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Review

The relationship between mercury exposure and epigenetic alterations regarding human health, risk assessment and diagnostic strategies

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ABSTRACT

Background: Exposure to the environmental toxicants poses a serious threat to human health. The extent of exposure and the development of diseases are interrelated with each other. Chronic exposure to mercury (Hg) increases the risk of developing serious human disorders from embryo to adulthood.
Objectives: The purpose of this review is to highlight the most common human disorders induced by Hg exposure on the basis of epigenetic mechanisms. A growing body of evidence shows that Hg exposure leads to alterations in the epigenetic markers.
Methods: We performed an organized search of the available literature using PubMed, Google Scholar, Medline, Reaxys, EMBASE and Scopus databases. All the relevant citations, including research and review articles in English were evaluated. The search terms included mercury, Hg, epigenetics, epigenetic alterations, DNA methylation, histone modifications, microRNAs (miRNAs), and risk assessment.
Results: Data on human toxicity due to Hg exposure shows broad variations in terms of chemical nature, doses, and the rate of exposure. Hg consumption either via foods or environmental sources may create deleterious health effects on various physiological systems at least partially through an epigenetic mechanism.
Conclusion: Hg exposure could trigger epigenetic alterations, hence leading to various human disorders including reduced newborn cerebellum size, adverse behavioral outcomes, atherosclerosis and myocardial infarction. Similarly, in adults, occupational Hg exposure has been associated with an increased risk of autoimmunity. It has been revealed that miRNAs in the woman's cervix are a novel responder to maternal Hg exposure during pregnancy. Hg-induced epigenetic alterations analysis of kidney tissues showed a significant interruption in renal function. DNA methylation and histone post-translation modifications are predominant types of Hg epigenetic alterations.

1. Introduction

Mercury (Hg) is naturally occurring metal present in the air, water and earth's crust. It can also be part of different daily routine household products such as food preservatives and disinfectants [1]. Hg is a toxic harmful metal that inhalation of its vapors causes numerous deleterious effects on various organisms of the body within the digestive, immune, urinary and nervous systems. Like most toxicants, Hg may affect human body via ingestion through the oral route, inhalation, and also skin contact [2,3].

Hg contamination may happen through fish consumption, dental restorations Hg amalgam, cosmetics and water resources [4]. According to the United States Environmental Protection Agency, Hg ranks as top three among the potent toxic agents [5]. There are three forms of Hg including organic, inorganic and elemental that all exhibiting toxic effects. Besides oceans, burning of remnants is the major source of elemental Hg, while disinfectants and medicinal compounds are adding an inorganic form of Hg to the environment. Similarly, organic Hg can be found in pesticides and antiseptics [6]. Virtually every organ of human body is affected by Hg, however, skin, nail, hair and kidneys are the main contaminated parts that accumulate high concentration of Hg [7,8].

The epigenome of human beings acts as a bridge between the genome of an individual and its response to the different environmental

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toxicants. In fact, the variations in human's epigenome statues can serve as a picture of that individual response to the diverse types of environmental factors and the known interpreter of a person's vulnerability to the future toxicants exposure and consequent disease outcomes [9]. In order to fully understand such association, it would be helpful to conduct the investigations that mutually compare available epigenetic data with the functional effects, regulation of the gene expression and toxicants exposure consequences, yet there will be a halo of ambiguity which needs to be addressed [10].

Recent studies have indicated that epigenetic changes may be a key regulator of the mechanisms associated with Hg exposure and the development of a variety of human disorders [11]. Human epigenome carries the inherited alterations to the genome that directly influences the regulation and expressions of genes. Epigenetic alterations are genetically heritable modifications that do not affect the already existing DNA sequence (a change in the phenotype without a change in the genotype), but rather result in changing the expression of the genes. The examples of epigenetic alterations are perturbations of the promoter methylation pattern, histone modifications and non-coding RNA dysregulations [12]. As mentioned, the interventions of epigenetic alterations and different human diseases (i.e. diabetes, hypertension and Alzheimer) were proven frequently. For instance, mutations in various enzymes of the epigenetic machinery have been associated with neurodegenerative processes; primarily those are affected in the Alzheimer's diseases such as learning disabilities and memory formation [13,14]. Alterations in DNA methylation is one of the main mechanisms of the epigenetic modulations, involving modifications of the DNA methylation patterns at the cytosine and guanine residues (CpG sites) of the existing DNA sequence. Environmental toxicants exposure (i.e. Hg) has been connected to the changes of the DNA methylation patterns both in humans and other animal models [15].

Hg exposure leads to different pathological complications such as acute myocardial infarction risk and neurodevelopmental disorders, mostly happening following chronic prenatal exposure [16,17]. In a study conducted on rats exposed to the developmental period of Hg, after Hg exposure, there was a decreased methylation pattern in the promoter regions of the certain genes and in the expression levels of the important enzymes responsible for the DNA methylation pathway [18]. On the other hand, prenatally Hg-exposed mice showed an opposite pattern of DNA methylation such as hypermethylation of the selected gene. Regardless of the available evidence on the effects of Hg on the epigenome of animal models, still there is lack of data on the pathological impact of Hg on human epigenome [19,20].

At the moment, epigenetic alterations can be considered as potential biomarkers to assess the effects of environmental toxicants exposure and to predict the early onset of relevant diseases. Furthermore, epigenetic alterations are heritable traits having high stability outfit in evaluation of health related hazardous outcomes, hence it will exhibit the inheritability of the toxicants-induced gene expressions against maternal exposure to various toxicants [21]. For that reason, epigenetics data would potentiate several parameters such as toxicodynamics, toxicokinetics and the mechanism of action toxicants within the body, thus eventually will contribute to the risk assessment processes [22].

Though, metal-linked epigenetic alterations, have not well been evaluated in the gene specific expression profiling in utero [23]. Such an epigenetic library can be considered as an alternative to the conventional biomarkers such as human body fluids, or certain specimen including urine, blood, and hair sample [24].

To recognize the susceptible subgroups, the ecogenetic concept will drag the attention to each environmental and genetic factor of exposure, while in terms of the ecotoxicology and human health outcomes, the majority of studies are focusing on determination of the environmental related factors such as the toxicant level in the exposed species [25]. Yet, this is an essential stage in Hg risk assessment management, nonetheless, it has narrow applications in calculating the risk process. The science of Hg is reaching to a conclusion, where the ecogenetic methods can be applied in order to recognize the liable groups and most probably, it will reduce the dependence on uncertain factors that can influence the toxicokinetics of Hg [26].

Studies on the risk assessment of Hg have mostly focused on its pathological impacts on the community groups that are already uncovered to the toxic concentration. Although, other investigations have explored the relationship between low doses of Hg and their toxic effects on the nervous, immune, and cardiovascular systems. However, the exact mechanism of the chronic and minimum doses of Hg are still unclear [10,27]. Furthermore, it has been extensively suggested that Hg exposure causes epigenetic alterations providing a deep understanding into the underlying mechanisms of Hg toxicity. Such mechanisms need to be carefully explored in human subjects [28]. This literature review focused on epigenetic alterations induced by Hg exposure, their impact on human health, the related risk assessment and the diagnostic strategies.

2. Literature search methods

We performed an organized search of the available literature (only in English language) using; PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (https://scholar.google.com), Medline (https://www.medline.com), EMBASE: (https://www.embase.com), Reaxys (https://www.reaxys.com), and Scopus (https://www.scopus.com) databases. All the relevant citations, including research and review articles in English were evaluated and gathered. The search terms included; mercury, Hg, epigenetics, epigenetic alterations, DNA methylation, histone modifications, microRNAs (miRNAs), and the risk assessment.

Further, studies on the pathological impact of Hg on human health and diagnostic strategies were incorporated. The exclusion criteria were the language of the published reports other than English, reports lacking regular abstracts and studies on Hg those were apart from its epigenetics effects. Those were considered that focused on environmental epigenetics and the biomarkers for the disease's identification. Studies not indexed in PubMed were obtained by manual searching in Google Scholar, and 17 such reports that met the inclusion criteria were additionally retrieved. Therefore, a total of 122 studies were included. Original research and review articles that were published between 1991 and 2017 were included in the review process. The search strategies, inclusion and exclusion criteria are summarized in Fig. 1.

3. Sources of mercury exposure

Being a natural element, it is abundantly found in the environment and almost 10,000 tons of Hg is produced by degassing of the earth crust, while around 20,000 tons per year is being added to the environment via human activities [29,30]. The emission of Hg from coal burning is the major source of anthropogenic release and it has been estimated that Hg emission will increase at a rate of 5% per year. Discarding medical devices such as thermometer, sphygmomanometer and other household objects as fluorescent light lamps, the emission of Hg is already contained in such appliances [31,32]. Hg from the air, is ultimately mixed with water reservoirs (i.e. lakes, rivers and oceans), after being carried by the wind. Further, Hg in the atmosphere mixes with the raindrops, hence affecting human life. Hg is also released from the organic wastes of the factories, which directly add untreated wastes into the water streams. This polluted water causes acidic rain, contaminating all water reservoirs [33,34]. Furthermore, algal blooming and the falling leaf seasons also result in elevating the level of methylmercury (MeHg) in the ground surface water resources, leading to elevation of MeHg levels in fish sources [35,36].

Populations that predominately depend on foods derived from fish or other aquatic environment have greater chances of exposure to Hg. It has been verified that the areas where they consume seafoods in their

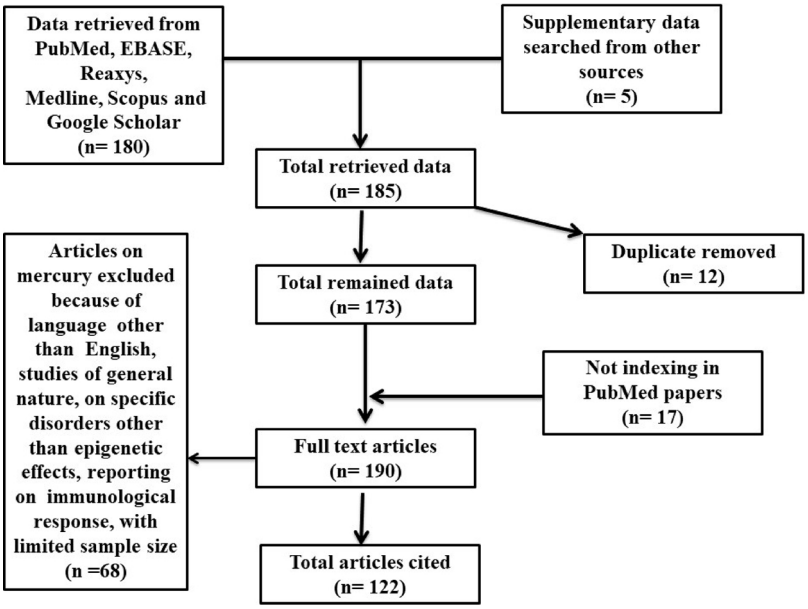

Fig. 1. Flow diagram of the included studies, representing the number of citations and resources that were screened, excluded, and/or included in the review.

daily routine, people are experiencing a high risk of Hg poisoning [37,38]. Other animals such as cattle and pigs, those were kept in areas with contaminated water had two folds higher Hg level in their blood and hairs samples [39,40].

It has been estimated that the concentration of Hg in the rice, can reach up to a maximum level of 569 μg/kg of the total Hg, where 145 μg/kg was in form of MeHg [41]. Among edible mushrooms, the highest concentration of Hg was found in the *Boletus picnicola* [42], while in vegetables commonly used in Southeast Asia, *Ipomoea aquatic*, a type of spinach mostly cultivated in the freshwater ponds, was found to contain several metals such as Hg and cadmium [43].

4. Mercury-induced epigenetic alterations

Environmental toxicants have the ability to facilitate the development of diseases through alterations in key regulatory signaling pathways mainly through modulation of the genes expressions. These alterations can eventually change the pattern of the gene expression and activity as well. During past few years, the term of epigenetic perturbations which refers to the effects of toxicants with the alterations in the expression of genes without changing the already existing DNA sequence, was widely spread [44]. Epigenetic alterations are responsible for the regulation of gene expression through three main distinct mechanisms commonly named as; DNA methylation, histone post-translation modifications and non-coding RNAs [45]. The newly emerging field of toxicoepigenomics is the study of the interrelationship between epigenetic dysregulations and the adverse effects exerted by the environmental toxicants. Toxicoepigenomics is getting importance in the field of environmental health sciences and it has been hypothesized that human epigenome is susceptible to the harmful effects of environmental toxicants, hence these alterations were associated with the progression and pathologies of the typical diseases such as diabetes and cancer [46,47].

4.1. DNA methylation and mercury exposure

DNA methylation is an essential regulator of the gene transcription process and its action in metal carcinogenesis was a topic of significant interest in the past several years. The perturbations in the DNA methylation pattern are very common in the development of different types of tumors. A broadly studied type of epigenetic alterations is hypermethylation. Hypermethylation inhibits the transcription of the promoter regions of the tumor suppressor genes, which lead to the silence of specific gene/s. Moreover, global hypomethylation is also considered as the main cause of oncogenesis [48].

It has been discovered that apart from the common nucleobases such as A, C, G, T and 5-methylcytosine (5 mC), there is an additional sixth base hydroxymethylcytosine (hmC), which is known to be an important epigenetic biomarker [49,50]. The precise function of 5-hmC is still unknown but it is thought that 5-hmC is actively complicated in the epigenetic regulation procedures or in the active demethylation processes [51,52]. Currently, it is assumed that 5-hmC could be a base involved in the epigenetic variation of the gene activities. 5-hmC has also been identified in embryonic stem (ES) cells and appears to play a crucial role in the ES cells regeneration [53]. Moreover, hmC directly controls the attachment of proteins to DNA throughout the epigenetic procedures. For example, the methyl-CpG binding protein 2 (MeCP2) is unable to bind with the corresponding sequences, thus, mCs are converted to hmCs in the CpG sequences, enabling it to bind to the correct sequences [54].

The alterations of the epigenome can be underlying mechanisms to assess the toxicity and the causal of the diseases development after exposure to the environmental toxicants. Experimental animal and human studies suggested that Hg exposure could actively influence on the DNA methylation patterns. It has been confirmed that exposure to both MeHg and inorganic Hg induces an alteration in the DNA methylation status at both global and gene-specific levels [10].

Merely few human studies have been dedicated to the environmental Hg exposure and the relevant changes in the pattern of DNA methylation. For instance, Hg exposure caused an increased DNA methylation at the promoter region of the glutathione S-transferase mu1 (GSTM1) in women. These results were obtained from the blood samples of the women, where an elevated level of Hg was observed (exceeding 2.9 μg/L). Though, no statistical association was detected between different levels of Hg and the GSTM1 in the exposed individuals and the study did not establish the expression level of GSTM1 [28,55]. In another study, the exposure level of Hg was measured in the hair samples of the exposed male individuals. Data confirmed, there was a close relationship between DNA hypomethylation of the promoter region of the seleno-protein P plasma 1 (SEPP1) and increased exposure level of Hg [10,55], but the expression level of the SEPP1 gene was not examined. Of note, there is an existing potential indicating that DNA

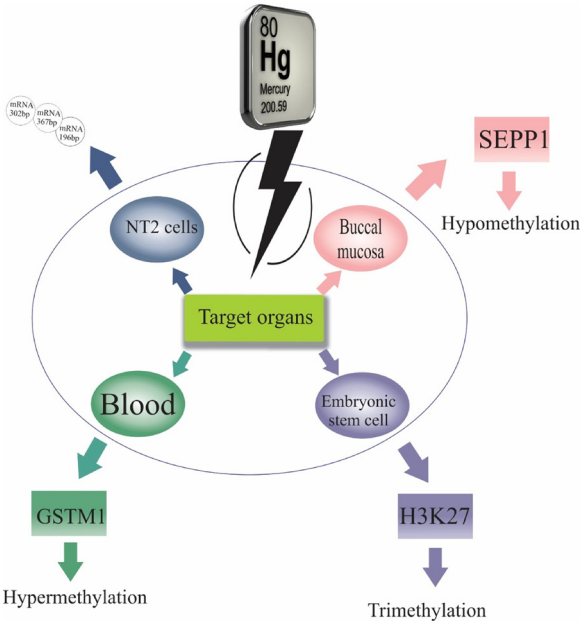

Fig. 2. Mercury-induced epigenetic alterations in various genes.

methylation alterations in the promoter region, would directly influence on the expression of these genes, which will modify the oxidative stress responses [56]. Hg-induced epigenetic alterations in the target genes are shown in Fig. 2.

Recent animal studies have proven that there is a close association between MeHg exposure and DNA methylation. Ecotoxicological studies conducted on polar bears and captive mink showed a positive connection between MeHg exposure and the global CCGG hypomethylation in some brain areas [10]. The rats exposed to MeHg at the early stages of life exhibited a reduced methylation pattern at the promoter region of the brain-derived neurotrophic factor (BDNF) gene [19,55].

It is still unclear, either the MeHg related decrease in the global DNA methylation pattern in one animal model could be extended to the other types or not? In a study conducted on archived tissues obtained from mink, chicken and yellow perch, such tissues were analyzed for Hg and global DNA methylation using the LUmunometric Methylation Assay (LUMA) to quantify global DNA methylation. LUMA uses a pair of isoschizomers, Hpall (methyl sensitive) and Mspl (methyl sensitive), in order to cut the DNA between the two cytosines of the recognition sequence 5′−CCGG-3′. The isoschizomers that run in matching reactions with EcoRI, which act as a normalizer for the DNA input. Significant reduction of the DNA methylation statues was observed. These results suggested that MeHg can be active epigenetically and it has the capability to alter the DNA methylation patterns in the mammals [57]. Similarly, upon MeHg exposure in the cerebral region of chickens, a decline of the global DNA methylation patterns was monitored, however it was not statistically significant. In the same manner, Hg was identified as a major contributing element in earthworms [58]. It has been recommended that the global DNA methylation changes can be a potential biomarker of Hg toxicity assessments. It is worth considering that although the global DNA methylation alterations can be a common sign of evaluating the stress level of epigenetics, its association with health outcomes has not been fully understood [11,28].

4.2. Histone modifications and mercury exposure

Histone modification is the covalent post-translation modification of the core histone proteins that involve methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation. Post-translation of histone proteins affects the expression of the gene by changing the structure of the chromatin. Histone modifications signify a beneficial set of the epigenetic marks that involves not only in the active cellular procedures including DNA and transcription but also implicates in the maintenance of the suppressive chromatin [59].

The majority of the studies on histone modifications and Hg exposure have been designed on the basis of animal preclinical models, rather than human subjects. In mice exposed to MeHg, it has been observed that there was an elevated trimethylation of the H3K27, together with a declined H3 histone acetylation of the *BDNF* gene. This study indicated that exposure to MeHg at the developmental levels, predisposed mice to depression and enhanced epigenetic suppression [19,55].

In another study, exposure to mercury chloride ($HgCl_2$) significantly decreased the amount of total histone proteins (THP), which was associated with decreased H3K27 mono-methylation [60]. MeHg exposure on chronic level showed modifications of the histone H3K4 trimethylation (H3K4me3) in *Caenorhabditis elegans* by the use of chromatin 21 immuno-precipitation sequencing. These modifications resemble the locations of 1467 genes with extra signals and 508 genes with decreased signals. The encoding GST, lipocalin-related protein and a type of cuticular collagen are good examples of the genes with enhanced signals. The chIP-seq, combination of the chromatin immunoprecipitation (chIP) assay and sequencing (Seq), development of these genes was verified with increased mRNA expression levels shown by quantitative real time polymerase chain reaction (qRT-PCR) [55,61].

4.3. Noncoding RNA dysregulation and mercury exposure

Noncoding RNA or miRNAs are endogenous and small RNAs that represent an extra layer of post-translational regulatory control of the gene expression. They are responsible for regulation of the majority of cellular processes, ranging from development and variation to the programmed cell death. Every miRNA can target a total of few hundred genes, resulting in regulation of maximum up to one-third of the gene expressions in animals [62].

In carcinoma pluripotent stems co-treated with methylmercuric chloride (MeHgCl), various mRNAs including miR-302b, miR-367, miR-372, miR-196b, and miR-14 were up-regulated. It was shown that the increased miRNAs expression is linked with the process of cell development and response to the stress mechanism. The miRNA profiling can deliver streamlined functional evaluation of the toxicity pathways that were involved in the age-related neurotoxicity in contrast with transcriptomics studies [55,63].

Today, practical analysis helped to recognize various Hg-related miRNA subgroups that can effect the reproductive system disorders. More precisely, the subsets of the genes that were enhanced in unusual morphological structures contained a set of mRNA targets, which were mostly controlled by let-7, miR-125b and miR-24, collectively. In other words, miR-205, miR-24 and miR-21 are greatly articulated during the malignancy development of the cervical region in comparison with the normal control. It has been confirmed that miR-205 acts as an important contributor to cervical cancer, therefore, it can be used as a decent cancer diagnostic biomarker in the plasma [64,65]. Additionally, a negative association between miRs-200c and 200b was monitored, when the maternal Hg levels were increased. It has been shown that the miR-200 family was elevated in the myometrium during pregnancy, hence this family adversely regulated various contraction-related genes such as the zinc finger E-box binding homeobox-1 and connexin 43 [66].

The miRNAs are also involved in the epigenetic regulation of different types of the brain developmental procedures including neurogenesis, differentiation of neurons and the outgrowth of the neurite. It was demonstrated that miRNA expression profiling can be a suitable approach to identify the *in vitro* age-related neurotoxicity. In order to evaluate this hypothesis, MeHgCl-induced alterations of the miRNAs expressions were assessed by comparing the carcinoma pluripotent

Table 1
Mercury-induced epigenetic effects in various cells/tissues.

Toxicant	Epigenetic alterations	Target organ	Effects	Target gene	Dose	References
Hg	DNA methylation	Blood sample	Hypermethylation	*GSTM1*	2.9 μg/L	[28]
Hg	DNA methylation	Buccal mucosal samples	Hypomethylation	*SEPP1*	0.31-0.44 μg/g; 0.60-0.83 μg/g	[10]
Hg	Histone modifications	Embryonic stem cells	Trimethylation	*H3K27*	Low concentration for 1-h & 24-h	[60]
Hg	mRNA	NT2 cells	Genome level; ↑mRNA-302b ↑mRNA-367 ↑mRNA-372 ↑mRNA-196b ↑mRNA-141		400 nM MeHgCl for 2-36 days	[63]
Hg	DNA methylation	Embryonic stem cells	Hypermethylation	*Rnd2*	1 μg/L	[69]
Hg	DNA methylation	Brian cells	Hypermethylation	*BDNF*	0.5 mg/kg/day	[19]

↑, increased; NT2, carcinoma pluripotent stem cells; *Rnd2,* Rho Family GTPase 2; *BDNF,* brain-derived neurotrophic factor; MeHgCl, methylmercuric chloride.

stem cells with that of human embryonic stem cells at the initial stage of the differentiation of neural progenitor pledge into neuronal lineage. The obtained data clarified that the miRNAs expressions profiling can be a proper candidate to assess the developmental neurotoxicity pathway perturbation, which may contribute towards improving the prognostic human toxicity analysis. Hg-induced epigenetic alterations are shown in Table 1 [67,68].

5. Mercury-induced epigenetic alterations in various body systems

Mutations in genes that affect global epigenetic profiles and heritable patterns of gene silencing mechanisms in multicellular organisms may induce human diseases, which can be inherited or somatically acquired [70]. The importance of epigenetic variability is covering a broad range of disease risk and includes cancer, autoimmune disease [71], body mass index [72], type 1 diabetes [73], aging and pediatric syndromes [74].

Hg exposure and/or contamination are considered as potent contributors to health issues; ranging from physiological to the psychological disorders. For instance, Hg exposure inspires central nervous system defects and erethism as well as arrhythmias, cardiomyopathy, respiratory failure and kidney damage [75]. In addition, Hg could function as immunostimulant and suppressant factor, providing pathologic sequelae such as lymphoproliferation, hypergammaglobulinemia, and total systemic hyper- and/or hypo-reactivities [76].

In the upcoming sections, we have highlighted the Hg-induced epigenetic alterations in various body systems. Also, it has been shown that there is a close relationship between toxicants-induced epigenetic alterations and the development of human disorders including birth defects, neurological and organ abnormalities [77]. Populations chronically exposed to Hg may develop some genotoxic alterations as chromosome aberrations and micronuclei; or may face deficiency in DNA repair, which the affected individuals may suffer from the exposure-related increase of health risk factors, either from continued exposure or where they are threatened by other genotoxic agents [78]. Among various epigenetic mechanisms involved in the pathogenesis of such disorders, the DNA methylation and histone post-translational modifications are predominant [79–81]. Recently, epigenetic regulations were considerably implicated in the pathogenesis of several diseases. For example, in acute kidney injury, inhibition of histone deacetylases (HDACs) results in enhancement of protein acetylation and causes more severe tubular injury, as well as renal dysfunction [79].

Today, several therapeutics have been formulated to manage the epigenetic-induced/involved diseases and pictured a prosperous sight in the pharmaceutical market or industrial society, either alone or in accompany with other therapies. Basically, epigenetic medications are classified into two main groups; DNA cytosine-5 methyltransferases (DNMTs) and HDACs inhibitors, of which Azacitidine and Decitabine belong to the former group. Vorinostat, Romidepsin, Belinostat and Panobinostat are the major subgroups of HDACs inhibitors [82]. It is evident that different environmental toxicants such as MeHg, bisphenol A (BPA), formaldehyde, arsenic, nickel and vinyl carbamate are potently able to initiate epigenetic alterations, hence, that will lead to the development of various human disorders including metabolic, reproductive and behavioral impairments [83].

5.1. Nervous system

Multiple studies have found associations between chemicals; in terms of environmental toxicants and particularly metals exposure; also neurodevelopmental and psychological impairments, as such, the epigenetic alterations may be involved in some. The neurotoxic effect of Hg is mainly coming from MeHg, highly accumulated in seafoods. Upon exposure, MeHg readily crosses via the placenta and the blood-brain barrier (BBB), and then concentrates inside the fetus tissues at exceeded levels. Hence, there is an increased risk of fetus exposure during the embryonic developmental stages [84]. Hg exposure was found to persuade deleterious neurodevelopmental disorders including reduced newborn cerebellum size, adverse behavioral outcomes, central nervous system damage, and cognitive developmental delays [85].

Even prenatal exposure to MeHg triggers detrimental learning and motivational changes in offspring, suggesting that intrauterine environmental toxicants contamination may persuade serious neurodevelopmental disorders and adverse intellectual effects in infant and adult animals [45]. Disruption of fetal epigenetic programming could help to explain the neurodevelopmental effects of Hg in animal models [86].

In mice, prenatal exposure to MeHg induced epigenetic suppression of *BDNF* gene expression in the hippocampus dentate gyrus and grounded several epigenetic alterations in *BDNF* promoter region IV, including DNA hypermethylation, increased histone methylation and decreased *BDNF* mRNA expression and H3 acetylation [19]. MeHg exposure in polar bears resulted in global CCGG hypomethylation of the lower brain stem region. Similarly, cerebrum tissues of MeHg-exposed mink (*Neovison vison*) exhibited the same methylation pattern and the *DNMT* enzymatic activity was reduced. Together, MeHg was found to be epigenetically active and is able to affect DNA methylation in mammals. The epigenetic reactions to MeHg may be proportional to the inter-taxa changes or variations between the exposure routes and duration; as well as the different life stages of the animals [10].

It was shown that MeHg (2.5 or 5.0 nM) exposure decreased global DNA methylation and *DNMT3B* expression in neural stem cells (NSCs) and this might be associated with altered cell cycle regulators and senescence-associated markers in these cells. Interestingly, these epigenetically alterations were inheritable to the daughter cell under MeHg free condition [87]. In a similar study, the authors obtained the very same results within the NSCs. Accordingly, they found chronically

prenatal exposure to MeHg induced a long-lasting repressive effect on the chromatin structure at the *BDNF* promoter region including DNA hypermethylation, increased histone H3-K27 tri-methylation and decreased H3 acetylation at promoter IV in mice [88]. *EMID2* hypomethylation was identified to be linked with in utero toenail Hg exposure, adverse infant neurobehavioral outcomes, physical health conditions and also disease complications [85]. In an epigenome-wide study, the *PON1* umbilical cord blood DNA methylation was associated with child cognitive function in females at early childhood, although it was weakened along mid-childhood. Perplexing, it was illuminated that prenatal Hg exposure hypomethylated DNA at the *PON1* locus independently from cord blood samples. The authors concluded that the DNA methylation of the *PON1* can control linkage between Hg exposure and their respective cognitive growth, based on the fact that the epigenetic modifications lead to the functional genomic changes [86]. Inorganic Hg may increase oxidative stress within the Hg-exposed brain cells, as well, it can modulate the *PON1* gene expression and reduce its activity. In return, homocysteine levels rise up, which this correlates with the genome-wide DNA hypomethylation and could impact both neurodevelopment and autism prevalence [89].

Once MeHgCl (400 nM) was introduced to the neuronal/glial culture, driven from the carcinoma pluripotent stem cells (NT2 cell line), a number of cellular miRNAs (miR-302b, miR-367, miR-372, miR-196b and miR-141) were overexpressed. These types of miRNAs are believed to contribute to the developmental neurotoxicity signaling pathways that affect axon guidance and learning and memory functions. A number of case-control trials investigating Hg, as a risk factor of amyotrophic lateral sclerosis (ALS) revealed that Hg was not associated with ALS initiation, while in a case of an 81-year-old woman diagnosed with ALS, Hg intoxication was speculated as the main reason for the diseases [90,91]. Together, the epigenetic alterations were found to possess transgenerational effects and could increase the susceptibility to the neurodevelopmental and neurobehavioral disorders in adulthood [63].

5.2. Cardiovascular system

The vascular effects of Hg have been expanded to the various physiological and anatomical aspects of the body. Hg or MeHg exposure increases oxidative stress and inflammation; reduces oxidative defense, thrombosis and mitochondrial dysfunction [92]. In blood vessels, Hg manipulates blood pressure, stimulates thrombosis and endothelial dysfunction. In addition, Hg oxidizes the blood vessels and cholesterol in a way that leads to the arterial plaque formation [93]. Also, Hg inactivates the enzyme paraoxonase (plays an important role as an antioxidant of low-density-lipoprotein cholesterol (LDL-C)), thus induces dysfunctional high-density lipoprotein (HDL) and subsequently reduces reverse cholesterol transport to the liver and initiates atherosclerosis [92]. Various epidemiological studies have indicated that prenatal Hg exposure also contributes to the cardiovascular disease and several other related risk factors such as myocardial infarction or blood pressure. Of interest, while the developing brain is the organ target for MeHg in children, the cardiovascular system may be the best MeHg objective in adults [94].

Elevated MeHg has also been linked with the selenoprotein P plasma 1 (*SEPP1*) promoter hypomethylation in male adult blood samples, specifically, *SEPP1* encodes a kind of protein that implicates in Hg toxicity protection, indicating the point that the methylation process may be exposure-responsive [10]. Kato and colleagues discovered that 12 genetic loci points involved in vascular smooth muscle and renal function, could influence on blood pressure in company with DNA methylation [95]. In a study on early life newborns, genome-wide DNA methylation data evidenced a corresponding association between Hg and DNA methylation at the TCEANC2 region in cord blood cells, reflecting a Hg-associated shift [96]. Global DNA methylation decline was found impressive on the aging process in association with Hg exposure in red blood cells of wild American alligators [97]. In a pre-birth cohort trial, prenatal maternal Hg exposure was shown to make persistent changes in both global DNA methylation and hydroxymethylation, as significantly decreased global 5-hmC of blood DNA in early (2.9–4.9 year), but not in mid-childhood (6.7–10.5 year) [86].

5.3. Immune system

Autoimmune disorders cover a variety of complicated multisystem diseases that originate from interactions between a vulnerable genetic background and external environmental risk factors [98]. Systemic lupus erythematosus, rheumatoid arthritis, diabetes type 1, Sjogren's syndrome, mixed connective tissue disease, and multiple sclerosis are classified as the most famous autoimmune disorders. Epigenetic modifications have also been implicated in such disorders since the global deregulation of the DNA methylation was found to be commonly affected by many autoimmune diseases [9]. Today, the hypothesis that exposure to life-threatening environmental factors results in overall failure of epigenetic homeostasis maintenance in the nervous system and might cause aberrant gene expression and/or nervous system dysfunctions, is well accepted [91]. Autoimmune analyses showed that Hg is able to motivate necrosis in somatic cells and even at low levels, it may induce the immune cell proportion changes in association with epigenetic variability and white blood cell composition in utero [9]. In adult humans, occupational Hg exposure has been associated with increased risk of autoimmunity; for instance, in two separate case-control studies, it was verified that both occupational and environmental Hg intoxication enhanced the risk of systemic lupus development [99,100]. Recently, molecular analysis showed up-regulation of miR-92a and miR-486 increased the activation of inflammatory cytokines such as nuclear factor κB (NF-κB) and cyclooxygenase-2 (COX-2), which this may be representative diagnostic biomarkers for occupational Hg toxicity in exposed workers [101].

In addition to the physical modifications of certain loci, the epigenetic regulations underlie differentiation process of a naive T cell conversion into the active T helper (Th)1/Th2 cells and induce epigenetic chromatin alterations in several genes. This indicates that autoimmune responses are under intense epigenetic control [102]. Aforementioned, the environmental toxicants are capable of altering the DNA methylation pattern and as a result of such aberrant changes, the normal antigen-specific $CD4^+$ T lymphocytes are converted into the self-reactive and pro-inflammatory cells, which elicit the lupus-like autoimmunity in genetically predisposed mice and humans [103]. In systemic lupus erythematosus, both global and gene-specific DNA methylation changes have been observed, even histone deacetylase inhibitors were reported to reverse the expression of involved genes in such disease [104]. Of the most common demethylating drugs that might induce lupus; 5-azacytidine, hydralazine and procainamide seem more applicable. 5-azacytidine inhibits *DNMT1* activity during replication through integration to the DNA and causes genome-wide hypomethylation as well as alterations in expression of multiple genes [82,105]. Hydralazine decreases *DNMT1* and *DNMT3 A* levels, while procainamide acts as a competitive inhibitor of *DNMT* inhibitors. In all cases, the interaction of T cells and demethylating drugs induced demethylation in lupus-like condition [105–107]. Some of the specific miRNAs, such as miR-155, miR-101 and members of the miR-17-92 cluster, have also been implicated in mechanisms of lupus, therefore, miRNA profiling seems beneficial for diagnosis and prognosis of the autoimmunity disorders [108].

5.4. Reproductive system

Hg intoxication was evidenced to trigger reproductive disorders, such as stillbirth or spontaneous abortions, congenital malformations, lower fertility ratio, inhibition of ovulation and menstrual cycle abnormalities in both animals and humans [109,110]. Hg-inducing

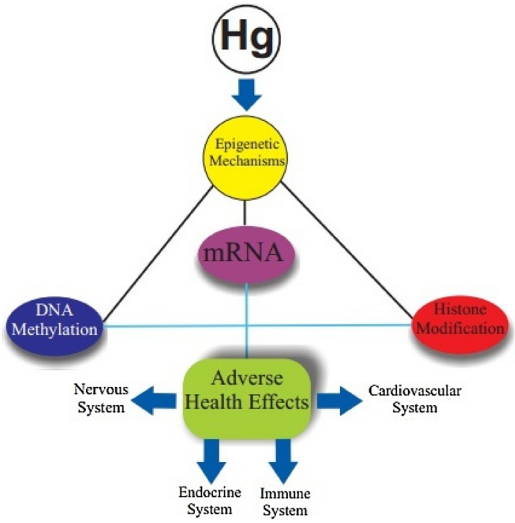

Fig. 3. Epigenetic mechanisms underlying Hg exposure and associated adverse health effects.

reproductive effects can be mediated as a result of the epigenetic modifications [11]. Hg exposure induced DNA methylation at the gene promoters of GSTM1/5 of CpG sites in whole blood samples of women undergoing *in vitro* fertilization (IVF) treatment. Although no statistical correlation was found, data was conceivable that the deleterious reproductive outcomes may be associated with the low-level exposure to the widely distributed environmental pollutants and to the subsequent altered epigenetic factors [28]. Newly, it was found that miRNAs in the women cervix are the novel responders to maternal Hg exposure during pregnancy. Quantified cervical examination of pregnant women disclosed a negative association between miRNA expression with toenail-Hg levels, as the 74 miRNAs expressions status were changed inside this region upon Hg exposure [111]. It has been investigated that developmental MeHg exposure (0, 1, 3, 10, 30, and 100 nM) inspired the epigenetic transgenerational inheritance of sperm epimutations of phenotypic alterations including visual deficits, hyperactivity, and altered retinal electrophysiology in Zebrafish (unexposed descendants F2 second generation), which more precisely may impact on its associated species, particularly human. In addition, they proved that the differential DNA methylation regions (DMRs) in the F2 generation lineage sperm were changed, as well, the translation associated genes in the neuroactive ligand-receptor interaction and actin-cytoskeleton pathways were affected. So far, most researches have indicated that in MeHg-exposed cells, global DNA hypomethylation and downregulation of *DNMT3B* is predominantly persisted in the daughter cells even after removal of MeHg. Further, dysregulation of those genes that are related with decreased cell proliferation (tumor suppressor *p16* and *p21*; mitochondrially encoded NADH dehydrogenase 3 (*MT-ND3*); mitochondrial cytochrome *b* (*Cytb*); and B cell-specific Moloney murine leukemia virus integration site 1 (*BMI1*)) showed same persistency in next generation cells [112]. In contrast, when *Tigriopus japonicas* (a type of copepod) was exposed to $HgCl_2$ treatments (0, 0.5, 1, 10, and 50 μg/l) for five continual generations, Hg did not induce any epigenetic or parental effects and its toxicity was rapidly deteriorated in later offspring, where Hg was cleared from the environment. Yet, phenotypic plasticity was contributed to the copepod Hg adaptability [113].

5.5. Renal system

Hg exposure is also one of the underlying reasons of renal problems and induces nephrotoxic effects like glomerular and tubular injury as well as aged kidneys; which may cause kidneys to not be functional at their full capacities [114]. On the other hand, cellular aging is known to downregulate miR-335 and miR-34a; resulting in elevated oxidative stress and cellular injury by over-expression of oxidative related enzymes such as superoxide dismutase 2 (SOD2) and thioredoxin reductase 2 [115]. Epigenetic analysis of DNA from kidney tissues of MeHg treated animals, showed a significant interruption in the renal function mediated by aberrant changes in methylation of proteolysis matrix metalloproteinase 9 (MMP9) and subsequent cytoskeleton disruption. MeHg caused nephrotoxicity via an enhancement of MMP9 expression at protein and mRNA levels, hence encouraged demethylation of MMP9 regulatory region and promoted its expression. In this manner, MeHg demethylated the CpGs in the first exon of MMP9 and declined the CpG methylation in response to limited access of methyl binding proteins to the methylated CpG sites. This could hamper the transcription process and results in losing of methylation of MMP9 gene promoter [116]. Besides, chronic exposure to MeHg showed the same epigenetic alterations of histone H3K4me3 marks in transparent nematode *C. elegans*, which improved the expression of a number of genes encoding oxidative stress in both adult animals and in utero. In the mouse embryonic stem cells, exposure to $HgCl_2$ resulted in a reduction of total histone proteins, and this decrease was mainly attributed to decline in mono-methylation of the H3K27 [60].

5.6. Liver cells

Liver histopathological changes have been linked to the inorganic form of mercury toxicity. Prepubertal female rats offspring exposed to MeHg (2 mg/kg/day), were diagnosed with hepatic inflammation, vacuolation and hypertrophy; but no hyperplasia, necrosis or changes in liver weight. In these animals, hepatic analysis showed MeHg exposure, in gestation (day 1) until postnatal (day 21) caused significant reduction in mRNA level for *DNMT1*, *DNMT 3A* and *DNMT 3B*; also decreased the methylation of CpG sites (position −63 to −29) in the promoter of the cyclin-dependent kinase inhibitor 2 A (*CDKN2 A*) that encodes the tumor suppressor gene $p16^{INK4a}$. This indicates that MeHg blood contamination could result in physiological disorder and liver toxicity, also could affect DNA methylation system in this organ [18]. The Hg associated epigenetic mechanisms and respective adverse health effects are shown in the Fig. 3.

6. Application of epigenetic data in mercury risk assessment

Risk assessment evaluates an association between certain changes in health status of an individual after exposure to a particular environmental toxicant. In this process, there is regulation of the level of exposure based on which the negative health effects are reduced [22]. It is a systematic process and it can be determined by assessment of the existing data and one can identify the mechanistic association among various types of environmental toxicants as well as their respective adverse health effects [117,118]. For instance, it was confirmed that the increased Hg level induces DNA hypomethylation at the promoter region of *SEPP1* [10,68]. This data provides a basis that would ultimately lead to an update on the dose-responses phase in the process of Hg risk assessment.

Metals-induced epigenetic perturbations and stimulation of cell signaling pathways in response to such trigger, along with their interactions in the development of diseases, can also be considered as the hazard identification process. For example, Hg-induced epigenetic alterations in miRNAs may be involved in regulation of stress-induced cell signaling pathways [63]. Together, this information will provide a turning point through which miRNA regulation may help specify the hazard identification phase of Hg risk assessment process [45].

The risk assessment of Hg and consequent management decisions have been disadvantaged due to major inconsistency in terms of exposures and health outcomes both in human subjects and wildlife. In case of MeHg exposure in human populations, controversies are still in progress regarding individual variations in terms of adverse

neurodevelopmental outcomes; i.e. differences in outcomes in Faroe vs Seychelles studies; propagation of cardiovascular diseases (i.e. the risk of hypertension); and those disagreements on Hg exposure and adverse health effects that can last from several weeks to years [119]. Till now, biological factors including age and gender; as well as other environmental toxicants combination are used to justify such inconsistency, although the inclusion of such variables has been faced fewer chances of success [17].

Being an environmental toxicant and a threat to the global society, along with Hg's possible risk assessment and management strategies can be explored from an ecogenetic consideration. There are already published reports by the panels of experts and renowned scientists indicating that exposure to Hg is attributed to a wide range of subclinical and adverse health outcomes both in humans and wild animals [17]. These reports also revealed that there is a great difference between individuals and species in terms of danger and exposure, also there is a close interaction between the genes and environment as well as the underlying variations, those are still unsolved. Such differences are major obstacles in the way of decision making organizations [120].

To recognize the vulnerable subgroups to Hg exposure, the ecogenetic philosophy pleas for care of both the environmental and genetic elements that were in danger and/or exposed. In the area of ecotoxicology and their association with human health, the majority of the Hg studies are exclusively concentrated on determining the factors that are mostly related to the environment and exposure (i.e. to know that what are the exact levels of Hg in both fish and consumers?) [119]. Though, this was an important step in evaluating Hg risk assessment, on the other hand, its usage is limited when employed alone in the prediction of risk. The science of Hg in the near future will focus on the points that whether the ecogenetic techniques are used to recognize the vulnerable groups and/or they are able to reduce the degree of dependency on ambiguous factors [119]. Recently, the number of studies has been augmented, specially wherever the genetic and epigenetic factors may interfere with Hg toxicokinetics and toxicodynamics. As an example, in a study conducted on monozygotic and dizygotic twins, it has been revealed that Hg biomarkers variance stems in both additive genetic effects and also unshared environmental effects, where the genetic component was only responsible for 30% of the variance in Hg concentrations [121]. The epidemiological studies carried out on populations exposed to occupational inorganic Hg (i.e. dentists and miner), or those were exposed to MeHg (i.e. populations consuming fish), specified polymorphisms in various genes that were responsive to the environment. This can clarify the differences in the Hg biomarker values and the health outcomes. Such findings are the beginning to elaborate our knowledge of understanding the potential mechanisms of action of Hg and to possibly identify the candidate biomarkers of vulnerability; hereafter, this will lead to more precise risk assessments and better decision making [119].

The exposure properties like toxicant nature, dosage source, duration of exposure frequencies of population genotype and selection of standard analysis or sample collection methods seems determinative to expand the comparability and significance of evidence for different epigenetic studies [122]. The recent advancements in the field of technology, now allow the investigations of lots of genetic alternatives through a single nucleotide polymorphism (SNP) arrays. Applying such epigenome-based technologies can help unveiling the main polymorphism in the genomic regions and will expose a much clear image of those sites of the epigenome, which have been targeted by Hg. This will provide a mechanistic association between Hg exposure and toxic health outcomes [1,119].

7. Conclusion

With the passage of time, the number of research publications on metal toxicities and their epigenetic alterations is on the rise, although, still there is an obvious gap in such area of research that needs to be addressed before its incorporation and application in the process of risk assessment. Furthermore, the epidemiological and toxicological studies are required to investigate the possible connection flanked by epigenetic modifications, functional cellular effects and adverse health outcomes. The aforementioned evidence indicates that exposure to toxic metals such as Hg can alter the DNA methylation patterns as well as both gene-specific and global histone posttranslational modification marks; indicating the significance of epigenetics as a possible mechanism underlying the toxic effects associated with Hg exposure. It is worth considering that Hg-induced epigenetic modifications are not the only driving force leading to the unfavorable health effects, but in fact, apart from other toxicological effects, the epigenetics is also imperative. The transmissible changes of the phenotype will be a key epigenetic basis for future groundwork; introducing the epigenetic alterations as a promising aspect of molecular diagnosis of a wide range of diseases that caused by Hg toxicity. Hg-induced epigenetic alterations may be sufficient to cause anomalies in biological functions that are heritable in the majority of the exposed cases and may be associated with transgenerational risks. Considering the metal-induced epigenetic disorders, epigenetic therapies have been effectively employed to target the defective genes or the gene regulatory systems. Such treatment strategies can specifically manage the affected genes without being harmful to the normal cells and can deliver a better quality life for those affected individuals. Even though the exact epigenetic mechanism underlying Hg exposure and their associated disorders require further investigation, in the present study we described a novel approach that pointed to the importance of early life exposure to Hg, which plays a vital role in altering the gene activity pattern through epigenetic perturbations and may affect on the function of various body systems. Moreover, it will be clinically valuable to investigate which particular epigenetic alterations are associated with a specific disorder as a result of Hg exposures in human subjects. We have highlighted various epigenetic mechanisms that may be the cause of pathogenesis of various diseases in different body systems in response to Hg exposure. The epigenetic mechanisms that we have summarized in the present study can be used as a potential biomarker in future studies to diagnose Hg-associated disorders. This will help in facilitating preventive medicine and therapeutic approaches to alleviate associated disease risk.

Author contributions

MA conceived the study and supervise whole things. FK and SM drafted the paper. All authors approved the final version of the manuscript as submitted.

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Conflict of interest

The authors declare no conflict of interest.

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