcs and their auto-phosphorylation. Conformational changes in DNA-PKcs make the DNA ends accessible to other NHEJ players, in particular Artemis that is involved in end processing and XRCC4-Ligase IV that performs the final ligation steps [1]. In addition to the above-described classical NHEJ, some DSB are repaired by alternative pathways not involving DNA-PK [1]. Finally, higher-order chromatin structures and the 'epigenetic code' are restored, presumably not always perfectly, thus potentially leading to 'epimutations' [33].

The NHEJ models [27–30] account for the major steps in biochemical processing of DSB and their kinetics. The attachment and action of repair enzymes are often expressed using the law of mass action as a system of kinetic equations (set of ordinary differential equations). There are two limiting aspects to these approaches: First, continuous models with reaction rate equations require that the numbers of DSB and repair enzymes are relatively large. For typical radiation doses leading to small DSB numbers, discrete stochastic models are more appropriate [28]. Second, the spatial aspects of NHEJ, on which the experimental information is unfortunately by far not as mature as the knowledge on the enzymes involved, are commonly neglected in the modelling, although they critically influence both the kinetics and the outcome of DSB joining. For instance, opening of the DSB is needed already for the Ku ring to attach to the DNA end and presumably even more for larger enzymes such as DNA-PKcs. Importantly, spatial aspects govern the ratio of proper vs. improper joining as well as the formation of CA. According to the breakage-and-reunion theory, only breaks (more precisely, broken ends) that come close together during the course of repair may get ligated and form aberrations.

This drawback of insufficient representation of spatial aspects in repair models has been removed by the NHEJ simulation module [34–36] in the PARTRAC biophysical modelling suite [37]. The simulations start by assessing DNA damage by overlapping space- and time-dependent radiation track structures with detailed models of DNA and chromatin structure. Namely, individual energy deposits to DNA and surrounding water molecules, production of reactive species, their diffusion and mutual reactions, and attacks to DNA are simulated. Multiple levels of chromatin structure are considered, from the DNA double-helix and nucleosomes to chromatin fibres, domains and territories that represent human cell nuclei in the interphase. An atomic DNA model enables predicting radiation quality-dependent complexity of DNA damage. The NHEJ module [34–36] follows in addition to the temporal development (i.e. the course of enzymatic processing) also the spatial movement of DNA ends based on the following hypotheses: First, following the chromatin remodelling step, the DSB 'opens' and forms a chromatin break, i.e. the break ends get mobile. Their mobility is limited by attachment sites where the fibre is anchored to the nuclear scaffold but not by tethering to the other end. Note that, on the contrary, other DSB repair and CA models treat DSB as a single entity, i.e. assume that the two free ends of any DSB are steadily held in proximity to each other, and CA result from (unspecified) pairwise interaction of DSB, not from joining wrong DNA ends. The second underlying hypothesis extends the first one by assuming that the experimentally observed mobility of chromatin regions can be applied to these DSB-induced ends as well. Within the repair simulation, the movement of broken ends and their processing by NHEJ enzymes are modelled simultaneously by stochastic Monte Carlo methods. These two processes together decide on which end pairs become ligated, i.e. these two aspects together govern the repair outcome, including the formation of CA.

In this paper, we extend the PARTRAC NHEJ module to CA simulations and thereby provide a link between models of repair processes and of CA. This extension consists of the following issues: First, data on the positions of centromeres have been implemented into the chromatin structure module. Second, the chromatin model has been extended to distinguish between regions of different chromatin densities (condensed heterochromatin and more relaxed,