International Journal of Cell Science & Molecular Biology
ISSN: 2572-1100

Juniper Publishers
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Mini Review
Volume 7 Issue 1 - December 2021
DOI: 10.19080/IJCSMB.2021.07.555704

Int J cell Sci & mol biol

Ionizing Radiation and DNA Changes Underlying Inherited Recessive Gene/ Point Mutations

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Submission: November 21, 2021; **Published:** December 02, 2021

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Keywords: DNA; Gene conversion; Radiotherapy; Neutrons

Mini Review

Decision of the issue "What kinds of DNA changes underlie inherited radiation-induced recessive gene/point (intragenic) mutations in higher eukaryotes?" is extremely important from a scientific and applied point of view. In the former case, an experimental solution of this issue opens up the outlook of understanding the fundamental mechanisms underlying this enigmatic and still poorly studied class of inherited gene/point mutations in higher [1] and lower [2] eukaryotes. Among these mechanisms, trigger events (initial ionization, DNA damage) and repair pathways are key steps because they determine the spectrum and frequency of gene/point mutations in the germ cells of eukaryotes. Moreover, a comparison of the experimentally observed DNA changes with the results of modeling of yield of radiation-induced main initial DNA damage (single- and double-strand breaks, complex damage) makes it possible to establish a connection between initial damage and DNA changes recovered, as well as to specify the repair pathway leading to this DNA change. In the letter case, the solution of this issue creates a modern scientific basis for assessment the hazard (risk) of sparsely (X- and γ-rays) and densely (neutrons, heavy ions) ionizing radiation at the molecular but not at the phenotypic level, as it is considered now [3]. Assessment of the genetic hazard of different quality radiation is extremely relevant to-day when humans is increasingly exposed to radiation on Earth (nuclear power station, radiotherapy, neutron research, nuclear disaster etc.) and in outer space. The fact that gene/point mutations are responsible for almost half of the recessive Mendelian diseases persisting in modern human populations [4], and these mutations are mainly based on base substitutions and, to a lesser extent, deletions, insertions and duplications [5,6] raises the question of what the effectiveness of is sparsely and densely ionizing radiation in induction of these DNA change. Despite the topicality of this issue, experimental data on the nature and frequency of radiation-induced inherited DNA changes in the germline cells remain so far extremely limited by small sample of sex-linked Drosophila *vermilion* gene/point mutants induced by X-rays [7]. So, among thirteen DNA changes recovered, there were seven base substitutions (53.8%), three deletions with the sizes of 4-5 bp in length (23.0%), two indels (15.4%), and insertion (3bp in length) instead of extended deletion of 13bp in length (7.8%). It is important to note that two mutants had the clusters of DNA changes.

The results of other work [8] in which a larger sample of γ-ray- and neutron-induced point mutations at the autosomal Drosophila *black* gene was studied, showed a wider spectrum of inherited DNA changes among γ-ray-induced mutations which partially coincided with that in *vermilion* gene (base substitutions, indels, extended deletions, insertion instead of deletion). So, among forty-two DNA changes recovered in *black* mutations, there were twenty (47.6%) base substitutions, seven (16.7%) indels, six (14.3%) extended deletions, and one (2.3%) mutant with insertion instead of deletion. At the same time, new DNA changes were observed among γ-ray-induced *black* mutations, namely, there were mutants (11.9%) in which the paternal *black* gene was replaced by the maternal one marked by base substitutions (the so-called gene conversion event) and several mutants (7.2%) with duplication. Thus, as these data show, sparsely ionizing radiation most effectively induces base substitutions in both

sex-linked *vermilion* and autosomal *black* genes but, at the same time, γ-rays induces with certain rate the mutants with gene conversion events only in an autosomal gene what it could be explained either by a small sample of studied *vermilion* mutants or, more likely, by the absence of recombination-dependent repair (interallelic homologous recombination pathway, HR) in F1 females heterozygous for inversions in the X chromosome. New and important data are that γ-rays often induce clusters of independent DNA changes within a gene and even one turn of a double-stranded DNA helix [8].

Somewhat unusual spectrum of DNA changes was found in *black* mutants induced by neutrons [8]. So, there were extremely high frequency of *black* mutants with gene convention events (85.7%) and only a few extended deletions (9.5%) and one mutant with an insertion instead of a deletion (4.8%), while no base substitutions were found. As discussed earlier [8], the trigger for gene conversion events is apparently the gross or complex initial DNA damages in the induction of which densely ionizing radiation is known to be much more effective than sparsely ionizing radiation [9,10]. This explains the low frequency of gene conversion events among γ-ray-induced *black* mutations. Since monoenergetic fission neutrons of relatively low energy (0.85 MeV) were used in our experiments, it remains unclear whether such a high frequency of *black* mutants with gene conversion events is a feature of neutrons 0.85 MeV or whether it is characteristic of the genetic action of any neutrons in general at the DNA level. Further experiments with neutrons of different energies as well as with heavy ions could obviously solve this question. It is also important to note that DNA changes in the form of gene conversion could be established due to the fact that the maternal gene *black* was marked with base substitutions that were easily identified by sequence analysis. Otherwise, the replacement of the paternal gene by the maternal one would not have been detected among γ-ray- and neutron-induced mutants. An important consequence of gene conversion for populations exposed to ionizing radiation is the elimination of induced gene/point mutation by this genetic mechanism and, at the same time, doubling of the normal maternal allele. Could the discussed phenomenon (gene conversion) explain the negative results [3] of the search for genetic changes in the surviving people of Nagasaki and Hiroshima after irradiation with a high neutron content?

An important applied implication arising from the results of our work [8] is that for the first time the hazard of sparsely ionizing radiation was estimated at the molecular level in relation to the induction of base substitutions as the most frequent type of DNA changes in human spontaneous mutagenesis as well as in radiation mutagenesis in Drosophila. Using the gametic doubling-dose method, it was found that the doubling dose for γ-ray-induced base substitutions (1.2Gy) is almost five times lower than that for gene/point mutations detected at the phenotypic level (5.8Gy). Extrapolating these molecular data to the genome level, it could be assumed that molecular genetic consequences of this kind for the offspring of irradiated male parents can be expected anywhere in the genome of viable and fertile heterozygous progeny. This assumption requires the implementation of appropriate genomic studies that are in progress now.

Conclusion

Molecular genetic data for two different Drosophila genes are briefly presented here giving, in a first approximation, answer to the question posed above and show that phenotypically the same mutants can have completely different mutational DNA changes. These data show the presence of a certain similarity between the two genes in the spectrum of DNA changes induced by sparsely ionizing radiation. At the same time, they show certain features of this spectrum (gene conversion, duplication), apparently characteristic only for an autosomal gene, the mutation processing of which took place under conditions of structural homozygosity and interallelic recombination during the first mitotic cycle after syngamy, in contrast to structural heterozygosity and lack interallelic recombination for a sex-linked gene. It is important to note that the low frequency of γ-ray-induced mutants with gene conversion and high frequency of such mutants after exposure to neutrons correlate with the property of these types of radiation to induce with low and high frequency, respectively, the complex DNA damage repaired by HR pathway. Of course, these first findings show the need to continue such research and to carry out comparative studies in the Drosophila - mice system which is especially important to estimate the hazard of ionizing radiation for human.

Acknowledgement

This work was carried out with the financial support of Joint Institute for Nuclear Research (JINR)..

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How to cite this article: Alexandrov I, Alexandrova M. Ionizing Radiation and DNA Changes Underlying Inherited Recessive Gene/Point Mutations. Int J Cell Sci & Mol Biol. 2021; 7(1): 555704. DOI: 10.19080/IJCSMB.2021.06.555704

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DOI:10.19080/IJCSMB.2021.06.555704

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