Chronicle of Aquatic Science

TYPE: Mini-review
PUBLISHED: 31 July, 2023
ISSUE: Volume 1, Issue 2
ARTICLE ID: CoAS_V1IS2_06

OPEN ACCESS

EDITED BY
Ankures Bhattacharya
West Bengal University of Animal and Fishery Sciences

REVIEWED BY

Partha Sarathi Tripathy
Faculty of Biosciences and Aquaculture
Nord University, Norway

Durgesh Kumar Verma
ICAR-CIFRI, Regional center
Prayagraj, UP

*CORRESPONDENCE
Gowhar Iqbal
drgowhariqbal@gmail.com

RECEIVED 5 July 2023
ACCEPTED 20 July 2023
PUBLISHED 31 July 2023

CITATION
Iqbal et al., (2023) Genotoxicity Unveiled: A Mini-review of Mechanisms, Detection, and Implications. Chronicle of Aquatic Science 1(2): 44-50

Genotoxicity Unveiled: A Mini-review of Mechanisms, Detection, and Implications

Gowhar Iqbal[1], Shafiya Mushtaq[2], Ad Viral Kumar Ganpatbhai[1], Lukram Sushil Singh[1]and Sangeetha S[1]

[1]ICAR-Central Institute of Fisheries Education, Panch Marg, Yari Road, Mumbai-400061.
[2]Faculty of Fisheries, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir (SKUAST-K), Rangil-190006, Ganderbal.

The term "genotoxicity" is defined as the presence of a substance that has a detrimental effect on the genetic material (DNA, RNA) of the cell, hence impairing the integrity of the cell. Mutagens called genotoxins can potentially damage DNA or chromosomal material, resulting in a mutation. Genotoxins are substances that can harm DNA or chromosomal structure, resulting in mutations. It can be radiation or chemicals. Regulatory agencies worldwide demand data on the new drug's potential to cause genotoxicity as part of the safety evaluation process. While the damage to the germ cell will result in heritable disorders, the damage to the somatic cells will result in various diseases, including cancer. Regulatory agencies worldwide demand data on the new drug's potential to cause genotoxicity as part of the safety evaluation process.

Keywords

Genotoxicity, DNA Damage, Genotoxins, Cancer, Genotoxicity Assay

Introduction

The degree to which a chemical compound or a specific combination of chemicals can harm an organism is known as its toxicity. Toxicity can refer to the influence on an entire organism, such as an animal, bacterium, or plant, as well as the impact on an organism's cell structure or an organ, such as the liver, through cytotoxicity or hepatotoxicity. A key idea in toxicology is that a toxin's effects are dose-dependent; for example, drinking too much water can cause water intoxication, yet even a chemical as poisonous as snake venom has a safe dosage range below which there are no detrimental effects to be seen. The concept of toxicity endpoints is being maintained as newer paradigms and metrics are emerging to replace animal testing [1].

Genotoxicity

In genetics, the term "genotoxicity" indicates the presence of a substance that has a detrimental effect on the genetic material (DNA, RNA) of the cell, hence impairing the integrity of the cell. Mutagens called genotoxins can potentially damage DNA or chromosomal material, resulting in a mutation [19]. Radiation and chemicals are both potential genotoxins. The field of study known as genetic toxicology investigates agents or compounds that can harm a cell's chromosomes and DNA [11].

Genotoxins can be of the following category depending on their effects

- Carcinogens or cancer-causing agents
- Mutagens or mutation-causing agents
- Teratogens or birth defect-causing agents

In eukaryotic species, malignancy (cancer) may result from damage to somatic cells' genetic material. Alternatively, genetic damage to the germ cells may result in heritable mutations that cause birth abnormalities (Figure 1). Any type of mutation is possible, involving the duplication, insertion, or deletion of genetic data. These mutations may result in several issues in the host, from various illnesses to malignancy [3]. Finding the substance or chemical, such as antimutagens/antiiclastogens (which suppress or inhibit the mutagenesis process by directly acting on the cell mechanism) and demutagens (which partially destroy or inactivate the mutagens), is one of the best ways to control the damage caused by mutagens and carcinogens. or fully, thereby affecting less population of the cell) from the medicinal plants to be used as antimutagenic and anticarcinogenic food or drug additives [18].

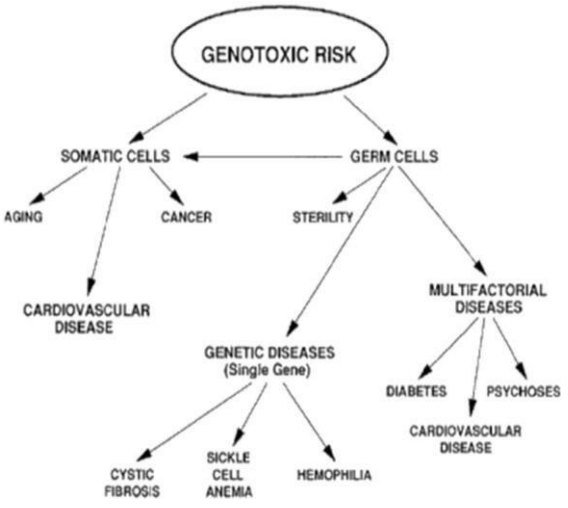

Fig 1: Risk of Genotoxicity Source [3]

Importance of genotoxicity

Genotoxicity investigations are various in vitro and in vivo tests intended to find any drug or substances that may damage genetic material directly or indirectly in various ways. These tests should make it possible to spot potential risks for DNA fixation and damage [7]. Only genetic change, which includes the repair of DNA damage caused by gene mutation, extensive chromosomal damage, recombination, or numerical chromosomal changes, plays a role in the intricate process of heritable effects and cancer [4]. When a substance tests positive, it can be determined if it has the potential to be genotoxic and carcinogenic. Regulatory agencies worldwide demand data on the new drug's potential to cause genotoxicity as part of the safety evaluation process [2]. Typically, the safety assessment includes consideration of genotoxicity and other toxicological endpoints [23].

Since both possible heritable germ cell damage and carcinogenicity have similar precursors, the same testing procedures are used in the early testing phases to anticipate both endpoints [18]. While showing a link between heritable disorders and exposure to specific chemicals has been challenging, a tie between the two has been established for carcinogenesis [26]. Studies on genotoxic effects have primarily been utilised to forecast a substance's carcinogenic potential [19].

Mechanism of genotoxicity

The interactions of the genotoxic chemical with the DNA structure and sequence damage the genetic material [26]. These genotoxic agents interact with the DNA structure at a particular site or base sequence, resulting in lesions, breaking, fusion, deletion, mis-segregation, or non-disjunction, which results in damage and mutation [24]. For instance, the transition metal chromium interacts with DNA in its high-valent oxidation state to cause DNA lesions, which result in carcinogenesis [5]. High-valent chromium has been classified as a carcinogen because studies have shown that the mechanism of damage and base oxidation products for the interaction between DNA and high-valent chromium are related to the in-vivo creation of DNA damage leading to cancer in the population exposed to chromate. (Fig2).

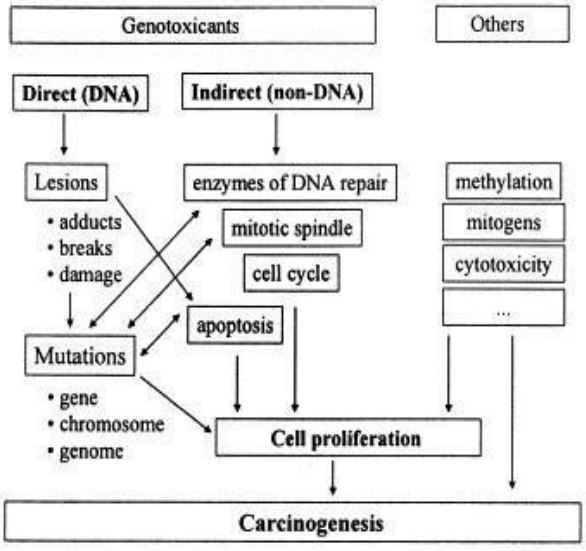

Fig 2: Mechanism of genotoxicity Source [7]

Reactive oxygen species cause one of DNA's most abundant oxidative lesions and are 8- hydroxy deoxyguanosine (8-OHdG), a potent mutagenic lesion. Reactive aldehydes, such as 4-hydroxynonenal (4-HNE), are produced by the breakdown of lipid peroxyl radicals, the major free radical intermediate of

lipid peroxidation [10]. Numerous studies have suggested that 4-hydroxynonenal might boost cell proliferation, differentiation, and cytoprotective response by impacting numerous signaling pathways [9].

Genotoxicity assay

A genotoxicity assay is performed to check the genotoxic potential of drugs and chemicals and the presence of Geno-toxicants inthe natural system (Geno-toxicant pollution) [21]. There are two approaches to genotoxicity assay

- In vitro assay
- In vivo assay

There are many in-vitro genotoxicity testing methods available. Some of the commonly used tests are as follows:

1. **Mammalian chromosome aberration test**

The primary goal of the mammalian chromosome aberration test is to find the agents that can alter the structure of chromatids, which are the most frequent type of structural alteration in chromosomes [25]. This test can also be used to detect polyploidy and duplication, two additional kinds of chromosomal abnormalities [7]. Although there isn't always a direct association, a positive test result indicates a possible mutagenic or carcinogenic substance [22].

2. **Bacterial reverse mutation test**

Ames developed bacterial reverse mutation testing. The bacterial reverse mutation test is used to identify the mutation spots, which may involve substitution, deletion, or addition of one or more DNA base pairs, in Salmonella typhimurium and Escherichia coli strains that require amino acids [9]. The basic idea behind the test is that once the mutation has been found, it may be corrected, restoring the mutant cell's capacity to synthesis histidine. The parent test strain's capacity to proliferate in the absence of amino acids is used in this test to distinguish between different bacterium cells [19]. As an initial screening test for genotoxicity or mutagenicity, the bacterial reverse mutation test is frequently employed since it is quick, affordable, and simple to carry out [13].

3. **Mammalian cell gene mutation test**

This test is used to identify gene mutations brought on by chemicals. The L5178Y mouse lymphoma cell line, the CHO, CHO-AS52 and V79 lines of Chinese hamster cells, and the TK6 human lymphoblastic cell line are examples of frequently used cell lines. Thymidine kinase (TK), hypoxanthine-guanine phosphoribosyl transferase (HPRT), and a transgene of xanthine-guanine phosphoribosyl transferase (XPRT) mutation are among the outcomes that are detected [20].

4. **Comet assay**

It is one of the often employed in-vivo assays for determining the risk of substances with the potential to cause genotoxicity or mutagenicity [12]. It aids in detecting DNA damage and finds a variety of primary DNA lesions that cannot be found with any other assays. A wide range of tissues or unique cell types can be subjected to this test. It needs a few cells per sample, can be finished quickly, and is sensitive to very low amounts of DNA damage [13].

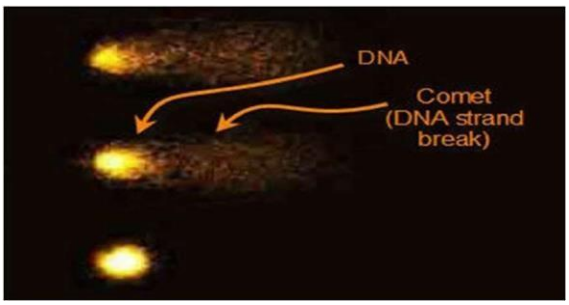

Fig. 3: DNA damage (Head, tail) Source[12]

5. Micronuclei test

It is a test to determine the extent of chromosomal or spindle damage. The cell may get damaged upon exposure to the mutagen, and upon division, it will produce a tiny micronucleus in addition to the main nucleus. Micronuclei form when replicating cell populations experiences chromosomal breakage by clastogens (agents that cause chromosomal breakage) or chromosome loss by mitotic spindle failure [17]. This test, which is equally sensitive to the time-consuming cytogenetic analysis, can also be used to evaluate the cytogenetic damage brought on by exposure to genotoxic substances [5, 23].

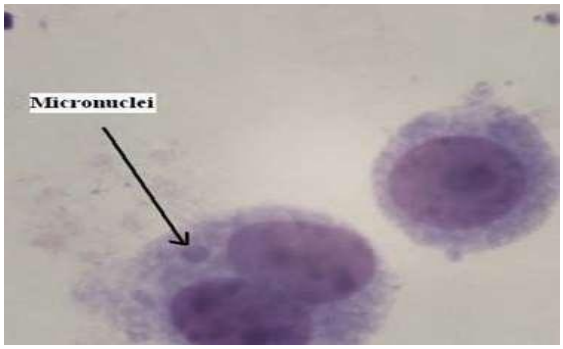

Fig.4: Micronuclei Source [7]

Conclusion

Genotoxins are substances that can interact with DNA, altering its structure and producing mutations that can result in cancer. Genotoxic agents interact with the DNA structure at a particular site or base sequence, resulting in lesions, breaking, fusion, deletion, mis-segregation, or non-disjunction, which results in damage and mutation. In eukaryotic species, malignancy (cancer) may result from damage to somatic cells' genetic material. Alternatively, genetic damage to the germ cells may result in heritable mutations that cause birth abnormalities. To prevent the potential harm that can result from it, it is crucial to conduct genotoxicity tests.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the manuscript was formulated in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. De Flora S, Izzotti A (2007) Mutagenesis and cardiovascular diseases Molecular mechanisms, risk factors, and protective factors. Mutat Res 621(1-2): 5-17.

2. Natarajan AT (1993) Mechanisms for induction of mutations and chromosome alterations. Environ Health Perspect 101 (Suppl 3): 225-229.
3. http://iosrjournals.org/iosr/jpbs/papers/vol issue2/P0124354. pdfid=4598
4. Savage JR (1976) Classification and relationships of induced chromosomal structural changes. J Med Genet 13(2): 103-22.
5. Hayashi, Makoto. "The micronucleus test—most widely used in vivo genotoxicity test—." Genes and Environment 38.1 (2016): 18.
6. Eker AP, Quayle C, Chaves I, van der Horst GT (2009) DNA repair in Mammalia cells: Direct DNA damage reversal: elegant solutions for nasty problems. Cell Mol Life Sci 66(6): 968-80.
7. Sedgwick B, Bates PA, Paik J, Jacobs SC, Lindahl T (2007) Repair of alkylated DNA: recent advances. DNA Repair (Amst) 6(4): 429-442.
8. Cimino MC (2006) Comparative overview of current international strategies and guidelines for genetic toxicology testing for regulatory purposes. Environ Mol Mutagen 47(5): 362-390.
9. Shah SU (2012) Importance of genotoxicity & S2a guidelines for genotoxicity testing for pharmaceuticals. Iosr Journal of Pharmacy and Biological Sciences 1(2): 43-54.
10. Phillips, D.H. and Arlt, V.M., 2009. Genotoxicity: damage to DNA and its consequences. Molecular, Clinical and Environmental Toxicology: Volume 1: Molecular Toxicology,.87-110.
11. Blattner, Georges, et al. "Gene editing and genotoxicity: targeting the off-targets." Frontiers in Genome Editing 2 (2020): 613252.
12. Frenzilli, G. I. A. D. A., M. A. R. C. O. Nigro, and B. P. Lyons. "The Comet assay for the evaluation of genotoxic impact in aquatic environments." Mutation research/reviews in mutationresearch 681.1 (2009): 80-92.
13. Glei, M., T. Schneider, and W. Schlörmann. "Comet assay: an essential tool in toxicological research." Archives of toxicology 90 (2016): 2315-2336.
14. Vandghanooni, Somayeh, and Morteza Eskandani. "Comet assay: a method to evaluate genotoxicity of nano-drug delivery system." BioImpacts: BI 1.2 (2011): 87.
15. Phillips, David H., and Volker M. Arlt. "Genotoxicity: damage to DNA and its consequences." Molecular, Clinical and Environmental Toxicology: Volume 1: Molecular Toxicology (2009): 87-110.
16. Baumstark-Khan, Christa, Christine E. Hellweg, and Günther Reitz. "Cytotoxicity and genotoxicity reporter systems based on the use of mammalian cells." Whole Cell Sensing System II: Applications (2010): 113-151.

17. Kirkland, David, "Recommended lists of genotoxic and non-genotoxic chemicals for assessment of the performance of new or improved genotoxicity tests: a follow-up to an ECVAM workshop." Mutation Research/Genetic Toxicology and Environmental Mutagenesis 653.1-2 (2008): 99-108.
18. Shah, Shaily Umang. "Importance of Genotoxicity & S2A guidelines for genotoxicity testing for pharmaceuticals." IOSR Journal of Pharmacy and Biological Sciences 1.2 (2012): 43-54.
19. Ku, Warren W., et al. "Strategy for genotoxicity testing—metabolic considerations." Mutation Research/Genetic Toxicology and Environmental Mutagenesis 627.1 (2007): 59-77.
20. Osman, Alaa GM. "Genotoxicity tests and their contributions in aquatic environmental research." Journal of Environmental protection 5.14 (2014): 1391.
21. Burlinson, Brian, et al. "Fourth International Workgroup on Genotoxicity testing: results of the in vivo Comet assay workgroup." Mutation Research/Genetic Toxicology and Environmental Mutagenesis 627.1 (2007): 31-35.
22. Albertini, Richard J., et al. "IPCS guidelines for the monitoring of genotoxic effects of carcinogens in humans." Mutation Research/Reviews in Mutation Research 463.2 (2000): 111-172.
23. Kurelec, Branko. "The genotoxic disease syndrome." Marine Environmental Research 35.4 (1993): 341-348.
24. Shackelford, Rodney E., William K. Kaufmann, and Richard S. Paules. "Cell cycle control, checkpoint mechanisms, and genotoxic stress." Environmental health perspectives 107.suppl 1 (1999): 5-24.
25. Al-Sabti, Kabil. "Handbook of genotoxic effects and fish chromosomes." Handbook of genotoxic effects and fish chromosomes. (1991).
26. Bassi, Christian, et al. "Nuclear PTEN controls DNA repair and sensitivity to genotoxic stress." Science 341.6144 (2013): 395-399.