Mutation Research 711 (2011) 174–186

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

Chromatin dynamics during cell cycle mediate conversion of DNA damage into chromatid breaks and affect formation of chromosomal aberrations: Biological and clinical significance

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ARTICLE INFO

Article history:
Received 2 November 2010
Received in revised form
30 November 2010
Accepted 17 December 2010
Available online 24 December 2010

Keywords:
Chromatid breaks
Chromatin dynamics
DNA damage
Chromosome aberration
PCC
Bystander effects

ABSTRACT

The formation of diverse chromosomal aberrations following irradiation and the variability in radiosensitivity at different cell-cycle stages remain a long standing controversy, probably because most of the studies have focused on elucidating the enzymatic mechanisms involved using simple DNA substrates. Yet, recognition, processing and repair of DNA damage occur within the nucleoprotein complex of chromatin which is dynamic in nature, capable of rapid unfolding, disassembling, assembling and refolding. The present work reviews experimental work designed to investigate the impact of chromatin dynamics and chromosome conformation changes during cell-cycle in the formation of chromosomal aberrations. Using conventional cytogenetics and premature chromosome condensation to visualize interphase chromatin, the data presented support the hypothesis that chromatin dynamic changes during cell-cycle are important determinants in the conversion of sub-microscopic DNA lesions into chromatid breaks. Consequently, the type and yield of radiation-induced chromosomal aberrations at a given cell-cycle-stage depends on the combined effect of DNA repair processes and chromatin dynamics, which is cell-cycle-regulated and subject to up- or down-regulation following radiation exposure or genetic alterations. This new hypothesis is used to explain the variability in radiosensitivity observed at various cell-cycle-stages, among mutant cells and cells of different origin, or among different individuals, and to revisit unresolved issues and unanswered questions. In addition, it is used to better understand hypersensitivity of AT cells and to provide an improved predictive G2-assay for evaluating radiosensitivity at individual level. Finally, experimental data at single cell level obtained using hybrid cells suggest that the proposed hypothesis applies only to the irradiated component of the hybrid.

Contents

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doi:10.1016/j.mrfmmm.2010.12.011

1. Introduction

1.1. DNA damage response at different cell-cycle stages leads to the formation of different types of chromosomal aberrations: a well accepted paradigm

Pioneer studies on the relationship between DNA replication and the chromosome damage caused by ionizing radiation offered a first description of the cell cycle. Cells duplicate their DNA during S-phase, preceded by G1-phase and separated from M-phase by the G2-phase. As cells are progressing through these different cell-cycle stages, their response to chromosomal aberration formation and sensitivity to the lethal effects of ionizing radiation varies. In general, late S-phase is most radioresistant, G2/M being most radiosensitive and G1 phase being in an intermediate position. Elucidation of the mechanisms underlying the formation of chromosomal aberrations is of particular interest since chromosome abnormalities are correlated to radiation sensitivity, cell killing, cell transformation and induction of cancer (for a review see [1]). At present, a well accepted paradigm is that DNA double strand break (DSB) is considered to be the critical lesion for chromosomal aberration formation [2–11]. Also, non-DSB oxidative cluster DNA lesions (OCDLs) consisting of a combination of single strand breaks, abasic sites and oxidized bases within 5–10 base pairs, have been shown to be a more complex deleterious form of DNA damage [12–20]. DSBs can result not only from exposure to ionizing radiation, but also endogenously from free radical byproducts of normal cellular metabolism or as repair intermediates during processing of OCDLs. Clustered DNA lesions have been also shown to accumulate in a variety of human tumor tissues at higher levels compared to controls [21] and, interestingly, it has been recently reported that DSBs and OCDLs were elevated in distant proliferative tissue from the tumor site in tumor-bearing mice [22].

In response to DNA damage, cells activate a network of cellular processes and rapid multiple enzymatic repair mechanisms to minimize the impact of such lesions and maintain the integrity of the genome. For double strand breaks there are two primary repair pathways, the non-homologous end joining (NHEJ) that operates on blunt ended DNA fragments and is error prone, and the homologous recombination (HR) that is error free since it relies on sequence homology and can only operate in late S- or G2-phases [23,24]. Recently Iliakis et al. [8,25] have proposed the existence of two types of NHEJ pathways: D-NHEJ (DNA-PK-dependent) and B-NHEJ (back up NHEJ). Other DNA repair mechanisms such as base excision repair (BER), mismatch repair (MR) and nucleotide excision repair (NER) respond also to damage such as base oxidation, alkylation, and strand intercalation. Such mechanisms are well organized in pathways that coordinate DNA damage recognition and signaling leading to cell cycle arrest by activating checkpoints at various cell cycle stages to facilitate DNA repair. Thus cells have evolved efficient responses to prevent replication in the presence of DNA lesions, transmission during cell division of altered genetic information to daughter cells and cell transformation. It is thought that unrepaired DNA damage can lead to cell death [6] whereas misrepair of DNA lesions may result into non-viable or viable chromosomal aberrations and rearrangements some of which are thought to be instrumental in cell transformation and the development of cancer [26,27]. DNA damage induced in different cell cycle stages leads to the formation of different types of chromosomal aberrations (Fig. 1). Radiation delivered during Go/G1 or S-phase of the cell cycle produces chromosome-type or chromatid-type aberrations and chromatid exchanges, respectively, whereas irradiation during G2-phase induces mainly chromatid breaks and not chromosome exchanges in mammalian cells. On the contrary, irradiation during M-phase can produce both. Also, cells mutated in some of the gene products such as ATM and Ku80 in NHEJ pathway display both chromosome and chromatid type aberrations after irradiation at G0/G1 stages [28,29].

Despite considerable progress over the past years, the precise mechanisms involved in the formation of such diverse chromosomal aberrations still remain a long-standing controversy in radiation cytogenetics. Particularly, the question arises as to how sub-microscopic DSBs or non-DSB clustered lesions can lead mainly to chromatid breaks and not to exchanges, following G2-phase irradiation, or to the formation of inter- or intrachromosomal exchanges, following G0/G1 or S-phase irradiation. In addition, it is not yet well understood how such diverse chromosomal aberrations can lead to the apparent differences in radiosensitivity when cells are irradiated at different cell cycle stages. It is also interesting to consider that only a very small number of DNA lesions give rise to the formation of chromosomal aberrations, even though the number of radiation-induced DNA lesions is initially large.

1.2. Chromatin dynamics may affect DNA damage response and the formation of different types of chromosomal aberrations

Quantitative interpretations of radiation-induced chromosomal aberrations have inspired numerous biophysical models to explain the relevant molecular processes underlying their formation. It is generally accepted that the type and yield of chromosomal aberrations depend on the status and efficiency of the different DSB repair pathways that operate at different cell-cycle stages [4]. Nevertheless, anyone of the models on DSB induction and repair used alone is still unable to explain all aspects related to the formation of chromosomal aberrations and the resulting variability in radiosensitivity at the different stages of the cell cycle [30]. Probably, this is because most of the biochemical and genetic studies have focused on elucidating the enzymatic mechanisms involved in recognizing, signaling and repairing DSBs, using simple DNA substrates [31]. At present, though, efforts have been geared towards understanding how the repair machinery deals with DSBs within the dynamics of chromatin fibers. It is now considered that the primary damage of DNA and its repair can be influenced by transcriptional activity, chromatin structure, organization and gene density. Sensor proteins are thought to detect the presence of a DSB and then recruit transducer proteins, which provide the signals to enzymes to repair the break in the DNA substrate. Such substrate is within the chromatin fibers and the nucleoprotein complex, which packages DNA inside the nucleus. Recognition, processing and repair of DSBs must occur, therefore, within the nucleoprotein complex of chromatin