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Review Article

p53 Mutation Possibility and Food Dietary Containing Heavy Metals

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ABSTRACT

Background: Several types of cancer have mutations in the tumor suppressor gene p53. Environmental mutagens such as heavy metals play an undeniable role in p53 mutations and leave the mutational fingerprint on the TP53 gene. Therefore, the study of p53 mutation spectra can reflect the past heavy metals exposure.

Results: The current study was found interesting results by reviewing the previous data published in the databases. These results were obtained by comparing the common mutational profile between Iran, India, and Pakistan, and the association of these mutations with metals. The mutations in codons 146 (TGG→ TGA, Trp→ Stop), 214 (CAT→CGT, His→ Arg), and 249 (AGG→AGT, Arg→ Ser) were common in both India and Iran, due to the contamination by zinc and arsenic; arsenic and copper; cadmium, arsenic, nickel, and copper poisoning, respectively. Moreover, the mutations in codons 248 (CGG→ CAG, Arg→ Gln), 220 (TAT→ TGT, Tyr→ Cys), 248 (CGG→ TGG, Arg→ Trr), and 273 (CGT→ CAT, Arg→ His) were common among these three countries that could be related to poisoning with arsenic and zinc; arsenic; copper and arsenic; zinc and arsenic, respectively. These results can give a possible explanation for the cause of mutational similarities in these three areas, which can help identify the cause of high rates of p53 mutation and cancer control in these areas.

Conclusion: However, concerning the effects of other environmental factors, we definitely cannot explain the cause of these mutations among the heavy metals mentioned, since it requires more detailed studies.

Keywords: Cancer, Mutation, p53, Heavy metal

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Introduction

A large number of deaths in developing countries are due to cancer (1). Finding a cause-effect relationship between heavy metals exposure and health is one of the environmental health challenges. The p53 tumor suppressor gene mutational spectra, as well as the frequency of these mutations, can provide information on heavy metals exposure and doses. Therefore, p53 mutations have been used to find out the relationship between cancers and heavy metals exposure through the diet. On the other hand, the relationship between heavy metals exposure and cancer is known (2). The gene encoding p53 protein is located on the short arm of chromosome 17 (17p13.1). The mutation in this location is seen in most human cancers, and most of the tumors have a p53 mutation (3). So, the mutation at this location can occur by compounds of metal such as arsenic, cadmium, copper, iron, and nickel. These metals are known as carcinogens because of their effects on human health (4). Heavy metals directly or indirectly affect p53 (5). This means that heavy metals: (1) change p53 folding by interacting with it (6); (2) inhibit the main repair systems of deoxyribonucleic (DNA), in which the mutations are accumulated and the genomic instability occurs (5); (3) create oxidative DNA damage by creating oxidative stress (7) and activate cell growth-stimulating signaling cascades (8, 9). Frame shifts and point mutations are the common mutations in p53 that lead to the mutated protein expression due to amino acid changes (10) and decreased expression of p53 protein, respectively (11). While wild p53 is considered a tumor suppressor because of the cell cycle arrest activity, the mutated p53 loses apoptotic ability and causes tumorigenesis and metastasis (12).

Animals and humans can significantly absorb heavy metals through food, especially cereals (13). Rice is one of the commonly used cereals throughout the world and is the main food in Asian countries such as Iran. Given that the great share of the imported rice is from India and Pakistan, the heavy metals concentration in the imported rice from the two mentioned countries must be further taken into consideration in comparison with Iranian rice. High concentrations of heavy metals in Hindi and Pakistani rice have been reported in previous studies (14-18).

The present report implies the important consideration of heavy metals in Hindi and Pakistani rice and possible relationship with cancer problems in Iran and determines comparative p53 mutation profiles for Iran, Pakistan, and India.

Search strategy

This review was conducted and reported according to quality standards described in the PRISMA 2015 checklist. Two reviewers independently performed study selection, evaluation, and data extraction. The discrepancies in the reviews were resolved by consensus.

Databases PubMed, Web of Science, and Scopus were searched based on the following keywords: “heavy metals”, “heavy metal contamination”, “rice contamination”, “p53”, “ROS”, “p53 mutation”, “dietary contamination”, “environmental contamination”, “Iran”, “Pakistan”, and “India”.

As inclusion criteria, the study objective of the publications was checked regarding the association of heavy metals involvement in p53 mutations and prevalence of heavy metal contaminations in rice. The exclusion criteria were studies investigating the mentioned objectives in countries other than Iran, Pakistan, or India.

The information related to the author, year of publication, studied population, and study design was noted and summarized. Studies that did not evaluate any relationship between heavy metals and p53 mutations in terms of environmental and food contamination were excluded from the study.

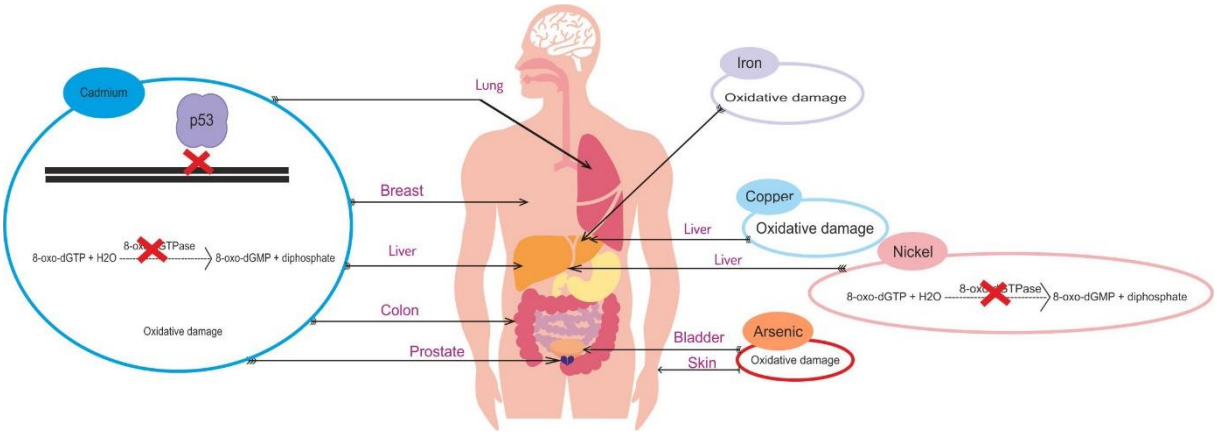
Heavy metals and p53

Heavy metals affect the TP53 gene and protein through three potential mechanisms: 1) producing reactive oxygen species (ROS): Hydroxyl radicals and other anions are produced by the Fenton and Fenton-like reactions. Most DNA damage is caused by hydroxyl radicals (19, 20); 2) Changing p53 transcription and protein expression: Epigenetic alterations such as methylation can affect the p53 gene expression (21, 22); 3) Unfolding p53: Some heavy metals like mercury, cadmium, and copper destroy the p53 protein function by replacing zinc metal in wild protein structure (23-25). In some studies, the association between the accumulation of

some metals such as iron and copper with an aberrant p53 expression in cancer has been shown (26-28). So, heavy metals can change the p53 function, folding, and expression. A summary of the effect of the metal on p53 is shown in Table 1 and Figure 1.

Table 1. Summary of the effect of the metal on p53

Metal	Cancer	Mutations and Aberrations	Effects	Refs
Cadmium	Colon; Hepatocellular carcinoma; Prostate; Breast; and Lung cancer	Chromatid gap and break; Chromosome gap and break; Acentric fragment; Tetraploidy; Dicentric	Efficiency binding of tumor suppressor p53 to DNA inhibited; 8-oxo-dGTPase inhibited; Oxidative damage caused	(87)
		G:C to T:A		(88)
		G → T		(89)
Copper	Liver	G:C to T:A; C:G to A:T; C:G to T:A	Oxidative damage caused	(27)
	-	C→ T		(44)
Iron	Liver	G: C to T:A	Oxidative damage caused	(27)
	Hepatocellular carcinoma	A:T to C:G; G:C to C:G; G:C to A:T; G:C to T:A		(51)
Zinc	-	G → A	Decrease of Apoptosis; Increase of p53-dependent mRNA and protein expression through p21 and p53 upregulated modulator of apoptosis (PUMA)	(90)
Nickel	Lung	G:C to T:A	Increase of 8-oxo-dGTP	(74, 89)
Arsenic	Skin	G:C to T:A; C → T; G → A; G → C; T → A; G→ T; T→ C; C→ A; less frequent A:T to T:A; G:C to C:G; G:C to T:A; A:T to C:G	Oxidative damage cause	(39)
	Bladder	G:C to T:A; A:T to G:C		(91)
		G:C to T:A		(90)
		G:C to T:A		(92)



1. ROS AND p53

The innate immune response in the exposure to heavy metals is producing ROS such as hydroxyl radical (˙OH), superoxide anion (O_2^-), and peroxynitrite ($ONOO^-$) (29). The radical hydroxyl possesses a potential danger for genomic instability through the mutation in purine, pyrimidine, as well as the sugar backbone (30).

The effect of ROS on p53 can be destructive; structural integrity, and therefore, the activity of p53 is affected by ROS because it is a redox-sensitive protein (31). The ten cysteines involved in the binding of the protein to the DNA, make p53 sensitive to ROS (32). The binding of cysteine to metals, nitrosylation, glutathionylation, and oxidation formation by ROS, destroy the p53 protein function (33). The p53 conformational changes are induced by the creation of an oxidation-induced electron-hole. These structural changes occur in DNA-bound p53 protein (34, 35).

It has also been shown that reactive species may cause various damages to DNA, the most common of which is guanine damage that led to breaks in DNA strands and DNA–protein crosslinks. Guanine damage inhibits the replication and transcription, which is mutagenic (36).

2. Arsenic

The arsenic carcinogenic potential has been proven in cancers such as skin and lung cancers (37, 38). ROS plays an essential role in arsenic-induced toxicity in humans. In arsenic-related skin cancers, G:C to T:A; G:C to C:G; C:G to G:C; A:T to C:G, and A:T to T:A is observed in Tp53 (39).

In addition, arsenic can alter protein expression by decreasing DNA methylation (40). Arsenic, through a mechanism dependent on the methyltransferase/S-Adenosyl methionine (MTase/SAM) pathway, modulates the DNA methylation of the tumor suppressor genes. In this pathway, the methylation of DNA is dependent on the dose of arsenic. Thus, high and low doses of arsenic cause hypomethylation and hypermethylation, respectively. DNA methyltransferase (DNMTs) is an enzyme that participates in DNA methylation, which in collaboration with SAM (the methyl group donor), transfers a methyl group to carbon atom that is located at position 5 of the cytosine nucleobase. The low arsenic concentration by inhibition of DNMTs increases SAM levels, which result in high cytosine methylation, hence, hypermethylation will occur. So the tumor suppressor gene expression will be suppressed (40). Genomic instability increases with the loss of tumor suppressor activity, and thus, the suppression of the cell cycle checkpoint control (41). Therefore, low-dose arsenic can make people more susceptible to cancer. In a report from smelter workers, it has been shown that people who were exposed to low doses of arsenic show more cancer cases than those who were exposed to high doses (42).

High concentrations of arsenic can reduce the methyl groups, which are essential for SAM activity. This methyl group reduction is through the arsenite MTase enzyme that consumes them. So SAM levels decrease, which results in low cytosine methylation. This pathway ultimately leads to genomic hypomethylation. This hypomethylation also leads to increased chromosome fragility and genomic instability, and ultimately, cancer (40).

3. Copper

Copper is one of the metals that play a role in the formation of hydroxyl radicals (˙OH), as well as membrane lipid peroxidation. Copper acts as a catalyst for the production of these two agents (43). In most tumors, like the bacterial DNA that is exposed to copper, C → T transitions are often observed (44). Several mutations associated with copper toxicity have been observed in the liver of patients with Wilson's disease, such that mutations included transversions and transversions such as G:C to T:A at codon 249; C:G to A:T and C:G to T:A at codon 250 (27).

P53 activity can also be affected by copper so that zinc cation (Zn^{2+}) in the p53 structure is displaced by cuprous ion (Cu^+), therefore, p53 loses its activity by changing the conformation (45).

4. Iron

Iron is one of the most important metals that many biological processes, such as respiration, require iron (46). Hydroxyl radicals are formed by iron exposure, which results in DNA damage (44). In a study on colon cells, single-stranded mutations were observed for p53 in cells with iron overload (47). Ferritin and Hemin are two important molecules that prevent oxidative

damage by binding to the p53, and thus, prevent its loss of conformation (48, 49). Transcription factors such as neuronal PAS domain protein 2 (NPAS2) receive redox signaling by a hemin signaling molecule (50). P53 degradation, nuclear exports, and p53-DNA binding are facilitated through this signaling by the mediation of hemin (48).

In a study on liver tissue samples in patients with Wilson's disease or hemochromatosis, transversion at 240 and 250 codons with G:C to T:A, C:G to A:T, and C:G to T:A was observed, respectively (51). They have shown that the risk of liver cancer increases with reactive oxygen-producing, especially Nitric oxide synthase 2 (NOS-2) (52). Also, transition mutations, especially G:C to A:T, have been observed in colorectal neoplasms, which are produced by increasing NOS-2 levels (53, 54).

5. Cadmium

Cadmium is a toxic metal that has a genotoxicity effect through the production and enhancement of ROS amount and subsequent DNA damage (55, 56). There is also evidence that p53 needs to bind zinc to fold and function correctly. However, cadmium can be displaced by zinc. This displacement changes the p53 tumor suppressor conformation and function (57). It has also been shown that the cell cycle is arrested in G1 and G2/M phases by cadmium exposure. A study proposed that the suppression of the cell cycle in human breast cancer (MCF-7 cells) was due to conformational changes of p53 zinc finger domain that results in altered protein function, and consequently, inhibits its binding to DNA (57, 58).

A study showed that the apoptotic pathways could be influenced by cadmium, and the interaction of cadmium for cellular proliferation pathways was also identified (59). The same study reported that the expression of some genes, including tumor suppressor genes (also p53), the caspase family protease encoding genes, and some apoptotic pathway regulators such as BCL2-associated X protein (BAX), decreased. It was also shown that the anti-apoptotic B-cell lymphoma 2 (Bcl-2) gene expression is increased in cells exposed to cadmium (55).

It is shown that the concentration of this metal is higher in the cigarette. Therefore, one of the common causes of p53 gene mutations in smokers is cadmium exposure. It is shown that mutation of G:C to T:A is the most common mutation in these people (60).

6. Nickel

Nickel is one of the metals found in the environment, especially in soil and sediment. Nickel adsorption, which is usually carried out only through contaminated food and water, can lead to negative reactions in people (61). Creating allergic inflammation such as asthma or shortness of breath is the included effect of nickel use (62). In addition, studies have also shown that nickel plays an important role in several types of cancer such as lung and nose (63-66).

Experimental studies have reported that multiple molecular mechanisms have played a role in nickel-induced carcinogenicity (62). Nickel compounds can induce both direct and indirect DNA damage. In direct DNA damage, nickel enters the nucleus that leads to the formation of reactive nickel-oxygen complexes by binding to DNA and reacting with hydrogen peroxide (H_2O_2) (67, 68). The productions of these compounds are the oxidized form of thymine and cytosine accompanied by 8-OH-dG formation (67). Extreme DNA damage, as well as inhibition of its repair pathways, are generated by oxidative stress (69). Indirect DNA damage is induced by ROS production (70, 71). In kidney epithelial cells exposed to nickel, a T→C transition point mutation in the p53 gene at codon 238 has been observed (72, 73). In another study, high levels of 8-oxo-dG were reported with the mutation of G:C to T:A in lung cancer (74).

Prevalence of p53 mutation in India, Pakistan, and Iran with a similar food basket

The presence of metals in the soil and water causes problems for all organisms (75) and endangers human health by bioaccumulation in the food chain (76-79). In recent decades, the increased use of different industrial products such as chemical dyes, metals and the economic development of industries such as cement, petrochemicals, energy, and others has contributed to surface water and underground water pollution in Pakistan. The imbalance of economic and social growth in the recent decade has caused environmental challenges in Pakistan (80). Environmental pollution by metals (including soil, water, sediment, and rice

samples) of central India is reported. The total heavy metals concentration, such as arsenic and other elements (i.e., iron, nickel, copper, etc.) in the samples, like water, soil, sediment, and rice grain were higher than the standard levels (81-83). Heavy metals contamination, also affects the environmental samples (i.e. water, soil, dust, food, etc.) in Pakistan (79, 84, 85). Environmental factors, like exposure to heavy metals, predict cancer development (76, 86). As a large part of the Iranian food basket containing Hindi and Pakistani grain products, especially rice, it seems that some of the similarities of common mutations in these three areas are the result of this case.

In Table 2, similar mutations in these three areas are arranged; and the possible association of these mutations with heavy metals in the food basket has been studied.

Table 2. Mutations of p53 by metals

Codon	Intron/Exon	Nucleotide Change	Amino Acid Change	Iran	India	Pakistan	Metal	References
146	Ex5	TGG→ TGA	Trp→ Stop	+	+	-	Copper; Iron; Zinc; Arsenic	(93, 94)
214	Ex6	CAT→ CGT	His→ Arg	+	+	-	Arsenic	(60, 94)
220	Ex6	TAT→ TGT	Tyr→ Cys	+	+	+	Arsenic	(94-96)
248	Ex7	CGG→ CAG	Arg→ Gln	+	+	+	Copper; Iron; Zinc; Arsenic	(60, 94, 96, 97)
248	Ex7	CGG→ TGG	Arg→ Try	+	+	+	Copper; Arsenic	(93, 97, 98)
249	Ex7	AGG→ AGT	Arg→ Ser	+	+	-	Cadmium; Arsenic; Nickel; Copper	(99, 100)
273	Ex8	CGT→ CAT	Arg→ His	+	+	+	Copper; Iron; Zinc; Arsenic	(60, 94, 96, 97)

Conclusion

Heavy metals induce P53 damages by three potential mechanisms. At high concentrations of heavy metals, the formation of ROS induces mutations in the P53 gene. However, some metals at lower concentrations are more damaging. For example, P53 protein expression, at low concentrations of arsenic, is affected by reducing DNA methylation. In another way, in some heavy metals such as copper, the zinc in the p53 protein is displaced with the copper, and then, unfolds it.

The study of the similar patterns of P53 mutations in different countries and finding the causes of the similarity of P53 mutations occurrence plays an important role in reducing p53 mutations and increasing public health. A recent study has shown that the p53 mutation patterns in some codons were similar in Iran, India, and Pakistan, so that the same heavy metals-contaminated food basket, like crops can be the reason for these similarities. However, further studies are needed to find out the relationship between heavy metals concentration in foods like crops and the occurrence of similar mutagenic patterns in P53.

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Conflicts of interests

The authors declared that they have no conflict of interest.

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