Mutation Research 701 (2010) 86–91

Contents lists available at ScienceDirect

Mutation Research/Genetic Toxicology and Environmental Mutagenesis

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

Relationship between chromatin structure, DNA damage and repair following X-irradiation of human lymphocytes

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ARTICLE INFO

Article history:
Received 5 March 2010
Accepted 9 March 2010
Available online 16 March 2010

Keywords:
FISH–Comet assay
DNA repair
Heterochromatin
CpG islands
DMSO
Radical scavengers
Exchange aberrations and chromatin architecture

ABSTRACT

Earlier studies using the technique of premature chromosome condensation (PCC) have shown that in human lymphocytes, exchange type of aberrations are formed immediately following low doses (<2 Gy) of X-rays, whereas at higher doses these aberrations increase with the duration of recovery. This reflects the relative roles of slow and fast repair in the formation of exchange aberrations. The underlying basis for slow and fast repairing components of the DNA repair may be related to differential localization of the initial damage in the genome, i.e., between relaxed and condensed chromatin. We have tried to gain some insight into this problem by (a) X-irradiating lymphocytes in the presence of dimethyl sulfoxide (DMSO) a potent scavenger of radiation-induced •OH radicals followed by PCC and (b) probing the damage and repair in two specific chromosomes, 18 and 19, which are relatively poor and rich in transcribing genes by COMET–FISH, a combination of Comet assay and fluorescence in situ hybridization (FISH) techniques.

Results obtained show (a) that both fast appearing and slowly formed exchange aberrations seem to take place in relaxed chromatin, since they are affected to a similar extent by DMSO, (b) significant differential DNA breakage of chromosome 18 compared to chromosome 19 in both G0 and G1 phases of the cell cycle as detected by Comet assay, indicating that relaxed chromatin containing high densities of transcriptionally active genes shows less fragmentation due to fast repair (chromosome 19) compared to chromosome 18, and (c) that relaxed chromatin is repaired or mis-repaired faster than more compact chromatin.

1. Introduction

Ionizing radiation (IR) is an efficient inducer of chromosome aberrations (CA), which represent the outcome of very complex events, involving the conversion of DNA double strand breaks (DSBs) and other lesions through various DNA repair pathways into microscopically detectable events. Though IR is expected to induce DNA lesions in a random manner in the genome, some studies using FISH technique with chromosome specific DNA probes, have reported that the frequency of radiation-induced chromosome exchanges was proportional to the length or to the DNA content of target chromosomes [1–3], whereas other studies have reported that the induction of chromosome exchanges is non-random among the chromosomes studied [4–10]. The possible causes for this reported non-random distribution of exchanges have been attributed to various factors such as, differential primary damage of DNA and its repair which could be influenced by transcriptional activity [11–14], chromatin structure [4,5,15,16] and gene density [17,18] of the studied chromosomes. This implies that CA we observe, which are the consequences of mis-repair of IR induced DSBs, may not reflect the initial distribution of DNA damage in the genome. Earlier studies using the technique of premature chromosome condensation (PCC) by fusion with mitotic cells, have shown that in human lymphocytes, exchange type of aberrations are formed within a few minutes, following low doses (<2 Gy) of X-rays where the two lesions required to produce the exchange are significantly generated by one ionization track, whereas at higher doses where the probability of the two lesions being produced by two independent tracks is higher, these aberrations increase with the duration of recovery [19,20]. This reflects the relative roles of slow and fast repairing components of induced DNA double strand breaks (DSBs) leading to CA. The underlying basis for the slow and fast repairing components of the DNA breaks may be related to the differential localization of the damage in the genome, i.e., between relaxed and condensed regions. The genome is highly het-

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doi:10.1016/j.mrgentox.2010.03.005