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Research Article

EFFECTS OF ELEMENTS ON THE CANCER SUPPRESSING GENE p53

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ABSTRACT

There are evidences to show environmental and occupational exposures of people to excess levels of elements resulting in health risk. Though p53 is generally known as a cancer suppressor gene through its expression and production of anti-cancer protein, elements with carcinogenic properties, like arsenic, cadmium, mercury, nickel, chromium VI, affect both p53 expression and its functions such as DNA repair, cell growth arrest and apoptosis. There is one more mechanism of element indirect interference with p53 over expression by affecting its regulatory agent of MDM-2. In addition to carcinogenic effect, certain other elements e.g., cobalt, beryllium, etc., at minimum doses involve in p53 expression to act as cancer preventive agents.

INTRODUCTION

The prevalence of cancer in the world is increasing and in certain cases the causal factors and mechanism of occurrence could not be identified. p53, is a gene, which codes for a protein regulating the cell cycle. It performs as a tumour suppressor gene. In cells of multicellular organisms, it conserve chromosomal stability by preventing genome mutation and popularly known as 'Guardian of Genome'. Arnold J Levine was widely acclaimed researcher of cancer biology for the first time discovery of p53 in 1979. In-vitro introduction of p53 in to p53-deficient cells has been shown to cause rapid death of cancer cells or prevention of further division.

Rapid industrialization is discharging toxic heavy metals into the environment. Several studies have indicated over exposure of human beings to the elements which are found in drinking water, food and air beyond the permissible limit of the World Health Organization. Further, certain elements namely arsenic, lead, mercury, etc. exist ubiquitously in the environment, and exhibits carcinogenicity. Consequently, health hazards like neurologic, cardiovascular, and dermatologic abnormalities and cancers are associated with the rising environmental pollution (Arshad *et al*. 2015). Occupational exposure to metals such as cobalt and beryllium represents a risk factor for immune-mediated and respiratory diseases.

When different types of elements participating in multiple physiological roles, enter and accumulate in different tissues of body, their nature of effects is many fold. In the present review, the significant association of elements and p53 gene are discussed.

Structure, role and regulation of p53

In human being, p53 gene is situated on the 17th chromosome (17p13.1). The name is because of its molecular mass with 53 kilodalton fraction of cell proteins. The p53 protein is a phosphoprotein made of 393 amino acids and consists of four units. In normal cells, the p53 protein status (level and function) is low. DNA damage and stress signals may cause the raise of p53 proteins, which have three major functions, namely growth arrest, DNA repair and apoptosis (cell death). The growth arrest stops the progression of cell cycle and replication of damage of DNA. During the growth arrest, p53 may activate the transcription of proteins involved in DNA repair. Lastly, apoptosis has to avoid proliferation of abnormal DNA of cells.

The concentration of p53 is correctly controlled in cells. While it can suppress tumours at normal level, high level of p53 may cause harmful effect of enhancing aging process by

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excessive apoptosis. The major regulator of p53 is MDM2, which can trigger the degradation of p53 by the ubiquitin system. p53 is a transcriptional activator, regulating the expression of MDM2 (for its own regulation) and the genes involved in growth arrest, DNA repair and apoptosis.

Effects of Chemical Pollutants

If the p53 gene is damaged, tumor suppression is severely reduced. People who inherit only one functional copy of p53 will most likely develop tumours in early adulthood, a disease known as Li-Fraumeni syndrome. p53 can also be damaged in cells by mutagens (chemicals, radiation or viruses), increasing the likelihood that the cell will begin uncontrolled division. More than 50 percent of human tumors contain a mutation or deletion of the p53 gene. Elements causing cancer may affect p53 and their interference may be in the functions of p53. Abernathy *et al*. (1999) reported that after 24 hr arsenite treatment/exposure, altered expression of p53 and change in cell cycle distribution were caused in cell lines and cells transfected with a mutant p53 gene showed increased arsenite sensitivity. Sanjay mishra *et al*. (2010) related water sources of elements (As , Cr, Ni, Pb, and Hg) and their effects on p53 and cause of cancer.

In healthy condition, p53 is continually produced and degraded in the cell. The degradation of p53 is associated with MDM2 gene binding. The gene (MDM2) encodes a nuclear-localized E3 ubiquitin ligase. The encoded protein can promote tumour formation by targeting tumor suppressor proteins, such as p53, for proteasomal degradation. Over expression of the gene is detected in a variety of different cancers. In a negative feedback loop MDM2 is itself induced by p53. However mutant, p53s often don't induce MDM2, and are thus able to accumulate at very high concentrations. Worse, mutant p53 protein itself can inhibit normal p53 (Blagosklonny, 2002). The elements acting as mutants may interfere with MDM2.

Lead

Lead (Pb2+) is a poisonous heavy metal that causes many pathophysiological effects in living systems. Liu *et al*. (2018) pointed out its toxicological effects are well known as it causes apoptosis of several cell types and tissues. When the apoptotic effects of Pb2+ (0, 32, 64, and 125μM) were investigated for 12-48hr on Siberian tiger fibroblasts in vitro, typical apoptotic effects were observed after Pb2+ exposure. Pb2+ strongly blocked DNA synthesis in the G0/G1 phase and induced cell apoptosis in a dose- and time-dependent manner. The gene expression levels of p53 were increased along other genes (Bax, caspase-3, -8, Fas), while that of Bcl-2 was decreased.

Lead acetate

Sharifi *et al*. (2011) reported that compared to controls, the significant over-expression of pro-apoptotic proteins, including Bax, caspases-9, -3, and p53, with no significant change in anti-apoptotic Bcl(2) protein were obtained in lead-treated cells using western blotting analysis. There was a significant increase in DNA fragmentation in treated Mesenchymal stem cells (MSCs) compared to controls using flow-cytometry. Finally, it might be concluded that lead acetate could induce cell toxicity and apoptosis in MSCs, causing instability in mitochondria and in turn activation of the intrinsic pathway including over-expression of Bax, caspase 9 and caspase 3, leading to DNA damage and activation of p53.

Lead (Pb) toxicity is one of the commonest environmental problems in our life; it causes many reversible and irreversible changes in our tissues. Tousson *et al*. (2011) indicated that exposure (for 21 days) to rabbits to lead acetate (2) caused a significant increase of apoptosis protein p53 and decrease in the antiapoptotic BCl2 proteins.

Nickel

Nickel is a human carcinogen that acts as a hypoxia mimic by activating the transcription factor HIF-1α and hypoxia-like transcriptomic responses (Luczak and Zhitkovich 2017).

Chromium VI

Ceryak *et al*. (2004) observed that under certain conditions, a few hexavalent chromium [Cr(VI)] compounds are toxic and carcinogenic in the human respiratory tract and showed that they induce apoptosis and/or cell cycle arrest in a p53-dependent fashion. They suggested that both p53-dependent and -independent apoptotic and growth-inhibitory pathways are markedly affected by Cr(VI) exposure.

Cadmium

Cadmium (Cd) is a carcinogenic and neurotoxic environmental pollutant and induces apoptosis in chicken kidney tissue by activating the PI3K/AKT/Bcl-2 signalling pathway (Bao *et al*. 2017). Antoniali *et al*. (2015) indicated showed that non-toxic treatment of neuronal cell lines, with pro-mitogenic doses of Cd, promotes a significant time- and dose-dependent down-regulation of DNA polymerase δ (POLD1) expression through a transcriptional mechanism with a modest effect on Polβ, XRCC1 and APE1. They further elucidated that the observed transcriptional repression on Polδ is acted by through competition by activated p53 on Sp1 at POLD1 promoter and by a squelching effect. Antoniali *et al*. (2015) indicated that Cd-mediated impairment of Base Excision DNA Repair (BER) enzymes pathway, besides acting on the enzymatic functions of some key proteins, is also exerted at the gene expression level of Polδ by acting on the p53-Sp1 regulatory axis. Thus, it is obvious that cadmium causes not only the Cd-induced neurotoxic effects but also the potential carcinogenicity.

Three different human cell lines with wild type p53, viz., A549, HEK293 and HCT116 were exposed to different concentrations of cadmium chloride (CdCl2) and all the cell lines showed decrease in viability and p53 was transcriptionally down regulated in all the three cell lines, but with different extents, in response to increasing concentration of cadmium (Ravindran *et al*. 2016). One of the possible mechanisms by which cadmium manifests its cytotoxic effect is through the transcriptional down regulation of p53 gene.

Arsenite

After 14 days of exposure of human keratinocytes (HaCaT) to environmentally relevant concentrations of arsenite, Hamadeh *et al*. (1999) observed that arsenite reduced p53 levels while concomitantly increasing the p53 regulatory protein mdm2 levels in a dose- and time-dependent manner. They proposed the disruption of the p53-MDM2 loop regulating cell cycle

arrest as a model for arsenic-related skin carcinogenesis and it may be important in tumours with elevated MDM2 levels.

Chemicals can affect the balance between replication and death of cells in a number of ways (Schulte-Hermann *et al*. 1999). Firstly, genotoxic carcinogens induce genetic damage which subsequently leads to activation of the suicide machinery, involving genes such as p53. Secondly, toxic doses of genotoxic or nongenotoxic agents induce acute or chronic injury, leading to cell death and subsequent regenerative proliferation. Thirdly, nongenotoxic carcinogens which are primary mitogens may increase the birth and/or inhibit the death of cells by direct interference with growth signalling pathways.

Dose Dependent toxicity of arsenite

Exposure of long-term (14 day) low dose (0.1 microM) arsenite caused a modest increase in p53 expression in WI38 normal human fibroblasts, while only toxic (50 microM) concentrations increased p53 levels after short-term (18 h) exposure (Vogt and Roassman 2001). So, arsenite action is dose dependent.

No change in P53 expression

Arshad *et al*. (2015) showed that As(+3) ions have a dose- and time-dependent cytotoxic effect on a human epithelial carcinoma cell line through the activation of the caspase-dependent apoptotic pathway. In the human cells during exposure to heavy dosage of As(+3) (7.5 µg/ml) for 1 h significantly increased the mRNA levels of p21 and p27 and caspases 3, 7, and 9, but there was no change in the expression levels of p53, which plays an important role in G2/M phase cell cycle arrest. During the sudden exposure of cells to arsenite, (As+3) cytotoxicity and mitochondrial-mediated apoptosis were observed with the result of up-regulation of caspases and without alteration in p53 expression.

Mechanism of As-induced apoptosis

Kim *et al*. (2011) showed that arsenic trioxide (AsTO) efficiently induces apoptosis in the malignant cells of APL in vitro. In TM4 Sertoli cells, As TO-provoked cytotoxicity and cell death mechanism. Exposure of these cells to AsTO generates reactive oxygen species and alters mitochondrial apoptosis, inducing cell death via both caspase-dependent and caspase-independent pathways. As TO-induced apoptosis was concomitant with the downregulation of p53, phosphorylation of p53 at serine residues, and G2/M cell cycle arrest.

Lead and Mercury

Ali (2018) showed that IC50 of lead was (732.72µg/mL) and for mercury was (885.83µg/mL), and treating cells with the IC50-concentration of Pb or Hg or their combination using half IC50 of both of them induced severe DNA-damage. Bax-expression was increased, while p53 and Bcl2-expressions were decreased. In conclusion, Pb and Hg can induce oxidative stress and change the expressions of apoptosis-related proteins in human lung cells (WI-38).

p53 role in excessive manganese toxicity

Chronic exposure to excessive manganese (Mn) has been known to lead to neuronal loss and a clinical syndrome resembling idiopathic Parkinson's disease (IPD). p53 plays an integral role in the development of various human diseases, including neurodegenerative disorders. Wan *et al*. (2014) showed that p53 was critically involved in Mn-induced neuronal apoptosis in rat striatum through both transcription-dependent and -independent mechanisms. Western blot and immune his to chemistrical analyses revealed that p53 was remarkably upregulated in the striatum of rats following Mn exposure. Importantly, p53 was progressively upregulated, and accumulated in both the nucleus and the cytoplasm. The cytoplasmic p53 had a remarkable distribution in mitochondria, suggesting an involvement of p53 mitochondrial translocation in Mn-induced neuronal apoptosis.

Anticancer function of elements

Cobalt

Malignant glioma is the most aggressive brain tumor. Hypoxic condition has been explored for killing cancer stem cells or drug-resistant tumor cells. Cheng *et al*. (2017) investigated the effects of hypoxia on autophagic death and the possible mechanisms. Exposure of human malignant glioma U87-MG cells to cobalt chloride (CoCl2) increased cellular hypoxia-inducible factor-1α levels and concurrently decreased cell viability concentration- and time-dependently. In parallel, treatment with CoCl2 suppressed proliferation of human U87-MG cells. Autophagic cells and levels of LC3-II were concentration- and time-dependently induced in human U87-MG cells after exposure to CoCl2. Therefore, their study showed that CoCl2 treatment can induce autophagy of human glioma cells and subsequent autophagic apoptosis via a p53-dependent pathway. Hypoxia-induced autophagic apoptosis may be applied as a therapeutic strategy for treatment of glioma patients.

Consistently, Law *et al*. (2017) reported anti-cancer functions of cobalt complexes 1-6 towards multidrug-resistant cancers have suggested the protective and non-toxic properties of cobalt metal-ions based compounds in anti-cancer therapies. As demonstrated in xenograft mouse model, their results also confirmed that the identified cobalt complex 2 was able to suppress tumor growth in vivo. The anti-cancer effect of the cobalt complex 2 was further demonstrated to be exerted via the induction of autophagy, cell cycle arrest, and inhibition of cell invasion and P-glycoprotein (P-gp) activity. These data have provided alternative metal ion compounds for targeting drug resistance cancers in chemotherapies.

Cobalt and Beryllium

Paladini *et al*. (2011) showed that the two metals have a divergent effect on peripheral T lymphocytes and monocytes: BeSO (4) induces cell death in monocytes but not in T lymphocytes, which instead respond by producing Interferon gamma (IFN-γ); conversely, CoCl (2) induces apoptosis in T lymphocytes but not in monocytes. Interestingly, both metals induce p53 over expression but with a dramatic different outcome.

Table 1 showing a few toxic elements causing apoptosis through up regulation of the gene p53

SN	Element/ its compound	Tissue used for in vitro studies	Nature of p53 expression (up regulation)	Reference
1	Pb2+	Siberian tiger fibroblasts in vitro	gene expression levels of p53 were increased along other genes	Liu et al. (2018)
2	Lead acetate	Pb acetate treated cells	Significant over-expression of pro-apoptotic genes p53 and Bax, caspases-9, -3.	Sharifi et al. (2011)
3	lead acetate (2)	Pb acetate treated cells	Significant over-expression of pro-apoptotic genes p53 and others	Tousson et al. (2011)
4	Cr(VI) compound	Treated cells	Significant over-expression of pro-apoptotic genes p53	Ceryak et al. (2004)
5	Cd	Chicken kidney tissue	Induced apoptosis	Bao et al. (2017)
6	Cd	Neuronal cell lines	Activated p53 expression	Antoniali et al. (2015)
7	Arsenite	WI38 normal human fibroblasts	Increased p53 expression levels	Vogt and Roassman (2001)
8	High Mn	Rat striatum	High p53 expression	Wan et al. (2014)
9	CoCl(2)	Human glioma cells	Increased p53 expression	Cheng et al. (2017)
10	Arsenate	Pregnant LM/Bc dams	p53 and bc1-2 high expression	Wlodarczyk et al. (1996)

Table 2 showing a few toxic elements causing apoptosis through up regulation of other genes and down regulation of p53 gene

SN	Element/ its compound	Tissue used for in vitro studies	Nature of p53 expression (up regulation)	Reference
1	Pb and Hg	Treated human lung cells (WI-38)	Low of p53 and Bcl2 genes and high of Bax expressions	Ali (2018)
2	CdCl(2)	Human cell lines	p53 expression was decreased	Ravindran et al. 2016
3	Arsenite	Treated cells	Reduced p53 levels and increased p53 regulatory protein mdm2 levels	Hamadeh et al. (1999)
4	As(+3)	Human epithelial carcinoma cell line	No change in the expression levels of p53 and up-regulation of caspases	Arshad et al. (2015)
5	Arsenic trioxide	TM4 Sertoli cells	Low p53 and high caspase expression	Kim et al. (2011)

Arsenate Inhibits but not Induce cell Proliferation

Wlodarczyk *et al*. (1996) reported that when pregnant LM/Bc dams were injected intraperitoneally on gestation day (GD) 7:12 (day:hour) and 8:12 with 40 mg/kg of arsenate, there was a significant upregulation in the expression of bc1-2 and p53 at gestational day 9:0, compared to their control values. The heightened expression of both of these genes suggested that arsenic inhibits cell proliferation, rather than inducing apoptosis, which delayed normal neural tube closure (NTC) and ultimately led to the neural tube defects observed in exposed embryos.

Formation of free Radicals and Oxidative Stress by Metal Toxicity

Valko *et al*. (2005) indicated that metal-induced toxicity and carcinogenicity, with an emphasis on the generation and role of reactive oxygen and nitrogen species, is reviewed. Metal-mediated formation of free radicals causes various modifications to DNA bases, enhanced lipid peroxidation, and altered calcium and sulfhydryl homeostasis. metal-induced formation of free radicals and the role of oxidative stress in the carcinogenicity and toxicity of metals.

Two Patterns of toxic Element effects

Based on functional improtances, elements are of three types namely toxic (harmful), essential, and non-essential or non-toxic or inert. In the table 1 are shown the enhanced expression of p53 gene in different tissues caused by toxic elements (Pb, Cr (VI), Cd, As, high Mn, and CoCl). The table 2 shows down or decreased p53 expression in the other types of tissues caused by toxic elements (Pb, Hg, As, Cd).

When both the effects of toxic elements (Pb, Hg, As, Cd) either up or down regulation of p53 are found, the difference in the expression pattern may be due to the variation in the tissues used for in vitro

CONCLUSIONS

Exposure to excessive levels of carcinogenic elements from environmental and occupational sources is related to over expression of p53 gene or other genes (caspase etc.,) leading to apoptosis and their carcinogenesity is by means of damaging DNA and death of cells through oxidative stress, etc. A few essential elements, zinc, selenium, calcium, chromium III, etc. involve in antagonistic effects to reduce impact of carcinogenic elements. Cobalt is used at a specific concentration used for treatment of cancer. Thus, elements in different forms, states and doses function either as poison of normal cells or medicine of cancer cells. The p53 gene function also varies due to the difference of the tissues selected for the in vitro studies.

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