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Review Article

Genotoxicity: mechanisms and its impact on human diseases

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ABSTRACT

The most important danger of living and working in a very complex and technologically advanced society is that we are consistently exposed to several hazardous toxic substances that contaminate our living environments. These hazardous substances are mainly of anthropogenic origin, more or less have property to induce genotoxicity directly or indirectly, andmay lead to the onset of many diseases like asthma, hypertension, neurodegenerative diseases and several types of cancers in human population. These substances include different types of radiations, food preservatives, coloring agents, industrial wastes, heavy metals, fungal and bacterial toxins, etc. Genotoxicity is the mechanism by which cell injury is induced and cause direct alterations and modifications of the genetic material and includes DNA damage, gene mutation, chromosomal effects and aberrations of genetic content. The present review is an attempt to discuss the effects of these hazards on human health and in the wake of genotoxicity alterations in exposed cells either due to occupational or accidental process, including carcinogenesis.

INTRODUCTION

The most important risks of living and working in a complex and technologically progressive world is that we are continuously accessible to harmful or toxic materials, which are present in our living environments. Accumulating evidences suggest that there are over 70,000 chemicals now in commercial production and additionally 700-3,000 new chemicals are being introduced every year (Chou, 1987; Spiegel and Maystre, 1998). In particular, the mechanism by which cell injury is induced and affecting its cellular integrity that cause direct alterations and modifications of the genetic material, which includes DNA damage, gene mutation, chromosomal effects and aberrations, and affect RNA of cell systems is called genotoxicity (Kastan and Bartek, 2004; Cavalieri et al., 2012). A substance that has the property of causing genotoxicity is known as a genotoxin. Genotoxin may be a chemical agent, radiation, heavy metals and others like fungal and bacterial toxins. Usually, genotoxicity is often mixed up with mutagenicity; however, it is an interesting fact that all mutagens are genotoxic, whereas not all genotoxic substances are mutagenic. The nitrogen mustard was the first example of a chemical mutagen, while other examples are the base analogs, such as bromouracil, aminopurine; chemicals that alter structure and pairing properties of bases, such as nitrous acid, nitrosoguanidine, methyl methanesulfonate, ethylmethanesulfonate; intercalating agents that cause frame shifts mutations for example, cisplatin, acridine orange, proflavin, ethidium bromide; and agents that alter DNA structure, for instance, psoralens and peroxides. The various radiations that act as mutagens are the ionizing radiation (IR) i.e. X- and gamma-rays, and non-ionizing radiation like UV radiation (Pechura and Rall, 1993; Alonso et al., 2006; Udroiu et al., 2010; Blank and Goodman, 2011; Miyakoshi, 2013; SCENIHR, 2015; Almaqwashi et al., 2016). Apart from these genotoxic agents, some heavy metals such as arsenic, copper, bismuth, cadmium, chromium and their compound are also known to have genotoxic properties which bind to DNA forming adducts and change its structure and function (Flora et al., 2008; Tchounwou et al., 2012; Jaishankar et al., 2014; Mishra et al., 2016; Nagpure et al., 2016).

The genetic alterations have direct or indirect consequences on the DNA such as the induction of mutations (Errol et al., 2006). The heritable modifications affect either germ cells is associated with the inheritance or somatic cells of the organism (Jablonka and Lamb, 1998). The cells avert the genotoxic mutation expression by either DNA repair mechanism or inducing apoptosis; but, the damage may perhaps not always be modified or repaired facilitating mutagenesis or more severe disease such as neurodegenerative diseases and cancer (Ghosal and Chen, 2013; Torgovnick and Schumacher, 2015). Assessment of the impact of genotoxic molecules is based on the level of DNA damage in cells exposed to these substrates. The DNA damage can be either in the form of single- and double-strand breaks or loss of excision repair, cross-linking, alkali-labile sites, point mutations, and structural and numerical chromosomal aberrations, while instable integrity of the genetic material is well known to cause several diseases (Coussens and Werb, 2002; Bajpayee et al., 2005; Colotta et al., 2009). Hence, numerous advanced techniques including the Ames assay, in vitro and in vivo toxicology tests, comet assay and micronuclei test have been established to assess the genotoxic potential of various types of toxicants that cause DNA damage or instability leading to diseases (Tice et al., 2000; Mishra et al., 2016).

MECHANISMS OF GENOTOXICITY

The genetic content of living beings is present in the nucleus of the cell and stored in the DNA, which is a long chain molecule with helical structure made up four bases- adenine, thymine, guanine and cytosine that code the genetic information. When the sequence of these bases is altered or damaged, the original functions of the cell are disturbed and initiate different kinds of severe defects in the cellular organization and these defects enhance with an increase in age. Genotoxicity mechanisms can occur through multiple pathways and broadly classified: direct genotoxicity and indirect genotoxicity (Fig. 1) (Kirsch-Volders et al., 2003). Direct genotoxicity is occurring in association of genotoxin or its metabolite with DNA. While, the indirect effect is related with genotoxin interacting with non-DNA targets and promotes the genetic damage. Genotoxicity induces several damages to the DNA, including chemically induced reactive oxygen species (ROS), ionising radiations, environmental factors that cause inappropriate sequence of bases leading to errors in copying the genetic information, loss of bases, particularly adenine and guanine, changes or conversion of the bases like conversion of cytosine into uracil, interconnection of bases under the influence of UV light (XI et al., 2003).

Besides the damage to bases, other forms of the DNA damage also occur that affect individual DNA strand breaks; double DNA strand breaks; chromosome damage; micronucleus formation; sister chromatid exchange. The genotoxic substances induce damage to the genetic material in the cells through interactions with the DNA sequence and structure, or either in the form of base substitutions, frame shifts, large deletions, insertions, and translocations, transitions and transversions, which are common mutations caused by genotoxins. For instance, the transition metal chromium interacts with DNA in its high-valent oxidation state Cr(V) causing DNA lesions leading to carcinogenesis probably through reductive activation (Mulware, 2013). High-valent chromium act as a carcinogen and explained that the mechanism of damage and base oxidation products of the interaction between high-valent chromium and DNA are significant to in vivo creation of DNA damage resulting in cancer in chromate-exposed human populations (Sugden et al., 2001; O'Brien et al., 2003). When the nonessential chemical modifications are not frequently repaired, it will lead to severe damage to living cells, interestingly, cells have a well-organized repair mechanism that distinguishes errors and damage, and finally repairs the damage (Wood et al., 2001). Accumulating evidences suggests that a large quantity of the DNA strand breaks when left unrepaired result in weakening of internal repair mechanism that increase the number of gene defects in a cell leading to an increased risk of cancer and other diseases (O'Brien et al., 2003; Torgovnick and Schumacher, 2015).

Mutations can be inherited via the mother or the father's germ cells, and any exposure or disruption of biological functions that leads to enhanced mutation rates in either of the parents may influence the

susceptibility of the child to cancer. A dysregulated epigenome in progeny through reproduction potentially affect instability of genetic and disease ability (Aguilera and Gomez-Gonzalez, 2008; Aguilera and Garcia-Muse, 2013; Langie et al., 2015).

METHOD OF GENOTOXICITY ANALYSIS

Genotoxicity tests can be implemented in bacterial, yeast, and mammalian cells. The main challenge in testing genotoxicity is that reliability and sensibility to detect a large range of damages or a common cellular response to genotoxic materials. It is suggested that no single test can identify each genotoxin, consequently the concept of test battery has been applied in many regulatory guidelines testing (Billinton et al., 2008; Ouedraogo et al., 2012).

Bacterial Reverse Mutation Assay

The Bacterial Reverse Mutation Assay is also known as the Ames Assay, which is used in laboratories to test for gene mutations. The technique uses many different bacterial strains in order to compare the various changes in the genetic material. The result of the test identifies the majority of genotoxic carcinogens and genetic changes; the types of mutations detected are frame shifts and base substitutions (Mortelmans and Zeiger, 2000).

Micronuclei and Nuclear Lesions Tests

Micronucleus test is a simple method to evaluate chromosomal damage (Nagpure et al., 2015; Mishra et al., 2016). In particular, the micronuclei (MN) test is one of the most useful techniques, convenient and easy application for genotoxicological studies. The formation of micronuclei can take place in any of the dividing cells of any organism. Micronuclei occur from fragments of the chromosome or entire chromosomes, which break during cell division as a result of centromeric absence, centromere region damage, or cytokinesis shortcomings. These fragments are integrated in the secondary nuclei is known as micronuclei (MN). The micronuclei count has marked for the chromosome breaks index and dysfunction of the mitotic spindle (Ayllon and Garcia-Vazquez, 2000; Osman, 2014). The assessment of MN provides numerous benefits over other cytogenetic studies such as chromosome aberrations or sister chromatid exchanges. The micronucleus test is a sensitive, time saving, effective and simple method for in situ, in vitro and in vivo assessment of genotoxic characteristic. The Nuclear lesions (NL) are genotoxic analogues of MN, which occur as a consequence of the act of the genotoxic substances. Mostly, nuclear lesion has a similar origin as MN and is recognized to be an indicator of genotoxic. These types of cell division abnormality result in genetic imbalance, which may also be involved in carcinogenesis (Rodilla, 1993; Osman, 2014).

Comet Assay

The comet assay is one of the most widely used techniques for genotoxicity assessment in the case of in vitro and in vivo chemical exposure. It involves cells lysing using detergents and salts, which promote discharge of the DNA from the lysed cell and electrophoresed in an agaro segel in neutral and alkaline pH conditions (Merk and Speit, 1999; Tice et al., 2000; Azqueta and Collins, 2013; Mishra et al., 2016). In genotoxicity and biomonitoring research assessment, the comet assay is a sensitive method to require and measure DNA strand breaks occurring when toxic materials facilitated genotoxicity and to identify the result of the environmental mutagen product. In this case, cells encompassing DNA with a significantly high number of double-strand breaks migrate rapidly to the anode. Moreover, comet assay is also valuable in distinguishing small changes of the DNA damage and needs merely a small number of cells, easy, time efficient and simple to implement, relatively inexpensive than other methods, and outcomes can be rapidly perceived. The alkaline comet assay is helpful in identifying a wide range of DNA damages, including DNA single-strand breaks, DNA double-strand breaks, oxidative stimulated base damages, alkali-labile region, and enduring DNA repair sites (Azqueta and Collins, 2013; Osman, 2014). It has been also implemented to check DNA degradation caused by apoptosis. However, it does not identify the mechanism underlying the genotoxic effect or the exact chemical or chemical component causing the breaks.

SOS chromotest

The SOS chromotest is a biological assay and one of the quickest, economically feasible, efficient in monitoring and simple short-term test for genotoxins and is effortlessly adjustable for different conditions (Quillardet and Hofnung, 1993; Vasilieva, 2002; Kocak, 2015). The technique uses acolorimetric assay, which measures the expression of genes induced by genotoxic agents in Escherichia coli, through a fusion gene of the enzyme β-galactosidase (Fish et al., 1987; Kocak, 2015). The SOS chromotest is relatively similar in precision and sensitivity to conventional techniques such as the Ames test and is a convenient tool to screen genotoxic compounds.

The chromosome aberration test

The chromosome aberration test (CAT) is most normally used and well endorsed in vivo chromosome aberration tests. This test recognizes agents that cause structural chromosome or chromatid breaks, dicentrics and other abnormal chromosomes, particularly translocation, which is associated in the aetiology of several genetic and cancer diseases progression (Magdolenova et al., 2014). In the CAT, the mitosis is blocked in the metaphase phase with the use of mitotic inhibitor colchicine. Metaphase preparations are studied for chromosome breaks and/or chromosomal rearrangements. The number of cells with chromosomal breaks is a degree for clastogenicity of substances for this method (Nagarathna et al., 2013).

DISEASE PROGRESSION

Cells respond to DNA damage by triggering complex signaling pathways that select cell fate by facilitating not only DNA repair and survival mechanism but also cell death. The choice between cell death or cell survival after DNA damage based on several reasons that participate in identification of DNA damage and repair, as well as on factors associated with the initiation of apoptosis, autophagy, necrosis and senescence. The DNA damage response (DDR) is extremely significant for all kinds of cancer and several disease progressions. DDR is essential for the beginning of carcinogenesis, interestingly, most of the carcinogens are genotoxic substances, which targeting the DNA in a direct or indirect method. Several cancer stimulating conditions are recognized to gene mutations in the DDR pathways such as TP53, ATM (mutated in Ataxia-Telangiectasia), BRCA1/2 (Carney et al., 1998; Rotman and Shiloh, 1998; Beamish et al., 2002; Duker, 2002). DDR also executes development of malignant tumorigenic state, which is caused by mutations and chromosomal instability (Duker, 2002; Duijf and Benezra, 2013). Owing to the close interactions between carcinogenesis and DDR, most tumors have developed one or more compromised characteristic of the DDR to facilitate malignancy or to prevent cell death. Consequently, DDR assessment is very helpful for prevention, diagnosis and estimation of individual disease progressions predisposition. In addition, cellular exposure to genotoxic agents such as ultraviolet (UV) light, oxidative stress, and chemical mutagens, result in a variety of nucleotide alterations and DNA strand breaks. The DDR system activates the suitable DNA repair process, however, in the condition of permanent impairment or damage, stimulates apoptosis pathway. Accumulating reports suggest that the identification of several proteins associated with sensing and reacting to DNA damage has improved our understanding the pathways of genotoxic stress responses. Gene mutations in the pathways of DDR can lead to several genomic instability syndromes and disorders that often strengthened susceptibility to cancer and disease progressions (Duker, 2002; Duijf and Benezra, 2013). Immunodeficiency phenotype, another hallmark of these disorders, is affected by failure to repair DNA strand breaks that arise during immune system development. These phenotypes showed by genomic instability syndromes or DDR suggest the importance of proteins that receive, transmit, or transduce signals related to the genotoxic stress response pathway.

DNA damage induces a prominent pathway for cell inactivation is apoptosis. Specific DNA lesions that activate apoptosis have been recognized such as bulky DNA adduct, DNA cross-links, O6-methylguanine, base N-alkylations, and DNA double-strand breaks (Roos and Kaina, 2006, 2013). DNA Repair of these lesions is significant in inhibiting apoptosis process. Apoptosis induced by many chemical genotoxins is the result of DNA replication blockage, which facilitates DSB formation and replication fork failure. These formations of DSBs are vital downstream apoptosis-triggering lesions (Roos and Kaina, 2006). The damage DNA activated signaling and implementation of apoptosis is cell type and genotoxin depends on several mechanisms such as p53 status, death-receptor sensitivity, MAP-kinase stimulation and significantly, DNA repair ability (Roos and Kaina, 2006).

Understanding mechanisms of carcinogenesis depend on the different aspects of molecular and cellular analysis carcinogens in laboratory investigation. Cancer is one of the most prominent causes of human death worldwide and categorized chronic non-communicable diseases group. Effects of genotoxic substances, such as deletions, breaks or rearrangements, cannot repaired or instantly proceed to cell death then lead to cancer (Kastan and Bartek, 2004). Some genotoxic agents (pesticides or heavy metals) have the ability to induce fragile sites, which are regions sensitive to DNA breakage, on the chromosome where oncogenes are found and produce carcinogenic effects. DNA damage is also produced from endogenous metabolites, environmental and dietary carcinogens, some anti-inflammatory drugs, and genotoxic cancer therapeutics. The pathways that direct cell fate is abnormal and have crucial functions in cancer initiation and progression. Interestingly, genetic modifications in cancer are coordinated with the role of epigenetic mechanism like DNA methylation and different types of histone modifications such as histone acetylation, histone methylation, histone phosphorylation and histone ubiquitylation in regulation of gene expression (Srivastava et al., 2016). The stimulation of proto-oncogenes and tumor suppressor gene inactivation by mutations such as base substitutions, deletions, DNA rearrangements, etc. are well reported, the alterations in expression of cancer genes are justified by epigenetic mechanisms (Jablonka and Lamb, 1998). The relationship of chromatin modification during gene expression, DNA repair and mutagenesis by genotoxic or carcinogens agents is an important for further to understand the effect of genotoxicity during carcinogenesis (Jones and Baylin, 2002; Klein, 2002; Feinberg and Tycko, 2004). Furthermore, these pathways suggest the consequence of cancer treatment by genotoxic drugs. Understanding the molecular basis of these pathways is important

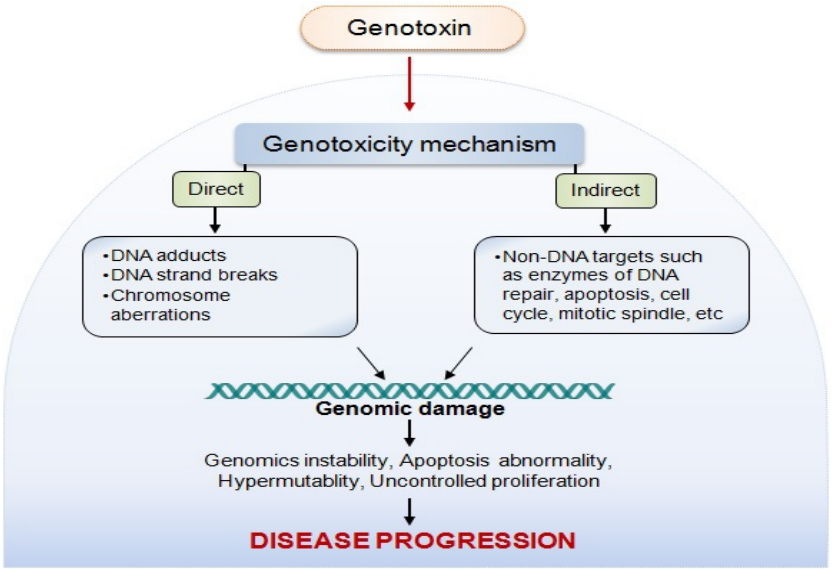

Figure 1. Schematic representation for direct and indirect genotoxicity mechanism and its consequence on disease progression.

not only for gaining insight into carcinogenesis, but also in promoting successful cancer therapy.

The integrity of genome is also critical for nervous system function and development. In particular, the nervous system is often intensely affected by genotoxic stress, which can lead to human diseases that are characterized by pronounced neuropathology. More broadly, DNA damage and abnormalities of DNA repair mechanisms in the nervous system have been associated to neurodegenerative syndromes such as amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson disease and neurodevelopmental disorders (McKinnon, 2009). Several emerging evidences suggest that pollution or toxic metals, such as methylmercury, arsenic and other heavy metals, stimulate cerebrovascular dysfunction, microglial activation, neuroinflammation, oxidative damage, and modifications in the blood brain barrier facilitate to central nervous system disorders (Genc et al., 2012; Faita et al., 2013; Crespo-Lopez et al., 2016). Understanding how genotoxin affects the nervous system will suggest a rational basis for treatments by improving the neurological related problems.

Several reports suggest that exposure to toxicants pollutants and chemicals could elevate the risk of cardiovascular disease and atherogenesis (Bhatnagar, 2006; Altura et al., 2016). Genotoxic effects play important roles in DNA fragmentation and damage of heart tissue of mammalian (Rjiba-Touati et al., 2012). Reports indicate that ROS facilitates apoptosis by different types of mechanisms, including direct intimidation of genotoxicity. Cardiomyocyte apoptosis arises in hypertrophied, ischemic, and failing hearts and leads to the development and advancement of heart failure and cardiac dysfunction (Giordano, 2005).

Genotoxic chemicals seem to have a significant effect on the relationship between cumulative DNA damage and age. Aging is defined as a gradual organic functional weakening, with loss of homeostasis and increasing the chance of the disorder and death. There are two types of aging have been described, replicative aging and chronological aging. Replicative aging is an aging model of mitotically active cells in which the lifespan of a mother cell is measured by the number of daughter cells formed before death. Chronological aging is an aging model of post-mitotic cells in which lifespan is defined by the survival time of cells in a non-dividing state. The sensitivity of cells to genotoxic substances promotes aging and age-related degenerative diseases. Chronic exposures to gentoxin causes mutations that perturb DNA damage processes and affect DNA damage repair are associated with premature aging in mammals (Hoeijmakers, 2009; Soria-Valles et al., 2016). The proficiency in DNA repair is compromised by genotoxic agents, leading to decreased cell-cell communication, the increase sensitivity of cells to stress, loss of function of several signal transduction molecules, which lead to accelerated aging and critical for onset of age-related disease for example, diabetes, Alzheimer and Parkinson disease (Hoeijmakers, 2009; Lee et al., 2010; Soria-Valles et al., 2016).

CONCLUSION

In conclusion, recent and several previous studies have shown that genotoxicant agent exhibited the geneotoxic effect lead to cascading events which ultimately affect human health in many ways. Genotoxicity occur in both, somatic cell and germ cell. Genotoxic alterations in the somatic cells induce many diseases such as different type of cancers. While in germ cells, it leads to sterility, genetic disease and multifactorial diseases. The genotoxic implications of toxic substance either physical, chemical or environmental factors in causing genomic instability are the hotspots in studying the genotoxic stress response, cell cycle and DNA repair. More precisely, genomic instability or DNA damage results in various diseases that will help in unraveling the treatment pathways of diseases at the molecular levels. Further, the concepts and ideas inferred from the literature can be used for the implementation of new drug targets and therapies for the dreaded disease.

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