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Indirect mechanisms of radiation induced genomic instability at repeat loci

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Abstract. Radiation triggers genomic instability which results in induction of untargeted mutation and delayed mutation. The radiation induced genomic instability has been studied mostly in tissue culture cells, but analyses have also been conducted in whole body systems in which repeat sequences are frequently used as markers of mutations. The past studies on radiation induced tandem repeat mutations yielded conflicting results and the lack of knowledge of the mechanisms hampers the interpretation of the results. In this article, some of the existing controversies of genomic instability are discussed in relation to the mechanism of repeat mutation. Analyses of published and unpublished studies suggest a mechanistic similarity between radiation-induced genomic instability at repeat loci and dynamic mutations of triplet repeats. Repeat sequences are well known to block progression of replication forks which are frequently resolved by recombination between sister chromatids. Irradiation of cells induces p53 dependent S checkpoint which can promote recombination mediated repeat mutations. Thus, genomic instability at repeat loci can be viewed as a consequence of cellular attempts to restore the stability of replication in the face of the stalled replication fork; this process can be induced either spontaneously or after irradiation. © 2007 Published by Elsevier B.V.

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1. Radiation induction of genomic instability in whole body systems

1.1. Radiation induction of genomic instability

The term “mutation” was coined in 1901 by Hugo de Vries to describe heritable changes in the phenotype of an organism. Elucidation of the structure of DNA by Watson and Crick clarified the nature of the target molecule for mutation. More recent studies on the

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molecular mechanisms of DNA repair and mutagenesis have demonstrated that mutation is a change in the DNA sequence which occurs by misrepair and misreplication of damaged DNA [1]. This direct mechanism of mutagenesis predicts that mutation is induced only transiently in a targeted fashion at the site of DNA damage. This straightforward concept of mutagenesis has been challenged in recent years by the discovery of radiation-induced genomic instability [2,3]. Genomic instability is induced as one of the pathways of radio-response in which the stability of genomic integrity is down-regulated. This down-regulation can be viewed as a mechanism to tolerate DNA damage at the expense of mutation as exemplified by the translesional DNA synthesis [4]. Genomic instability can also be brought about by the breakage-fusion-bridge cycle in which production of de novo DNA damage persists in irradiated cells and their descendants [5].

Radiation-induced genomic instability in tissue culture cells leads to several consequences including delayed gene mutation, delayed chromosome aberrations and delayed transformation [2]. The bystander effect is one of the mechanisms responsible for radiation-induced genomic instability of cells in culture in which reactive oxygen species (ROS) and other mutagenic/clastogenic factors produced by the irradiated cells damage bystander cells. Since DNA damage is involved in this process, mutation induction through the bystander effect is a targeted event where the mutation occurs at the site of DNA damage. However, it is still a non-targeted event since cells not hit by radiation are mutated as well.

Untargeted mutation is defined as mutation that occurs in a region of the genome with no DNA damage [1]. Untargeted mutation is known to exist in a variety of organisms. Classic studies on UV mutagenesis in bacterial systems have demonstrated an SOS response in which mutation occurs in bacteriophase and bacteria even without UV irradiation [6]. Genes involved in this SOS mutagenesis were later cloned and one of them was the translesional DNA polymerases [7]. Classic studies on untargeted mutation was conducted also in yeast in which fusion to X-irradiated cells lead to higher frequencies of recombination in non-irradiated cells [8].

Interests in untargeted mutation center on its mechanisms and biological significance and the role of untargeted mutation was tested at the whole body level to test its significance in radiation risk. Cancer in somatic tissues and germline mutation in germ cells are considered the major risks associated with radiation exposures. If untargeted mutagenesis operates in whole body exposures, the current understandings on radiation risks have to be reevaluated, thus attracting the attention of many researchers to the role of genomic instability in radiation induction of cancer and germline mutations [9].

The aim of the present study is to review the studies on radiation-induced genomic instability in whole body systems with particular attention on repeat mutations. Emerging features of radiation induced repeat mutations in whole body systems are analyzed and the mechanisms of untargeted and delayed mutations are discussed.

1.2. Problems of assessing mutations in whole body systems and the use of tandem repeat sequences

The lack of appropriate markers to detect mutations poses difficulties in analyzing the role of genomic instability in whole body systems. The study of mutations at the DNA sequence level in individual genes is rendered difficult by the extremely low frequency of

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