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General Studies of Induced Genotoxicity and Oxidative Stress on Horticultural Crops

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Abstract

Genotoxicity is a word in genetics defined as a destructive effect on a cell's genetic material (DNA & RNA) affecting its integrity. Genotoxins are mutagens; they can cause mutations. In genetics, genotoxicity describes the property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer. While genotoxicity is often confused with mutagenicity, all mutagens are genotoxic, whereas not all genotoxic substances are mutagenic. The alteration can have direct or indirect effects on the DNA: the induction of mutations, mistimed event activation, and direct DNA damage leading to mutations. The permanent, heritable changes can affect either somatic cells of the organism or germ cells to be passed on to future generations, the alteration can have direct or indirect effects on the DNA: the induction of mutations, mistimed event activation, and direct DNA damage leading to mutations. The permanent, heritable changes can affect either somatic cells of the organism or germ cells to be passed on to future generations.

1. Introduction

The process of mutagenesis the process of agent-induced mutagenesis consists of three parts: the induction of DNA damage, the sensing of the DNA damage by the cell (the DNA damage response), and the processing of the DNA damage by the cell, which may or may not result in a mutation. A key underlying concept is that mutagenesis is a cellular process, frequently involving DNA replication. Another key concept is that there is a distinct difference between DNA damage and mutation. Thus, mutagens, despite what their name suggests, generally do not produce mutations; instead, mutagens produce DNA damage. One of the best ways to control the damage due to mutagens and carcinogens is to identify the substance or chemical, *i.e.*, antimutagens/ anticlastogens (which suppress or inhibit the mutagenesis process by directly acting on the cell mechanism) and demutagens (which destroy or inactivate the mutagens partially or fully thereby affecting less population of cell) from the medicinal plants so that it can be used as antimutagenic and anticarcinogenic food or drug additives.

2. Importance of Genotoxicity Studies

Genotoxicity studies can be defined as various *in-vitro* and *in-vivo* tests designed to identify any substance or compounds which may induce damage to genetic material either directly or indirectly by various mechanisms. These tests should enable the identification of hazard with respect to DNA damage and fixation. Genetic change plays only a part in the complex process of heritable effects and malignancy which include the fixation of the damage to the DNA by gene mutation or large scale chromosomal damage or recombination or numerical chromosomal changes. These tests play an important role in predicting if the compounds have the potential to cause genotoxicity and carcinogenicity by testing them positive.

3. Mechanism of Genotoxicity

Engineered nanoparticles (NPs) are widely used in different technologies but their unique properties might also cause adverse health effects. In reviewing recent in vitro and in vivo genotoxicity studies we discuss potential mechanisms of genotoxicity induced by NPs. Various factors that may influence genotoxic response, including physico-chemical properties and experimental conditions, are highlighted. The damage to the genetic material is caused by the interactions of the genotoxic substance with the DNA structure and sequence.

These genotoxic substances interact at a specific location or base sequence of the DNA structure causing lesions, breakage, fusion, deletion, mis-segregation. Genotoxicity and mutagenicity analyses have a significant role in the identification of hazard effects of therapeutic drugs, cosmetics,

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agrochemicals, industrial compounds, food additives, natural toxins and nanomaterials for regulatory purposes. To evaluate mutagenicity or genotoxicity, different *in vitro* and *in vivo* methodologies exert various genotoxicological end points such as point mutations, changes in number and structure of chromosomes there covered the basics of genotoxicity and *in vitro* / *in vivo* methods for determining of genetic damages. The limitations that have arisen as a result of the common use of these methods were also discussed. Finally, the perspectives of further prospects on the use of genotoxicity testing and genotoxic mode of action were emphasized.

4. Importance of Genotoxicity Testing

Regulatory authorities all over the world require data on the genotoxic potential of new drugs, as part of the safety evaluation process. The pre-clinical studies are generally conducted to obtain the basic toxicological profile of new chemical entities (NCE). The toxicological data are used to evaluate the safety and efficacy of NCE, which will help in predicting the drug's likely risk/benefit assessment in New Drug Application (NDA) process. Genotoxicity assays have become an integral component of regulatory requirement. In addition to it, many people in India are not aware of genotoxicity that it has now become mandatory to include it in drug master file required by European and United States regulatory authorities. Genotoxicity testing of new chemical entities (NCE) is generally used for hazard identification with respect to DNA damage and its fixation. These damages can be manifested in the form of gene mutation, structural chromosomal aberration, recombination and numerical changes. These changes are responsible for heritable effects documented that somatic mutations can also play an important role in malignancy.

5. Purpose of Genotoxicity Assays

Assays even though inexpensive, have high statistical power and can be reproduced and have the ability to detect a wide variety of genotoxic end-points. It also allows the detection of a drug's potential to cause genotoxicity even in the early stage of drug development. They are designed in such a way that it can be more sensitive to damage so as to enhance the identification of hazard.

6. In-Vitro Testing Methods

There are many in-vitro genotoxicity testing methods available. Some of the commonly used tests which are also a part of the standard battery are, Epigenetic modulations underlie critical developmental processes and contribute to determining adult phenotype. Alterations to the phenotype, due to exposure to environmental insults during sensitive periods of development, are mediated through alterations in epigenetic programming in affected tissues. Originally prepared for the Organisation of Economic Cooperation and Development (OECD), this detailed review evaluates the potential role of chemical-induced epigenetic modifications to endocrine signaling pathways during sensitive windows of exposure as a mechanism of endocrine disruption, along with the examination of potential methods for assessing such disruption.

Potential targets of disruption along putative adverse outcome pathways associated with the signaling pathways are identified, along with assays that show promise in evaluating the target in a screening and testing program such that in vitro methods are used where possible, and animal experiments only where in vitro methods are not available.

Also, chromosomes' integrity may be altered through chromosome loss and clastogenic lesions causing multiple gene and multilocus deletions. The specific type of damage is determined by the size of the colonies, distinguishing between genetic mutations (mutagens) and chromosomal aberrations (clastogens). The SOS/umu assay test evaluates the ability of a substance to induce DNA damage; it is based on the alterations in the induction of the SOS response due to DNA damage. The benefits of this technique are that it is a fast and simple method and convenient for numerous substances.

Molecular validation of tests the epigenomic tests of greatest current value are those that study cytosine methylation, for reasons described earlier, and will represent the cornerstone of epigenomic testing for some time to come. Other valuable tests will include transcriptional profiling (of RNA and of small processed RNAs) and chromatin immunoprecipitation-based techniques. The validation of each requires a different type of assay. For cytosine methylation, the gold standard is the chemical mutagenesis of DNA with sodium bisulfite to create uracil where there existed an unmethylated cytosine in the original DNA, whereas methylcytosine remains unconverted. Quantitative single locus studies of PCR amplicons that compare the proportion of cytosine to thymine (to which the uracil is converted during PCR) measures the methylation at that locus.

Monitoring such epigenetic marks in response to toxicant exposure may in future provide a valuable tool for predicting adverse outcomes, The word "epigenome" is derived from "epigenetics," a term attributed to defined it as "the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being."

Waddington was looking for an explanation of how the same genome could be used to generate different cell types in multi-cellular organisms, suggesting a higher level of regulation acting on non-autonomous genes. The term "epigenetic" was resurrected more recently as a broad description of heritable processes that do not depend on changes in DNA sequence, to include phenomena such as genomic imprinting and X chromosome inactivation. In each of these examples, a locus on one of the two homologous chromosomes, almost identical (or completely identical in inbred mouse strains) in terms of DNA sequence, is silenced, with the other active. This is a

state that remains stable from parent to daughter cells, thus the heritability component.

7. Conclusion

Genotoxins are agents that can interact with the DNA thus causing mutations and damaging its structure and may lead to cancer. They act by changing the chromosomal structure by addition, deletion, duplication, forming rings etc. The mutations may lead to a wide variety of diseases to cancer. It is very important to do genotoxicity studies so as to avoid the potential damage that can be caused by it. These genotoxicity tests are done to identify if a drug or other substance have the potential to cause mutation and genotoxicity. By doing so they help us identifying the hazards in the early stage of drug development itself. Identification of the genotoxic agents helps us understand the mechanism of the mutation and genotoxicity thereby paving.

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