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Genetic and epigenetic modulations in toxicity: The two-sided roles of heavy metals and polycyclic aromatic hydrocarbons from the environment

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ABSTRACT

This study emphasizes the importance of considering the metabolic and toxicity mechanisms of environmental concern chemicals in real-life exposure scenarios. Furthermore, environmental chemicals may require metabolic activation to become toxic, and competition for binding sites on receptors can affect the severity of toxicity. The multicomplex process of chemical toxicity is reflected in the activation of multiple pathways during toxicity of which AhR activation is major. Real-life exposure to a mixture of concern chemicals is common, and the composition of these chemicals determines the severity of toxicity. Nutritional essential elements can mitigate the toxicity of toxic heavy metals, while the types and ratio of composition of PAH can either increase or decrease toxicity. The epigenetic mechanisms of heavy metals and PAH toxicity involves either down-regulation or up-regulation of some non-coding RNAs (ncRNAs) whereas specific small RNAs (sRNAs) may have dual role depending on the tissue and circumstance of expression. Similarly, decrease DNA methylation and histone modification are major players in heavy metals and PAH mediated toxicity and FLT1 hypermethylation is a major process in PAH induced carcinogenesis. Overall, this review provides the understanding of the metabolism of environmental concern chemicals, emphasizing the importance of considering mixed compositions and real-life exposure scenarios in assessing their potential effects on human health and diseases development as well as the dual mechanism of toxicity via genetic or epigenetic axis.

1. Introduction

The ever-increasing presence of environmental concern chemicals in the environment has raised significant questions about their potential impact on human health and ecosystems. These chemicals encompass a wide range of compounds, including heavy metals and polycyclic aromatic hydrocarbons (PAHs), which have been linked to various adverse health effects [1,2]. A mixture of various compounds rather than exposure to a single chemical entity often characterizes the real-life exposure to environmental concern chemicals [3,4]. This composition significantly influences the presence and severity of toxicity [4–11].

Understanding the metabolism and toxicity mechanisms of these chemicals is crucial for assessing their potential risks and developing effective strategies for mitigation and regulation [12]. The multifaceted nature of chemical toxicity is reflected in the activation of multiple pathways during exposure to environmental concern chemicals [13-16]. These diverse pathways collectively contribute to the toxic effects observed, highlighting the intricate web of interactions and responses in biological systems. This review aims to provide a comprehensive analysis of the metabolic pathways and toxicity mechanisms of environmental concern chemicals, with a particular focus on the influence of gene expression via epigenetic mechanisms and the involvement of small non-coding RNAs (sRNAs) in disease pathophysiology. Moreover, the impact of mixed compositions of concern chemicals on their toxicity will be explored, acknowledging the complex interactions that occur in real-life exposure scenarios.

2. Search string and databases

This literature review involved the search for empirical studies by engaging important keywords such as genotoxicity, heavy metals, environmental pollutant, polycyclic aromatic hydrocarbons, oxidative stress, genetics, epigenetics, noncoding RNA, and metabolism in databases such as Google scholar, PubMed, and Scopus. Major focus was on studies reporting the genetic and epigenetic changes from exposure to environmental concern chemicals without restriction or time frame for

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publications. Studies on particulate matter whose constituents were uncharacterized were excluded while only those whose constituents were characterized were included. Also included are studies with well defined mode of exposure.

2.1. Description of AhR receptor

The aryl hydrocarbons receptor (AhR) is a ligand dependent cytotoxic transcription factor, which mediates the toxic and biological effects of different environmental chemicals thereby regulating the transcription of certain genes (Gvenhrrich 2004; [4,17,18]). The activation of AhR is often accompanied by induction of metabolizing enzymes [19,20] suggesting AhR dependent mechanism of PAH metabolism. Bearing this in mind, it is critical to detail on AhR.

This regulatory molecule is ligand activated and usually located in the cytoplasm, bound to two HSP90 (90KDa heat-shock proteins) and AIP (AhR interacting protein) [21,22,17]. Among the AIP is the X-associated protein 2 (XAP2) [23] and a 23-KDa co-chaperone protein called p23 [24].

Upon activation after the binding of ligand, AhR is dissociated from HSP 90 and AIP and immediately translocated into the nucleus as ligand receptor complex forming a heterodimer with aryl hydrocarbon receptor nuclear translocator (ARNT); a transcription factor protein [17,18]. This AhR/ARNT complex can subsequently binds to specific DNA sequence known as xenobiotic-responsive element (XRE) which is located in the promoter region of CYP1A1 gene and initiates a transcriptional process [17,18]. Furthermore, AhR/ARNT complex can also bund to the promoter region of CYP1A2, glutathione S-transferase, UDP-glucoronosyl transferase, CYP1B1 and quinine oxidoreductase therefore activating their transcription [25,26]. These in fact explains the major role of AhR in the activation of phase 1 and phase II, III metabolizing enzymes and the contribution in the detoxification of xenobiotics [27,28]. Initial studies focused predominantly on halogenated aromatic hydrocarbons (HAH), polycyclic aromatic hydrocarbons (PAHs) and structurally related compounds as ligands involved in AhR activation. In the recent time, clear indications have begun to emerge about important chemicals that are chemically diverge from the aforementioned in the binding and activation of AhR.

2.2. Activation of AhR receptor is associated with the toxicity of environmental contaminants

Many environmental pollutants are chemically inert and often require metabolic activation [29-32]. In this regard, the mechanism of chemical toxicity is very complex [14]. Available studies have highlighted many pathways involved in xenobiotic metabolism primarily involving the CYP450 family [33]. Different factors including the structure, form, co-exposure and dose influence the metabolism and toxicity [6,4,9]. Because PAH and heavy metals are persistent environmental contaminants and forms the major component of environmental particulate matter with detailed data on their role and influence in the mediation of diseases, these two categories of toxicant will be the focus of this review. Here, studies highlighting specific modes with respect to metabolism and toxicity of PAH and heavy metals were reviewed and major emphasis were laid on the interaction of contaminants and expression profile, tissue and organ specific expression profile and process of disease perturbation.

Activation of AhR is an important cellular response induced by aromatic hydrocarbons [34,35]. Darwish et al. [36] in a bid to understand the mechanism of benzo[*a*]pyrenes (BaP) mutagenicity and oxidative stress in human colon (CaCo-2) cell lines showed that B(a)P metabolism was initiated upon the activation of the AhR pathway which resulted in the up-regulation of mRNA expressions of CyP1A1, CyP1B1 and epoxide hydrolase. In the same vein, phase II enzymes such as UGT1A6 and GSTA1 expression were down regulated thus creating disturbance between bio-activation and detoxification of B(a)P in the colon cells (Table 1). However, as a mode of bio-adaptation the colon cells had elevated mRNA expression of MDR1, and MRP2, which are ATP binding cassette (ABC) transporters responsible for the efflux of phase II metabolites of xenobiotics. On a conclusive note, the authors submitted that B(a)P mutagenicity in the colon cells was mediated via modulation of xenobiotics metabolizing enzymes and induction of oxidative stress.

PM 2.5 consisting mixture of heavy metals and predominantly PAH viz benzo (a) anthracene, benzo(a) pyrene and benzo (k) fluoranthene increased the mRNA expression of CyP1A1 (Table 1). This up-regulation was linked to the increase AhR protein level and the enhanced cytoplasm to nucleus translocation in P19 cell [37]. Attenuation of this activation process by a specific AhR antagonist validates this observation. The XME activation pathway was later proven to be linked to the

Table 1
Summary of contaminant's effects on AhR activation.

Toxicant	Cell type/Organism	Tissue/ Organs	Exposure level	Observation	Reference
Benzo[*a*]pyrene	Human colon (CaCo2) cell line	Colon	1, 5 and 50 nM for 24 hours	AhR activation resulted in the Upregulation of CYP1A1, CYP1B1, epoxide hydroxylase and down regulation of UGT1A6 and GSTA1	[36]
PM2.5 with mixture of high molecular weight PAH	Murine P19 cell line	Cardiac tissue	1, 10, 100 μg/ml for 48 hours	Increased activation of AhR and Cytoplasm to nuclear translocation of AhR	[37]
PM 2.5 and benzo[*a*]pyrene	Human alveolar epithelial cell (A549)	Lungs	10 μg/cm^2 (P.M. 2.5), 14 μM (Benzo[*a*]pyrene	AhR activation upregulated of CYP1B1	[38]
Mixture of heavy metals and PAH	Rats H4IIE cell line	Liver	Varied ration of toxicants extract	Increased AhR activation increased the CYP1A1 and EROD levels	Mennillo, [39]
Mixture of heavy metals and PAH	Fish PLHE-1 cell line	Liver	Varied ration of toxicants extract	Increased AhR activation increased the CYP1A1 and MROD levels	Mennillo, [39]
Hg, Pb, Cu	Murine hepatocellular (Hepa1c1c7) cell line	Liver	5 μM (Hg), 25 μM (Pb), 10 μM (Cu) for hours	Activation of AhR enhanced CYP1A1 levels and post translational regulation of CY1A1 by decreasing protein degradation	[20]
PM 10 predominated with high molecular weight PAH	Procrine airway epithelial tissue	Lung	3, 10 and 300 μg/ml	Upregulation of CYP1A1	[40]
Benzo[*a*]pyrene	HepG2 cells	Liver	0–2 μM	Increased activation of AhR more than naphthalene, phenanthrene and pyrene	[41]
Combination of benzo[*a*] pryrene, arsenic, lead and cadmium	HepG2 cells	Liver	0.1 μM (Cadmium), 0–10 μM (As), 0–50 μM (Pb) for 24 hours	Increased expression level of AhR gene	[41]
Combination of benzo[*a*]pyrene, naphthalene, phenanthrene and pyrene	HepG2 cells	Liver	0–2 μM (benzo[*a*]pyrene), 0.15 μM (other PAH) for 72 hours	Lowered activation of AhR than when exposed to benzo[*a*]pyrene alone	[41]

dysregulation of several other pathways involved in cardiovascular dysfunction.

Variation in the composition of the P.M 10 derived from the combustion of three different biomass; pellet, wood and charcoal influenced their effects on the activation of AhR in human lung (A549) cells. The charcoal and wood particulate matters that were abundant in PAH but low in heavy metals mainly induced xenobiotics response enzymes activation and cell apoptosis whereas the pellet PM which had abundance of heavy metals but low amount of PAH mainly induced mild inflammatory response, DNA damage, and cell cycle arrest in the G1 phase, which was subsequently accompanied by necrotic cell death. Among the treatments, only the wood biomass which had the highest PAH content induced CYP1B1 significantly whereas overall low induction of CYP1A1 was observed [42].

In similar studies, PM 2.5 and benzo (a) pyrene recorded up-regulation of CyP1B1 than the CyP1A1 in A549 cells [38]. This response of A549 cells could however be influenced by their behavior in a mixture of compounds [43]. Both CYP1A1 and CYP1B1 were up-regulated in different ways by individual PAH however, the behavior differs when the PAH were combined. Summarily, the effects of PAH combination on the metabolic genes could either be inhibited or enhanced depending on the concentration of each PAH in the complex mixture in an in-vivo system.

2.3. Heavy metal activation of AhR receptor

Mercury (Hg^{2+}), Lead (Pb^{2+}) and copper (Cu^{2+}) induction of CYP1A1 is AhR dependent and inhibition of AhR degradation further enhanced its mRNA induction [20]. Following Hepa1c1c7 cell's incubation with $Hg^{2+,}$ Pb^{2+} and Cu^{2+}, CYP1A1 induction was upregulated consistently with those obtained for halogenated aromatic hydrocarbon; most potent CYP1A1 inducer studied. In addition, co-treatment of Hg^{2+} and Pb^{2+} with (TCDD) 2,3,7,8-tetrahydrochlorodibenzo-p-dioxon further increased the induction of CYPlAl whereas Cu^{2+} together with TCDD diminished CYP1A1 induction. Obviously, this observation is a reflection of the alteration in synthesis and degradation rate of CYP1A1 mRNA [20]. According to the study, the induction of CYP1A1 mRNA by heavy metal is both a transcriptional and an AhR mediated event in a manner similar to that of TCDD. To support these findings the authors established insignificant change in the CYP1A1 mRNA half-life, indicating that increase in CYP1A1 mRNA transcript in response to heavy metals were not due to a post transcriptional stabilization of the mRNA, however the metals decreased the rate of CYP1A1 protein degradation implying a posttranslational regulation of CYP1A1 by heavy metals [44, 45]. By implication, heavy metals are capable of induing AhR expression which will result in the up-regulation of CYP1A1, and at the same time inhibit the degradation of CYP1A1 thereby increasing the half-life.

2.4. Mixed composition of environmental contaminants influence the activation pattern of AhR receptor

Considering the likelihood of divergence in the behavior of mixtures of environmental contaminants in the induction of xenobiotic metabolizing enzymes and subsequent toxicities, monitoring the individual and combinational influence of these chemicals on cellular metabolic machineries could influence current methods in health risk assessment and imitate what is applicable in human exposure to environmental chemicals. In this regards, different authors have investigated the implication of mixture of different environmental chemicals on the metabolic machinery. For instance, metalloids in combination with PAHs inhibited the induction of CYP1A1 and CYP1A2 at transcriptional and post transcriptional level [44-46] and consequently limited the genotoxicity of B (a)P as CYP1A1 mediated metabolism of B(a)P is prerequisite to its genotoxicity.

On another note, AhR induction and genotoxicity of PAH mixtures in HepG2 cells was dependent mainly on the most potent compounds i.e. B (a)P in the mixture. In addition, Cd in combination with B(a)P greatly enhanced genotoxicity whereas at low concentration, cadmium, chromium, arsenic and B(a)P mixtures caused similar degree of genotoxicity with Cd/B(a)P but increases in concentration mixture lowers it [4]. It is clear that interaction among the metalloids may affect their bioavailability and speciation in cells thus regulating their combined effects [47]. Unlike CYP1A1 induction in some other cell types, PM10 predominated by high molecular weight PAH induces up-regulation of CYP1B1 in procrine airway epithelial cell [40]. Some reports showed that CYP1A2 and CYP1B1 induction is less likely in human blood vessel endothelial [48-51]. Therefore, the CYP450 isoform induced upon exposure to environmental contaminant may be tissue dependent.

According to Farina et al. [52], CYP1B1 and not CYP1A1 were unregulated in response to urban PM 10. Based on other findings, CYP1B1 induction may be AhR independent, more so, CYP1B1 mRNA expression is reported as the most sensitive target across different cell models compared to the AhR target genes viz CYP1A1, AHRR and ALDH 3A1 (Hukkanen *et al.,* 2000; Strapáčová *et al.,* 2018).

Observations by Muthusamy et al. [41] indicated B(a)P as potent inducer of AhR than naphthalene, phenanthrene and pyrene in HepG2 cells. In addition, As, Cd and Pb or their binary combination failed to activate AhR in HepG2 cell whereas binary and ternary mixtures of B(a)P and As, Pb and Cd activated AhR than B(a)P alone. On a further note, B (a)P with binary and ternary mixture of Nap, Phe Pyr lowered the activation of AhR compared to B(a)P alone. The argumentation of AhR by B(a)P/metal mixture and lowered augmentation of AhR by B(a)P/pyrene, Phe and Nap mixtures was in parallel with the incidence of micronucleus and alteration in cell cycle parameters. According to the study B(a)P/metal mixtures increased micronucleus formation and cell accumulation at G2/M phase than B(a)P alone whereas B(a)P, Phe, Pyr and Nap mixtures decreased MN formation in HepG2 cells but cause no changes in the cell cycle parameters compared to B(a)P alone. This observation substantiated the reports associating PAH activations to their toxicity. B(a)P damaging effects was related to the activation of Ah receptor of the endothelial lining in the blood vessels [29].

Metabolic response to heavy metals and PAH can be specie specific. Using rats (H4IIE) and fish (PLHC-1) cell lines, Mennillo, [39] demonstrated the activation of AhR with downstream increase in CYP1A1 mRNA. The up-regulation of CYP1A1 paralleled by up-regulation of two different phase II biotransformation enzymes of EROD (7 ethoxyresoruffin-O-deethylase in the H4IIE but MROD (7-methoxyresorufin-O-deethylase) in the PLHE1.

During biotransformation, the contaminant that induces CYP expression subsequently becomes the substrate for the resultant enzyme induced. Although in some instances, the chemicals may block the active site of the metabolizing protein or prevent it posttranslational modification. In this context, measuring enzyme activity may reflect events that proceed posttranslational assembly of protein (Uehara *et al.,* 2016). The differences in the enzyme activity pattern in the two cell lines may reflect differences in the CYP1 isoforms that mediate catalytic processes as well as differential substrates specificity in the cell lines. From toxicological point of view, the biotransformation pathway induced in response to a chemical may modulate a contaminants metabolism to produce toxic/reactive metabolites thereby altering pharmacokinetics and reducing elimination rate [18].

2.5. Oxidative DNA damage as a mode of genotoxicity by environmental contaminants

Heavy metals and PAH mediated diseases especially cancer is linked to their ability to indirectly induce genotoxicity via oxidative stress and form adducts with DNA. Oxidative lesions and DNA damage are common features of heavy metals and PAH exposure [53-55]. Genotoxicity implies deleterious action on the integrity of genetic material of a cell and often time, substances able to cause genotoxicity are potential mutagens or carcinogens. Exposure to these genotoxic agents however

occur from several medium including workplace, lifestyle choices, and even medical treatments. For the assessment of endpoint genotoxicity however, certain biomarkers are employed for chemical exposure effects as well as individual susceptibility [56,57].

Just as expected, the nature of each environmental toxic chemical influences their genotoxicity mechanism. Polycyclic aromatic hydrocarbons for instance when metabolized generate free radicals i.e. reactive metabolites to induce oxidative stress [58]. These radicals can attack DNA and other biological molecules causing oxidative DNA damage which is hallmark for the pathogenesis of PAH related diseases [59-61]. The PAH reactive metabolites can also interact directly with DNA to form DNA adducts, consequently leading to genetic mutation [62]. Heavy metals on the other hand contribute to disease development through direct/indirect genotoxic and epigenetic mechanism [63,64]. However, each metal is unique in its genotoxicity mechanism and potentials. For instance, nickel induces genotoxicity by activating oxidative DNA damage [65]. On another vein, they could interfere with DNA damage repair process as well as alter stabilization of the chromatin [66] and cause DNA strand break [67].

Current knowledge of the mechanism of radical provoked DNA damage shows that pre-mutagenic changes in the events of oxidative DNA damage includes oxidation of purine and pyrimidine bases, as well as instability directly formed or by repair processes [68]. Despite the susceptibility of all the four nucleic acid bases to radical modification, mutations are usually related to modification of GC base repair, whereas that of AT base repair seldom leads to mutation [69,70].

A number of sensitive markers for oxidative nucleic acids genotoxicity includes the 8-hydroxygunanine (8-OHG), 8-hydroxy, 2' deoxyguanosine (8-OHdG), 5'-OH- 2' cytosine which is known to cause C:G to A:T mutations and 2-OH dATP that induces G:C and A:T mutations [69, 70]. Because 8-OHdG is directly excreted in urine and its high sensitivity for detection, it is the most common sensitive biomarker to measure the extent of nucleic acid damage and repair [71-73,69]. This biomarker is a product of oxidative chemical modification of guanine and can alter its configuration in the DNA consequently affecting its base pairing properties. Basically, presence of 8-OHdG in DNA template compromises the alpha-polymerase fidelity in the incorporation of nucleotides into the replicating strand [74,75] thereby perturbing the general macromolecular structure [76,74,77,78]. Unless repaired, the 8-OHdG in the DNA leads to a G:C to T:A transversion. Although, little is known about the repair of 8-OHdG, studies have shown its removal from isolated DNA without strand rupture [74,79]. Upon repair, the 8-OHdG products can be excreted in urine therefore, studies commonly measure the amount in blood and urine as indicator of oxidative DNA damage [69]. Measurement of 8-OHdG and other indicators of genotoxicity are presently being considered in many studies to unravel extent of exposure to chemicals,

Table 2
Evidence of toxicant's genotoxicity effects.

Toxicant	Cell type/Organism	Exposure level	Organ/Tissue	Observation	Reference
Traffic air containing Cd, Ni, As, Pb, Cu	Human cohort study	N/A	Buccal mucosal cells	Increased frequency of micronucleus on binucleated lymphocytes coupled with urinary excretion of 1-hydroxypyrene and 2-naphthol	[81]
Air heavily polluted with Heavy metals	Human cohort study	N/A	Buccal mucosal cells	Increased micronucleated frequency	[87]
Air pollutant dominated by high molecular weight PAH	Human (school children) cohort study	N/A	Buccal mucosal cells	Increased frequency of DNA damage indicated by increased tail moment	[88]
Cr, As and Pb	Human cohort study	N/A	Blood	Total blood concentration of 8-OHdG increased with significant damage to the DNA	[69]
Pb and 1-hydroxypyrene	Human cohort study and lymphoblast alveolar epithelial adenocarcinoma (A549)	N/A	Peripheral lymphocytes	Increased micronucleus formation and sister chromatic exchange in peripheral lymphocytes	[89]
PM 2.5 from Urban environment	Human	25, 50, 75, 100 μg/ml	Human lymphoblast	Oxidative DNA damage characterized by increased 8-OHdG levels in the lymphoblast	[70]
Coal dust with high concentration of arsenic, chromium and PAH	Mouse	0.25, 0.5, 1, 2 and 4% w/w	Blood	Increased micronucleus frequency	[90]
Benzo[*a*]pyrene	Mouse Liver cell (HepG2)	20 μM	Liver	Increased micronucleus frequency	[4,41]
Arsenic		0.25–2 μM		Increased micronucleus frequency	
Pb and Cadmium sseparately		0.25–2 μM		The toxicants micronucleus formation weakly	
Benzo[*a*]pyrene with either, arsenic, Pb or Cd		0–2 μM (Benzo[*a*]pyrene), 0.1 μM (Cadmium), 0–10 μM (As), 0–50 μM (Pb) for 24 hours		Increased micronucleus frequency than benzo[*a*]pyrene	
Benzo[*a*]pyrene with arsenic and cadmium		0–2 μM (Benzo[*a*]pyrene), 0.1 μM (Cadmium), 0–10 μM (As) for 24 hours		Higher micronucleus induction than binary combination of benzo[*a*]pyrene and metals	
Benzo[*a*]pyrene with naphthalene, phenanthrene and pyrene		0–2 μM (benzo[*a*]pyrene), 0.15 μM (other PAH) for 72 hours		Had no significant effect on micronucleus levels	
Arsenic and lead		0–10 μM (As) and 0–50 μM (Pb) for 24 hours		Increased micronucleus frequency than other metal combinations	
Cadmium and chromium		0.25–2 μM		Increased the micronucleus frequency than when arsenic alone was used	[4]
Chromium	H4-II-E-C3 Cells	0.275, 1, 10 μM	Liver cell	Stimulation of DNA repair gene with DNA damage ontology enrichment	[8]
Benzo[*a*]pyrene	Human umbilical vein endothelial cells	0.1, 1.0, 10 μM for 90 minutes	Endothelial cells	Increased DNA damage characterized by increased DNA tail moment	[29]
Benzo[*a*]pyrene	CaCo2 cell line	1, 5, 50 nM for 24 hours	Human colon	Increased ROS generation with increased frequency of mutagenicity	[36]

N/A: not applicable

oxidative status and risk of disease development [80,81].

In a bid to examine the relationship between urinary biomarkers of PAH and heavy metals as well as their interaction on the DNA damage, Huang et al. [81] measured 1-hydroxypyrene-glucuronide (1-OHPG), 8-OHdG and urinary metals of Taiwanese traffic conductors. 1-hydroxypyrene-glucuronide (1-OHPG) is a PAH metabolite used as biomarker of PAH exposure [82-84]. Both the level of 1-OHPG and cadmium (Cd) significantly correlate with the urinary concentration of 8-OHdG. As the concentration of both compounds increases i.e. Cd and 1-OHPG, the concentration of 8-OHdG also increases [81] (Table 2). The urinary excretion of products of DNA damage may be attractive biomarkers of exposure to carcinogens and may predict cancer risk. From previous studies, cadmium induces reactive oxygen species (ROS) generation, which are a class of free radicals, thereby depleting antioxidant defense system and as such, contributes to its genotoxicity potentials [85,86].

Huang et al. [81] suggested additive interaction between exposures to PAH and Cd and this interaction could enhance the burden of oxidative stress viz-a-viz oxidative DNA damage. Among individuals (Reboucal tunnel workers) occupationally exposed to traffic air pollution in Brazil, frequency of micronucleus in the buccal mucosa cells and binucleated lymphocytes increased significantly. 1-hydroxypyrene (1-HOP) and 2-naphthol (2-NAP) in urine were also significantly increased among the study population. Both 1-HOP and 2-NaP are hydroxyl metabolites of pyrene and naphthalene respectively. Taking into consideration other contributing factors such as smoking, medication, alcohol, x-ray exposure, age among others, Rainho et al. [91] found that the micronucleus frequency was directly correlated with pollutant exposure. Many other findings agree well with this observation. Among populations exposed to PAH [57], ozone [92] and heavy metals [87] micronucleus frequency increased in the buccal mucosa cells. In petrochemical industrial areas in Malaysia, school children examined for PAH exposure showed higher degree of DNA damage in the buccal epithelial cells as indicated by the tail moment and this degree was in pal with PAH concentration. From the study, high molecular weights PAH were predominant in the environment [88]. Both Human cytokines-block micronucleus (CBMN) and PIG-A mutation was increased in PAH exposed barbecue workers. PIG-A mutation frequency was better associated with urinary PAH metabolites (2-OHFLU, 2-OHPhe, 3-OHPhe, 4-OHPhe, as well as PAH exposure concentration, thereby posing the PIG-A mutation assay as promising genotoxicity assessment method applicable to human bio-monitoring studies [93].

In human vocal fold fibroblast cells of the larynx, oxidative DNA damage was evaluated based on the concentration of 8-OHdG. From observations, blocking of AhR or CYPlal by SiRNA's decreased the extent of cellular damage. Indicating oxidative pathway in the damage of the DNA [94].

There is a link in the PAH and 8-OHdG concentration with exposure duration, thus oxidative DNA damage is linked to acute and prolonged exposure [95]. This is clearly supported by the evidence that reported the decreased urinary concentration of oxidative DNA damage biomarkers; 2-OHF,3-OHF, 1-OHPG as well as urinary concentration of heavy metals and PAH in subject after electronic-waste (e-waste) control in a time dependent manner during a four-year monitoring study [96]. Similarly, Yang et al. [97] reported elevated chromium, arsenic, and selenium, manganese, and 8-OHdG levels during occupational exposure to municipal waste incinerator among workers in Shenzhen China. From the study, no correlation was found between the metal concentration and 8-OHdG thus concluding that no association exists between urinary heavy metal concentration and DNA oxidative damage. The study is however limited in that other organic contaminant such as PAH and their metabolites which are well established to contribute to oxidative DNA damage consequently elevated 8-OHdG level, were not measured. In addition, only arsenic and chromium seems to be the only carcinogenic heavy metals that were significantly elevated. Other metals such as cadmium, lead, mercury was not significantly elevated [97].

In Legnica copper foundry worker specifically examined for the contribution of lead, cadmium and arsenic to the total blood 8-OHdG concentration, the heavy metals and nicotine were found to elevate blood concentration of 8-OHdG and were said to damage DNA independently by similar strength [69]. Similar observation was reported among individuals exposed to asbestos, arsenic, and chromium [98-101]. Lead and PAH critically influenced cytogenetic parameters viz micronucleus and sister chromatic exchange (SCE) in peripheral lymphocytes of children from two most populated centers of Silesia province in Poland. DNA adduct (PAH-DNA adduct) and SCE were positively correlated. In addition, lead concentration also correlated positively to the micronucleus frequency [89].

Dose dependent exposure of mouse to coal dust contaminated sand significantly elevated DNA damage index and micronucleus frequency in peripheral blood in a dose dependent manner. The coal dust was suspected to contain carcinogenic heavy metals such as arsenic and chromium as well as PAH [90]. In a separate study involving alveolar epithelial cells (A549) which was also supported by human study where exposure to polluted air from the urban environment occurred, 8-OHdG concentration was present in the same amount in the A549 cell and human lymphoblast demonstrating similar mode and extent of oxidative DNA damage [70]. The 8-OHdG levels correlated with exposure level of PM 2.5 and PAHs [70]. The authors highlighted the possibility of using circulating lymphocytes as surrogate for assessing PM induced oxidative DNA damage. In liver cells (HepG2 cells), the toxicity varies depending on the concentration, number and type of chemicals present in the chemical mixture, the cells were exposed to. According to a study, As, Cd, Pb, Nap, Phe, Pyr and BaP individually, in binary, in ternary, quaternary and as well as seven-mixture component were combined. The result showed the capacity of Benzo(a)Pyrene (BaP) to independently increase micronucleus frequency where Napthalene, Phenanthrene and Pyrene were negative. Arsenic positively increased Micronucleus frequency among the metals but Pb and Cd showed weak response [41] (Table 2). Also, binary mixture i.e. BaP with each metal increased micronucleus frequency than BaP alone. Whereas, ternary combination of BaP, As, and Cd showed the maximum increase. While on the contrary the binary combination of the PAH declined the micronucleus frequency than BaP alone and in fact the quaternary mixture and seven compound mixtures had no significant effect on micronucleus formation when compared with BaP alone. Binary and ternary mixtures of the heavy metals increased the micronucleus formation than As alone (Table 2). The combination of As and Pb had the maximum value among the binary mixture of metals. The observation was somewhat linked to the influence of the individual and combined chemicals on the metabolizing enzymes [41]. In a separate study, the authors investigated the combined, single and mixed genotoxic effects of some PAHs and heavy metals except for the replacement of lead by chromium in HepG2 cells (liver cells) [4] and reported similar trend for micronucleus formation by the PAH's mixtures whereas Cd, and Cr exhibited higher frequencies than As. However, mixture of the metals again showed higher frequency than individual metalloid. Only chromium exhibited genotoxic effects when rat liver derived cell line (H4-II-E-C3) was treated with soluble salts of nickel, chromium, and cadmium based on the gene expression profile analyzed in an enrichment study. Among the three metals, cell treated with chromium expressed DNA repair genes with DNA damage ontology being enriched. Expressed genes included E2F as well as other DNA synthesis genes [8]. E2F is a transcription factor family that is required in the timely expression of genes required for cell cycle progression and proliferation. From the study, no direct marker of genotoxicity was measured and since the conclusion made on the metalloids was based on gene expression pattern, it is uncertain to conclude on the genotoxicity of nickel and cadmium. The result might rather explain possible differences in the mechanism of genotoxicity.

Different behaviors are actually possible for chemical agents depending on the cell where the toxicity effect is provoked and the presence of other agents. It is clear from several observations that each chemical agents inflict different level and type of toxicity. Again, in

human umbilical vein endothelial cells, pretreatment with β-naptho-flavone (BNF), a CYPlAl inducing chemical, benzo(a)pyrene induced higher level of genotoxic damage measured by the DNA tail moment. Only high concentration of benzo(a)pyrene induced genotoxic damage in cells untreated with BNF. When the cells were treated with CYP1A1 and CYP1B1 inhibitor (α-naphthoflavone (ANF), the benzo(a)pyrene induced damage was reduced. This observation suggested certain compounds may enhance or reduce the toxicity potential of benzo(a)pyrene [29]. In human colon, (CaCo-2) cells, benzo(a)pyrene provoked high level of mutagenicity which was counteracted by downregulation of phase I enzymes, upregulation of phase II detoxification enzymes and xenobiotic transporters upon treatment of cells with rosmarnic and ascorbic acids [36]. The extent of BaP mutagenicity in the colon cells was in parallel with ROS generation. The ROS generated was in dose dependent manner. Inhibition of cardiac differentiation in P19 mouse embryonic carcinoma stem cells, which differentiates towards cardiac lineage by extractable organic components of PM 2.5, was associated with γ-H2AX (Gamma Histone Family Member X) and AhR upregulation. The PAH mixture increased the AhR protein level and enhanced the translocation into the nucleus, which was later accompanied by β-catenin downregulation. The AhR antagonist (CH223191) reversed all this effect stressing on the possibility of therapeutic advantage [37]. It was concluded that AhR activation mediated the suppression of cardiac differentiation (Fig. 1). It was proposed that cardiac developmental toxicity mediated by the PAH mixture involves AhR dysregulation of cell proliferation, alteration of canonical wnt signaling and DNA strand break induction [37].

2.6. Genotoxicity mechanism of heavy metals and PAH involves alteration in DNA repair

Deficiencies of DNA repair system was observed to contribute to lung cancer in experimental mouse exposed to PM 2.5 found to contain high concentration of overall PAH and individual PAHs viz Benzo (b) fluoranthene, phenanthrene, Benzo (e) pyrene [102,103]. From this study, the authors indicated that PAH and heavy metals damaged the DNA directly by forming adducts or indirectly through oxidative stress as they clearly linked deficiency of DNA repair system with lung carcinogenesis [102]. Both nitro and oxy-PAH which are shown to be more mutagenic and carcinogenic than un-substituted PAH were identified and heavy metals such as Mn, Fe, Ni, Co, As and Cd were identified [102].

Sampling of mouse collected around coal mining areas showed accumulation of Cd, Cu, and Zn more than the other heavy metals measured in the liver. Expression of DNA damage response genes such as DDIT3 (DNA damage inducible transcript 3) increased and the increase

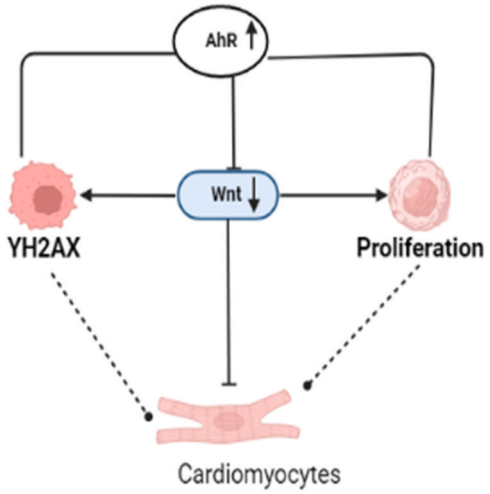

Fig. 1. AhR mediated differentiation of cardiomyocytes.

was linked to the high Zn content, which is known to be a component of important antioxidant defense proteins and DNA repair enzymes, a property that reinforces the role of Zn in the maintenance of genome integrity [104]. Overall pattern of gene expression in the study was linked to the mineral composition.

In an airway epithelial cell culture subjected to standard comet assay for DNA damage assessment after treatment with PM 10 dominated by six membered ring PAH and heavy metals like lead, zinc, chromium, cadmium and nickel, the amount of DNA in the tail as well as the tail moments significantly increased [40]. It was obvious from the study that components in the particulate samples could elicit significant genotoxic effects even under low concentration. It was demonstrated that high particle bound compounds most especially carcinogenic heavy metal and PAH induced DNA damage and can impact genotoxic effects leading to aberrant gene expression along with genetic mutation. Interestingly, Kandy city in Sri Lanka, which was the source of particulate matter used in the study, have increased incidence of lung cancers and other respiratory related diseases [105,106].

When particulate matters from indoor stove, fueled with either pellet, wood or charcoal, was tested on A549 cells (human lung cell epithelial cell lines), DNA strand breaks were evaluated by quantifying activated form of Ataxia telengiectasia mutated (P.ATM) and H2AX (phosphorylated histone) which reflects activation of DNA repair in cells [42]. Only the P.M generated by the pellet significantly increased P-ATM but H2AX slightly. This response was additionally linked to cell cycle arrest in G1 phase and cell death by necrosis. On the other hand, the PAH rich biomass, by inducing ROS could generate bulky adducts which are not recognized by the ATM whereas metals generating hydroxyl radical triggers accumulation of DNA strand breaks that finally activate ATM [107,108]. In summary, genotoxicity induction results in the activation of DNA repair mechanisms, however, heavy metals and PAH could modify this process to impair the repair of the damaged DNA.

2.7. Molecular mechanism associated with heavy metals and PAH toxicity

Having highlighted the link between activation of the AhR pathway by PAH and heavy metals in the initiation of their toxicity, the cross-talk existing between different pathways as well as the affected molecular signatures will be discussed in this section. It is also important to emphasize the estrogenic mechanism in the mode of contaminants induced cellular toxicity [109].

The estrogenic mechanism involved interference with the endocrine system and this is possible because of the estrogenic activity of environmental contaminant and as such be termed endocrine disruptors [110,111]. Darbre, (2018), has reviewed in detail the mechanism of endocrine disruption by environmental pollutants.

The sensitive mediators involved in the endocrine disruption process include the estrogen receptor (ER), aryl hydrocarbon receptor, Androgen receptor (AR), and thyroid receptor or glucocorticoid receptor (GR) [112-114]. These receptors have many roles including growth and development; energy homeostasis and reproduction. In addition, some physiology process such as cell proliferation and chemical detoxification relies on endocrine receptor mediated pathways. Upon interference with the normal physiological processes in these pathways by environmental pollutants, adverse health effects such as immunosuppression, altered neurodevelopment and reproduction and carcinogenesis can be unavoidable [1,2]. The unique role of AhR in chemical detoxification was highlighted in previous section, its dual role in the mediation of PAH toxicity was also presented. In addition to this, the activation of AhR receptor can trigger the induction of enzymes involved in hormone signaling and cell proliferation [115]. In tumor cells, independent of AhR ligands, AhR is often overexpressed and play critical roles in numerous stages of tumor progression. Zajda et al. [2] supported this explanation when COV434 cells and HGrcl cells were studied. From the study, AHR expression correspond with higher CYP1A1 and

catechol-O-methyltransferase (COMT) protein expression in tumor cells but lower expression of ARNT. Both COMT and CYP1A1 are xenobiotic detoxifying enzymes. The authors also showed increased level of lysophospholipid lysophosphatidic acid (LPA). The LPA is a receptor-active mediator involved in the promotion of cell motility, growth, and survival (Fang *et al.,* 2002; Luquain *et al.,* 2003a, b). Increased proliferation in cancer and non-cancer cells was associated with the up-regulation of lysosomal acid phosophatase activity, which is involved in the activation of LPA signaling.

Further consideration of the crosstalk between the AhR signaling and the oestrogen or androgen receptors was put forward for consideration because granulosa cells are expressed and regulated by activation of the oestradiol receptor [2]. Using in-vitro methods, it was evident that canonical and non-canonical AhR and endocrine mechanism of action in response to PAH could be cell line and chemical type dependent [2,113].

2.8. Mechanisms of cell death

Variation in cell death mechanisms of particulate matter has been associated to their chemical composition. Particles enriched with heavy metals cause cell death via the necrotic pathway while those enriched with PAH via early and late apoptosis [42].

Lead (Pb) on another note increased cell death percentage in rat lungs, decreased the expression of anti-apoptotic Bcl2 and increased RNA expression of TGF-α. Both TGF-α and Bcl2 are important modulators of apoptosis. In physiological state, apoptosis induction does not influence/induce inflammation, however, chemical toxins might cause leakage of intracellular content and stimulate inflammatory processes. Evidences from the report of Attaf et al. [116] showed that inflammation induction accompanied lung cell death. According to the authors, epoxide hydrolase (EphN) known to function in the detoxification of toxic epoxide intermediates was downregulated whereas CYPlAl was upregulated thus indicating the crosstalk between AhR and NF-kB signaling [116-118,2]. The intriguing fact remains that oxidative stress is involved in all this processes. For instance, redox sensitive signaling pathways such as the MAPK kinases, EPK1, JNK and the NF-kB cascade were all upregulated and in consequence cytokines and chemokines were produced [119–122]. Put together, activation of EPK1 and JNK molecules are important in inflammation, apoptosis, cell cycle, and immune response [123,124].

2.9. Cross talk between the AhR signaling and NF-kB pathway stimulate inflammation and oxidative stress process

Both NF-kB and AP-1 (Activator protein-1) were involved in the modulation of CYPlAl expression by heavy metals [20]. The authors in their previous study showed that heavy metals such as Hg^{2+}, Pb^{2+}, and Cu^{2+} decreased CYPlAl degradation through post translational regulation [6,20,125]. At first Hg^{2+}, Pb^{2+}, and Cu^{2+} increased ROS production in the Hepa lclc cells and expression of Hemeoxygenase-1 (HO-1) mRNA expression. The metals additionally depleted the GSH pool by binding to protein sulfhydryl group before eventual inhibition of antioxidant enzymes [6,20,125]. The GSH blockade aggravated oxidative stress and resultantly increased the metal mediated effects on CYPlAl activity thus connoting oxidative stress mediated mechanism of CYP1al expression modulation. The oxidative stress in addition triggers NF-kB and AP-1 activation and this potential was dependent on the capacity of each metal to alter redox status. It is a clear fact that both AhR and NF-kB crosstalk [126-128] and activation of NF-kB is observed to negatively modulate CYPlAl gene expression during heavy metal exposure. This discovery was achieved by either blocking or activating NF-kB and the resultant effects on nuclear AhR decrease or increase was determined. By inhibiting upstream signaling activators of AP-1 such as JNK, ERK, P38MAPK, it was observed that JNK and MAPK are positive regulator of CYP1Al activity whereas, ERK was a negative regulator. Put together NF-kB and AP-1 signaling can function in the modulation of CYPlAl gene expression by heavy metals. Howbeit, activation of the NF-kB signaling has negative modulating effect whereas activation of AP-1 and MAPK signaling are required for the induction of CYPlA1 gene by the heavy metals [46].

As previously described, AP-1 activation is under the influence of MAPK, family of proteins such as C-jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) and P38. The MAPKK4 specifically activates JNK and P38 and are regarded as important metastasis suppressor in different organs [129,130]. In fact, they appear as possible target for small ligand inhibition in therapies for TNF-α mediated disease [131].

In HepG2 cells, both B(a)P alone and mixture of PAH in particle extracts increased the activation through phosphorylation of JNK with no resultant effects on total JNK concentration, ERK phosphorylation and P38 phosphorylation [13]. In tandem with JNK activation, there was downstream increase in the phosphorylation of ATF2 (AP-1 transcription factor 2 and cJun, which are important proteins that form part of AP-1. The activation of JNK and AP-1 were both under the influence of MEK4 (MAPK kinase 4) because siRNA interference against MEK4 was accompanied by significant signaling reduction through JNK, ATF2 and cJun [13]. In addition, the JNK was established as the mediator of AP-1 activation when the inhibition of JNK also resulted in reduction of activated cJun, and ATF2. Genes under the transactivation of MAPK signaling and are involved in stimulating inflammation, apoptosis and proliferation viz; TNF-α, IL-8, TNF receptor superfamily member 6 (TNFR 6 or FAS) and EGFR (Epidermal growth factor receptor) were all upregulated in response to JNK activation (Fig. 2). Inhibition of the JNK resulted in down regulation, thus establishing the involvement of the JNK pathway and consequently MAPK as upstream signaling pathway for JNk activation [13]. It is clear that the cellular stress signaling due to nano molar (nm) PAH exposure involves the MEK4/JNK/AP-1 pathway.

In both human and mouse lungs exposed to cigarette smoke, apart from the activation of the xenobiotics/AhR receptor and oxidative stress

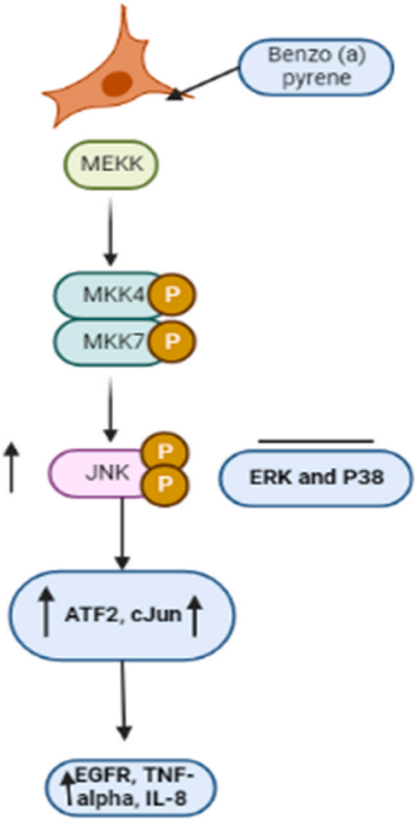

Fig. 2. Mechanism of PAH mediated inflammation via the MEKK Pathway.

defense/generation, the lipid/phospholipid metabolism and degradation were activated [15]. In this regard, the genes coding for phospholipases that hydrolyzes phospholipid into fatty acids to release modified lipids such as the arachidonic acid and second messengers that can stimulate intracellular signaling [15,16]. Sum up of these processes can result in immune cells activation and promotion of inflammation.

Kalkhof et al. [14], additionally identified alteration in the amino acid and carbohydrate metabolic processes due to benzo(a)pyrene in murine liver cell (Hepalclc7) by enrichment analysis. Aside the common inflammatory and oxidative stress signatures, energy metabolism were also affected. The authors observed some variation and similarities in the amount of cellular amino acids after subtoxic and toxic dose of B(a)P.

They monitored the early, mid and late changes in these signatures during the period of exposure. Glycine, serine, methionine and glutamate which are necessary in glutathione formation were found at maximum level during the 12 hrs measurement in the toxic B(a)P concentration exposed cell. In support of this observation, glutathione became depleted at the 24 hrs exposure duration. Also at this time, glutathione dependent protein such as glutathione S-transferase, were also upregulated [14]. A switch from glycolytic to oxidative phosphorylation as primary energy source was observed during the late hours [14]. This process was accompanied by higher level of glycolytic signatures. In numerous cancer cells, increased glycolytic process has been related to high-energy requirement of rapidly dividing cells.

All this crosstalk ranging from the affected cell division, proliferation, apoptosis, inflammation, oxidative stress, metabolism, and xenobiotic stress response signatures were explained by enrichment analysis (Fig. 3).

In another context, gene enrichment analysis of blood transcriptome after real life exposure of Wister rats to water soluble metals and particulate matter of different sizes showed differentially regulated genes involved in biological pathways such as inflammatory response pathways that may lead to carcinogenesis, cell cycle and apoptosis [132]. Specifically, MAPK signaling, p53 pathway, NF-kB signaling, T-cell receptor signaling pathway, TGF-β receptor pathway, and Myofibroblastic activation pathway of hepatic stellate cells recorded a number of altered genes involved in their processes. Most important from the study is the downregulation of prokinetisin-2 (PROk2) gene which is a member of prokineticin gene family that has been associated with certain physiological processes such as neurogenesis, angiogenesis, smooth muscle contraction, circadian rhythm regulation and reproduction [133]. The deregulation on the other end has been observed in cancer, ischemia, and neurodegeneration. The signaling pathways of prokineticin appear

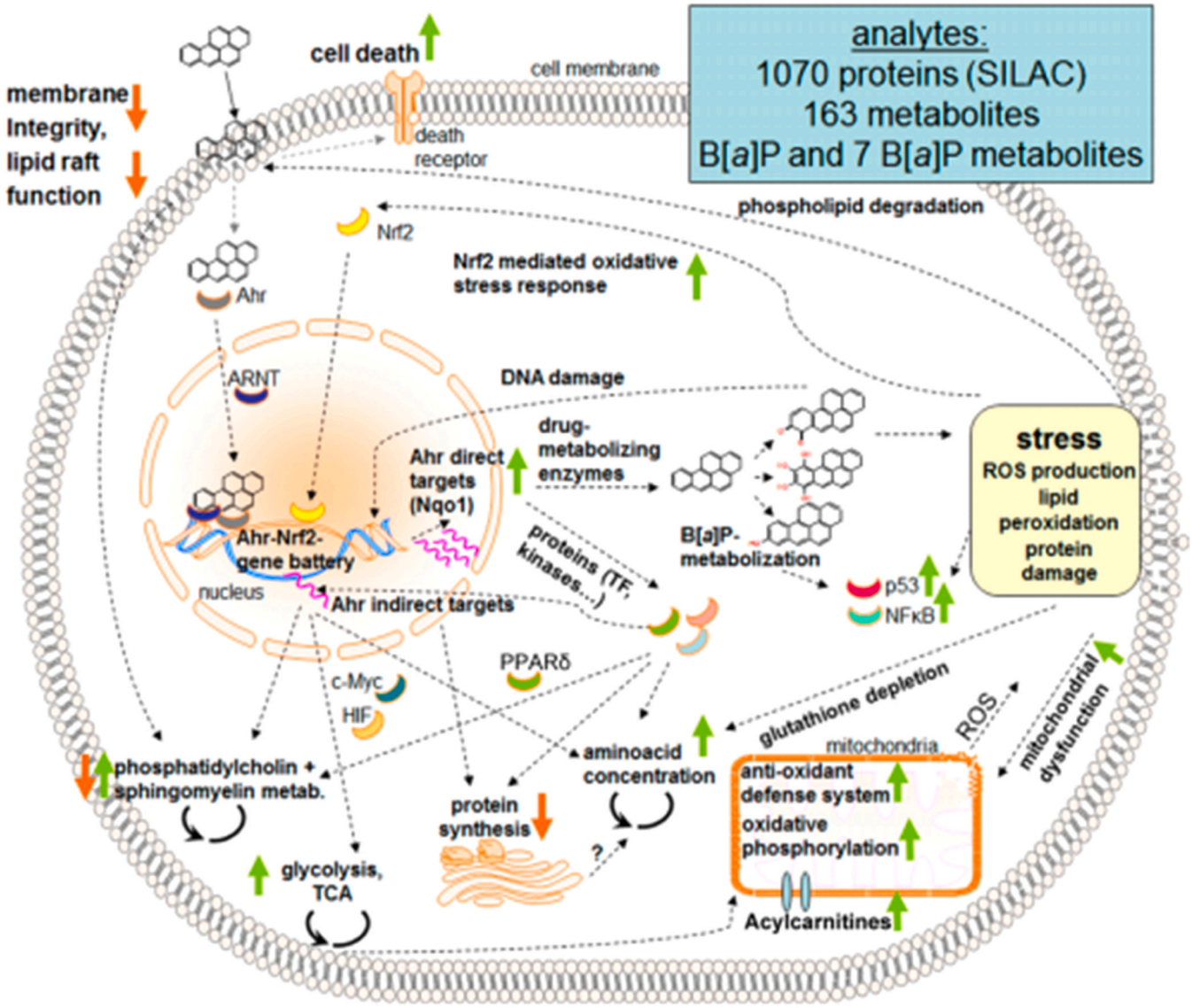

Fig. 3. Enrichment analysis of cell division, proliferation, apoptosis, inflammation, oxidative stress, metabolism, and xenobiotic stress response signatures [132].

to be a promising therapeutic target, more recently [134]. In PROK2 and PROKR2 knockout mice showed the involvement of specific phenotypes of the genes in development disorder that is characterized by impaired development of gonadotropin releasing hormones, neurons and infertility.

In a bid to reveal the possible mechanism of environmental contaminants in form of particulate matter related carcinogenesis, Kumar *et al.* [135] performed a toxic proteomic analysis of human lung epithelial cells exposed to steel industry ambient particulate matter. It was observed from the study that oxidative stress, which could lead to DNA damage and tumor related changes, was induced. In addition, the lowered cellular metabolism and energy production observed could reduce the systemic ability to overcome stress. The disequilibrium in the DNA damage and cellular repair ability can be consequential, resulting in genomic instability, which could drive carcinogenesis. Proteins involved in transcription and translation that elevates expression includes the POLR2C, POLR2A, POLR2H and POLR1C which are DNA directed RNA class II polymerase, some mRNA processing proteins were also upregulated as well as ribosomal proteins that function in apoptosis, DNA repair and oncogenesis (Fig. 4) [135,136].

In the concluding note, Kumar, *et al.* [135] inferred that the PAH and metals rich PM that was used affected energy metabolism and this could alter certain physiological response associated with normal cellular defense function. Chemicals vary in their toxicity efficacy and the concentration of each can reflect the severity and cellular response [5,7,8,10,11]. In rat hepatoma derived cell line (H4-II-E-C3) a concentration dependent effect was observed for chromium, cadmium, and nickel when Permenter et al. [8] attempted to identify the unique and common mechanism of toxicity for the three metals. For the three metals, oxidative stress, DNA damage, apoptosis, hypoxia and energy regulation signatures were all recognized. Interestingly, oxidative stress was a common cellular response to the three metals. However, the cells responded in a more subtle way to each of the metals. For instance, modulation of genes involved in glutathione production was evidence with nickel whereas, ROS induced endoplasmic reticulum (ER) stress was obvious with cadmium [8]. ER stress can lead to apoptosis and the data provided by the authors supported the claim in the cadmium-exposed cells. Nrf2 was activated in the case of these metals and key controlled genes such as Hmox1, sqstm1 and glutathione S-transferase, although, chromium showed the lowest level of induction [8]. Hmox1 is a ubiquitous stress response protein that functions in reducing oxidative stress and apoptotic effects [137]. Sequestosome 1 (SQSTM1) is useful for the sustained activation of Nrf2 also in response to oxidative stress [138]. Some other regulated genes apart from Nrf2 included Haol which was down regulated by the three metals, only cadmium showed enrichment for NFIC and FKHR while HSF1 and ATF-4 was common to both nickel and cadmium. HAO1 is liver specific and it converts α-hydroxy acid to α-keto acid with O_2 reduction to H_2O_2. The transcription of it is said to be downregulated in oxidative stress [139]. FKHR normally stimulate antioxidant metal proteins involved in antioxidant response [140] while HSF1 decrease oxygen radical regeneration to prevent further damage [141].

Apart from the common/shared responses, each also demonstrated some unique toxicity response in the hepatoma cells. Nickel was unique with hypoxic response, perhaps by disrupting chromatic structure [8]. Cadmium disrupted the retinoic acid signaling while chromium uniquely caused DNA damage. Retinoic acid is a hormone like molecule involved in cell differentiation and proliferation. Transcription factors including vitamin D receptor (VDR), retinoid family receptor gamma, and alpha, were also enriched in response to cadmium [8].

Specifically for nickel, the hypoxic response ontology bin (HIF-1α) pathway and transcription factor were enriched. HIF-1α is a transcription factor which controls /induce transcription genes involved in apoptosis, glucose transport, glycolysis and cellular processes affected by changes in intracellular oxygen concentration [142,143]. The glycolysis/gluconeogenesis canonical pathway and energy regulation bins that were enriched could also have been influenced by the HIF-1α. Certain caveats provided in the study might be related with the concentration of metals used and some limitations associated with the study [8].

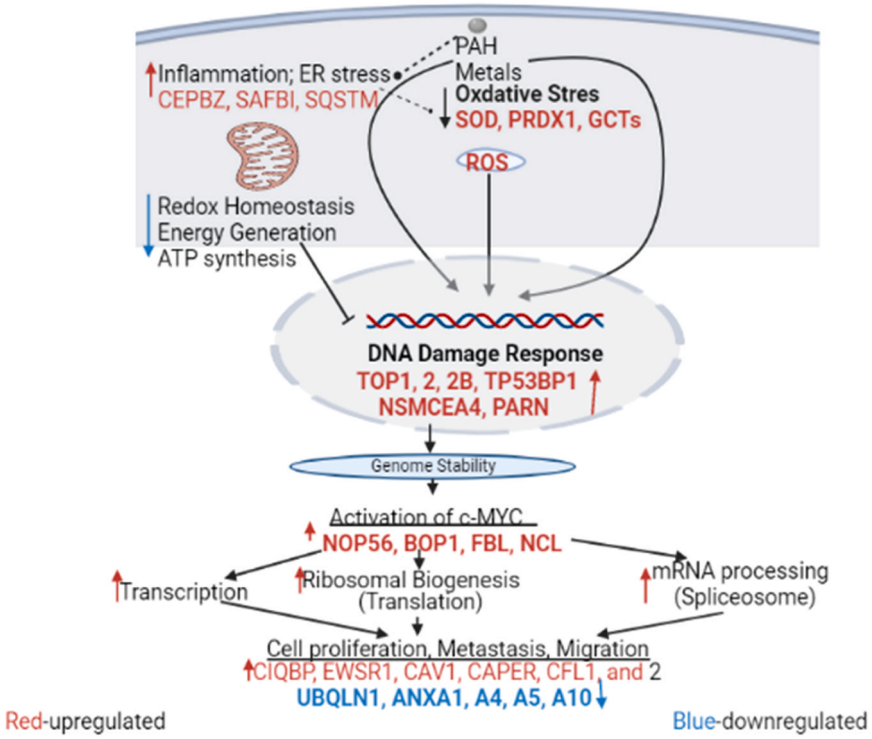

Fig. 4. Pathway illustrating the mechanism of toxicity of heavy metals and PAH.

2.10. Mitochondria damage is involved in heavy metals and PAH induced toxicity

Recognizing the unique role of the mitochondria in energy metabolism and being a major target during energy depletion, it is not just hypothetical to link energy degeneration to mitochondria dysfunction. There are adequate evidences to support mitochondrial damage as a key event associated with chemical toxicity [144,145,10,146,147]. During pathological and ultrastructural damage in heart, mitochondrial swelling and cristae disorder was observed by Li et al. [145] and in human SII-SYSY cells by Wang et al. [146]. Wei et al. [148] also found abnormal alterations of alveolar macrophage mitochondrial structure such as swelling, cristae disorder, and vacuolation. Decreased mitochondrial membrane potential and increased O_2 radical could initiate apoptosis and down regulate ATP generation with evidence in RAW 264.7 and alveolar macrophage cells [144,149] . Mitochondrial swelling as well as disruption of cristae can cause membrane rupture and dysfunction [150,151].

Mitochondria population decreased with increasing concentration of particulate matter 2.5 and the expression of mammalian mitochondria fusion genes; OPA1, mfn 1 and mfn 2 were increased. The mfn 1 and mfn 2 are located on the outer mitochondrial membrane whereas the OPA1 is located in the inner membrane [152,153]. Sum up of the process resulted in mitochondrial morphological damage and depletion in the mitochondrial population [148]. Evidence from human bronchial epithelial cells (BEAS-2B) exposed to heavy metals and organic rich particulate matter 2.5 showed that reduction in cell viability was associated with the inhibition of ATP synthesis through oxidative phosphorylation signaling. From the results, four enzymes involved in ATP synthesis, ATP5F (ATP synthase F subunit), COX7A (Cytochrome C Oxidase subunit 7A), NDUF (NADH dehydrogenase ubiquinone 1), UQCR (Ubiquinone-cytochrome C reductase complex subunit) and ATP itself was downregulated. This observation was accompanied by upregulation of RIP3 (receptor-interacting protein 3) a necroptosis indicator and two genes; ReLA (p65, a subunit of NF-KB), and CAPNI (calpains) involved in necroptosis were upregulated [154].

2.11. Heavy metal and PAH toxicity; influence of small/non-coding RNAs

Many cancer-causing environmental chemicals are characterized by their ability to cause genetic damage as a mode of toxicity; however, it has become glaring that without necessarily altering nucleotide sequence or inducing mutation, genes could be regulated to perturb normal function and result in disease pathogenesis. Epigenetics modulation by environmental chemicals is actually not a new area of study for better understanding of mechanisms including alteration of DNA methylation, histone modification, and non-coding RNA expression underlying chemical toxicity. Epigenetics generally represent gene regulations that are not associated with alteration in DNA sequence (mutation). These gene expression controls occur at both transcriptional and translational levels [155,37,156-158].

Given the contribution of ncRNAs in a wide range of pathological and physiological processes, they are among the epic epigenetic markers in the environmental health studies since they link biological effects and health outcome to environmental exposure [37,3,156,159,160].

ncRNAs comprises generally three types of RNAs which participate in the regulation of gene transcription, protein expression, protein complex assembly and activity but do not themselves encode protein [156,161]. They fine tune expression in response to various stimuli including external stimuli such as environmental toxicant [162]. The three RNAs include the micro RNAs (miRNA) comprising highly conserved family of approximately 22 nucleotide sequence that regulates post-transcriptional gene expression [163,161,155,164,156], either by translational suppression or degradation of target mRNAs [37, 165].

The long non-coding RNAs (lncRNAs) on the other hand have a sequence of over 200 nucleotides. They are localized in the nucleus or cytoplasm and regulate expression of genes through either contact with the target RNA and DNA or protein assembly and activity [156].

The third non-coding RNAs are the circular RNAs (circ RNAs) and are unique in that their structure shows a closed continuous loop style yet without 5'-3' polarity and the polyadenylated (polyA) tail. Their gene expression regulation function could be at the transcription or post transcription level [156]. Contrawise to the protein noncoding function of circRNAs, Pamudurti et al. [166] recently found some circRNAs coding for protein.

Studies highlighting the role of miRNA in the control of gene expression were predominantly based on gene silencing through translational repression and mRNA (messenger RNAs which are protein coding RNAs) degradation [167]. Clear evidences have additionally revealed the ability to induce transcription and translation [168,169]. These findings clearly shows that miRNA have a double-edge function that could include both the activation and silencing of gene expression. In addition, based on the circulating data in literature, it appears that miRNAs can be useful molecular biomarker in the diagnosis and prediction of diseases. Many of the studies have analyzed the expression levels of some of these miRNAs and evaluated their utility as biomarkers of environmentally mediated diseases [170-179]. Away from the common view with respect to mechanisms of environmental contaminants such as heavy metals and PAH to involve alteration of redox status, perturbation of inflammation and alteration of mitochondrial function, these environmental chemicals may exert their toxic effects through epigenetic mechanisms such as aberrant expression of miRNAs [155, 180-182,178].

In this review, we will attempt to identify specific ncRNAs affected by exposure to heavy metal and PAH (Table 3). The downstream effects mediated upon ncRNA expression will be characterized to understand their role in disease development and possible therapeutic advantage that could be annexed. Specifically, repression or expression of each ncRNA type will be noted and directly linked with the associated endpoint effects in cell culture and in-vivo system.

Variability in the expressed ncRNA type and level may be linked with the types of environmental stimulant. For instance, plasma alterations of miR-211, miR-572, miR-520c-3 and miR-148a was associated with increased lead exposure [191] whereas, negative relationship was observed between lead exposure and miR-146a (Table 3) [192]. According to Ochoa-Martínez et al. [188], women exposed to lead showed increased miR-155 level in serum whereas the level of miR-126 diminished. In another study, miR-155 in the carp head kidney-derived leukocytes increased after lead exposure [193] and also in serum of occupationally Pb exposed workers [194]. As a multifunctional non-coding RNA, miR-155 is associated with wide variety of pathological processes such as those related with inflammation, cardiovascular events, autoimmunity, cancer, and neurodegenerative diseases [195-198]. Specific mechanism of lead induced expression of miR-155 and miR-126 could involve generation of reactive oxygen species, DNA damage and inflammation [199-202] however, the exact perturbed pathways involved in this lead induced epigenetic changes needs to be further elucidated.

In acute myeloid leukemia [203,204] Alzheimer's diseases [205] and coronary heart disease patients [206], over expression of miR-155 level was observed in comparison to healthy controls. High expression of miR-126 in endothelial cells and hematopoietic progenitor cells is associated with physiological function of the cells [207-209]. Altered expression however is linked with impairment in carcinogenesis and inflammation. Alatas et al. [210]; Batra et al., [211]; Meister and Schmidt *et al.* [212], revealed altered expression in cancer, cardiovascular diseases, inflammatory disorders, psoriasis, and type-2-diabetes. In this respect, low level was found in association with type-2-diabetes mellitus, cardiovascular disease development, hypertension, and colorectal cancer [208,213-215].

Table 3
Some of the altered ncRNA and their targeted pathways during exposure to environmental contaminant.

Chemicals	NcRNA	Observation	Level of Exposure	Cell/Organism	Type of study	Tissue	Targeted Pathways/Effects	References
Manganese	MiR-16	Increased expression	50 μg/day for 7 days, 300 μM	Mouse and dopaminergic cell model (MN9D)	*In-vivo* and *In-vitro*	Brain	α-Syn and transferrin receptor 1 (TFR-1)	[183,184]
	miR-128	Increased expression	300 μM	dopaminergic cell model (MN9D)	*In-vitro*	Brain	ERK2 expression and regulation of autophagy-lysosome pathway	[183,185]
Arsenic	miR-210	Decreased expression	2 μmol/L	*In-vitro*	Immortalized human lymphoblast cell line (TK6) cells		Pathway of folic acid synthesis	[186]
	miR-22	Increased expression	2 μmol/L	*In-vitro*	Immortalized human lymphoblast cell line (TK6) cells		Pathway of folic acid synthesis	[186]
Cadmium and cigarette smoke	miR-101	increased expression		*In-vivo*	Mouse	Lungs	Repression of cystic fibrosis transmembrane regulator (CFTR) protein	[187]
Cadmium and cigarette smoke	miR-144	increased expression		*In-vitro*	Human airway epithelial cells	Lungs	Repression of cystic fibrosis transmembrane regulator (CFTR) protein	[187]
Lead	miR-155	Increased expression	N/A	*In-vivo*	Human cross sectional cohort study		carcinogenesis, oxidative stress and inflammation,	[188]
Benzo(a) pyrene	linc00673	Increased expression	0, 0.5, 2, 8, 32 μM	*In-vitro*	Non-human lung cancer (A549) cell line	Lung	Altered E-cadherin pathway and caused lung cancer metastasis	[189]
Lead	miR-126	decreased expression	N/A	*In-vivo*	Human cross sectional cohort study		Carcinogenesis, cardiovascular diseases, inflammation, and psoriasis	[188]
Arsenic	miR-21	Increased expression	N/A	*In-vivo*	Case control cohort		Albuminuria	[190]

N/A: not applicable

Certain miRNAs classified as inflammation regulating miRNAs most likely because of their influence on the expression regulation of pro-inflammatory genes [216,217] include miR-222, miR-21, miR-146a, miR-26a, miR-187, miR135a and miR-155 [192,218,219]. Some of these ncRNAs were associated with regulation of inflammation and target pro-inflammatory genes among children exposed to particulate matter [220]. Although contrasting evidence in the expression of miRNA due to PM 2.5 exposure are numerous in the literature.

In children, Li et al. [220] showed positive association between the expression of Let-7a, miR-146a-5p, miR-21–5p, miR-155–5p and miR-146b-5p and PM exposure level indicated by benzo [p] pyrene-r-7-, t-8,t-9,c-10-tetrahydotetrol-albumin adducts (BPDE-Alb). Consistently with previous report by Yamamoto et al. [221] who found upregulation of miR-21–5p in post exposure blood samples. Contrary to these observations, elevated time-weighted PM 2.5 concentration was associated with downregulation of miR-21–5p and miR-146a-5p [218] in young adults. Also, in elderly men, miR-21–5p and miR-146a-5p was negatively associated with PM 2.5 exposure [219]. No significant relationship between PM exposure and miR-21–5p and miR-146a-5p in the study reported by Bollati et al. [192]. The discrepancies in the observations might be explained by exposure level, chemical composition of the PM, individual or age characteristics and exposure duration. For instance, among children, in accordance with increased expression of miRNAs that targets pro-inflammatory genes, the expression of IL-6, CXCL8 and TLR2 correlated negatively with BPDE-Alb [220]. Quite an observation that was also supported by the study of Dai et al. [222] who reported decreasing trend in IL-6, IL-8 and c-reactive protein trends with increasing diesel exhaust exposure duration. Long-term P.M 10 exposure duration was also negatively correlated with fibrinogen level [223]. This observation contradicts the traditional knowledge that PM exposure influences inflammation induction. A possible explanation for the unique behavior in response to chemical exposure in the children is that the immune system is not fully developed and may influence children to manifest different response from adults. In addition, exposure duration might significantly contribute to the response pattern due to PM exposure [220]. As shown by Li et al. [220], air pollution resulted in immune damaging effects among schoolchildren by decreasing C3, C4 and B-lymphocyte counts. Ultimately, long-term exposure to PM may result in immune suppression.

Even though PM is a complex mixture of chemicals, the heavy metals and PAH components have emerged as major contributor accounting for the observed effects on miRNA and mRNAs.

Manganese (Mn) treatment of wild type human α-synuclein (αSyn) expressing MN9D dopaminergic cell models of Parkinson disease stimulate expression of small RNA in the exosomes than in the exosomes of control cells. From the study, expression of miRNAs involved in the regulation of protein aggregation, inflammation, autophagy, and hypoxia were noted [183]. miR-7 and miR-153 for instance down regulates α-Syn expression [224,225], but the inhibition of miR-34b, and miR-34c elevated α-Syn expression and the formation of α-Syn containing aggregates [226]. miRNAs are widely reported in the post-transcriptional regulation of α-Syn which is a major component of Lew bodies in PD.

miRNAs transfer between cells is possible through the exosomes as they have been identified in the exosomes [183]. By this means, they can mediate target gene repression in neighboring cells and stimulate disease progression [227,228]. According to Harischandra *et al.* [183], expression of miR-16, a member of evolutionary conserved miR-15/107 family was upregulated. This family plays important function in cell division, stress response, neurodegenerative disease, metabolic and cardiovascular disease [229,230]. MiR-16 putatively targets α-Syn and transferrin receptor 1 (TFR-1) [184]. The transferrin receptor facilitates Mn uptake [231] and miR-128, widely expressed in postnatal developing brain was expressed in Mn treated Parkinson's brain cell [183]. The miRNA was reported in the regulation of the excitability of dopamine D1 receptor expressing neurons in the stratum through increased ERK2 expression, thus protecting against Parkinsonian motor deficits in mice ([232]. On the other hand, miR-128 represses transcriptional factor EB (TFEB) a regulator of autophagy-lysosome pathway [185].

The hypotoxic promoting miR-210 was also increased significantly in the Mn model of the Parkinsonism cells [183]. MiR-210 specifically decrease mitochondrial function by directly targeting cytochrome C oxidative assembly protein (COX10) which is involved in the

mitochondria electron transport chain, leading to the generation of reactive oxygen species [233] and consequent dysfunction of oxidative phosphorylation [234].

Because miR-325 is known to suppress the apoptosis repressor with caspase recruit domain (ARC), its upregulation might have important function in the biological cell. The ARC is an anti-autophagic protein and thus miR-325 might be a promoter of the autophagic cascade [235]. During TNF-α mediated inflammation, upregulation of miR-325 has been observed [236] and during hypoxia reoxygenation injury [235].

In the Mn treated cell, miR-325 was upregulated together with pro-inflammatory miR-125b and aging associated miRNAs (miR-450b and miR-669b) [237,183,238].

MiR-450b and miR-505 are already identified as diagnostic markers of PD [239] and were found expressed in the Mn treated cell [183].

Sodium arsenite exposure in immortalized human lymphoblast cell line (TK6 cells) caused repression of miR-210 but increased the expression of miR-22, miR-221, miR-349 and miR-222 under folate deficient condition [186]. From the study, the miRNAs altered due to arsenic exposure were similar to those altered due to folate deficiency thus giving credence to the fact that arsenic may operate by altering one-carbon metabolism and thus downstream epigenetic effects. Folate deficiency has implication on S-adenosyl methionine, which is ultimate for cellular methylation reactions including those of proteins, DNA and Histones. Arsenic on another end has evidently been proven, since its excretion process involve metabolism through methylation, and can alter the availability of methyl-donor pool in cells [240].

Similarly in human after exposure to mercury (Hg), Lead (Pb), arsenic (As), and cadmium (Cd), miR-21 level was associated with urinary arsenic and lead level and microalbuminuria [190]. From all indication, it was evidenced that miR-21 is involved in the pathologic mechanism of albuminuria.

In the human airway epithelial cells, increased expression of miR-101 and miR-144, which are known suppressor of cystic fibrosis transmembrane regulator (CFTR) protein, was observed after cigarette smoke and cadmium exposure. In the lungs of mice, miR-101 was similarly upregulated due to cigarette smoke. Thus, there is a link between cadmium, cigarette exposure and CFTR suppression during chronic obstructive pulmonary disease [187] and this suppression might be via epigenetic mechanism.

From the report of Wu et al. [189] a long non-coding RNA was observed to be involved in benzo(a)pyrene induced migration, evasion and epithelial-mesenchymal transition (EMT) in A549 cells. The effects of BaP on A549 cells were likely prompted through inhibition of major epithelial biomarker of E-cadherin. The inhibition of AhR reversed the upregulation of linc00673 indicating that upregulation was AhR dependent. In addition, when linc00673 was silenced, migration, invasion, and EMT in A549 cells was abated thus showing epigenetic mechanism of BaP induced lung cancer metastasis.

Polycyclic aromatic hydrocarbon as a major constituent of organic components of coke oven emission is commonly associated with occupational toxicity among coke oven workers. This exposure is widely associated with cardiopulmonary diseases [241] and consequently prompted Huang et al. [159] to evaluate the association of PAH related miRNAs and heart rate variability (HRV). From the report, the level of miR-24–3p, miR-320b and miR-27a-3p was associated with HRV in workers with intermediate PAH metabolites. In the account of Deng et al. [58]; Deng et al. [3] certain PAH and metals associated with miRNAs were found in connection with chromosome damage, oxidative DNA damage and dose response decrease in oxidative lipid peroxidation in form of 8-isoprostaglandin-F2α (8-iso-PGF2α). Increased miR-27a-3p and miR-28–5p were found in association with the increase in 8-OHdG levels whereas, 8-iso-PGF2α decreases with increases in the miR-24–3p, miR-145–5p and miR-28–5p was associated with the level of both 8-OHdG and 8-iso-PGF2α.

From all indication, the plasma level of the miRNA had different influences on oxidative DNA damage and lipid peroxidation. This expression was associated with a dose-response increase in oxidative DNA damage but decrease in lipid peroxidation most especially in coke oven workers with lower PAH exposure levels.

Deng et al. [181] found lower expression level of miR-24–3p, miR-27a-3p, miR-142–5p and miR-28–5p but increased expression of miR-150–5p among workers exposed to PAH. The authors related the miRNA level with PAH exposure and frequency of micronucleus. The miRNA expressed in the studies have different functions, for instance, miR-24–3p can negatively regulate ARNT and the downstream gene, CYPlAl thus affecting the metabolism of PAH [242]. In addition, it can negatively regulate the double strand break repair gene (H2AX) [243-245], therefore, upregulation of miR-24–3p might decrease DNA repair activities and increase vulnerability to oxidative DNA damage. MiR-27a-3p on the other hand is an inhibitor of PPAR-γ; inhibition of PPAR-γ may repress antioxidant gene activation and improve the activation of pro-oxidant genes [246].

2.12. *Effects of heavy metals and PAH on Histone modification and DNA methylation*

Aside the changes usually observed in the expression of small RNAs, epigenetics changes such as Histone modification and DNA methylation changes [188] are prominent among the mechanism by which chemical substances onset the develop of several disease [247-249].

According to Ren et al. [250]; Hubaux et al. [251]; Miao et al. [252], arsenic exposure was reported to alter normal DNA methylation pattern with consequent implication in malignant transformation. Whereas, mixture of heavy metals and PAH decreased telomere length and increase DNA methylation [253]. In addition, post translational modification of Histone such as methylation, acetylation and phosphorylation after exposure to PAH triggers chromatin structure modulation [254, 220,118,255], and also induced methylation of mitochondria DNA [256]. Various effects of PAH on histone and DNA methylation as reported included suppression of Histone methyltransferase Dot 1-like protein [257], Long Interspersed Element-1 (LINE-1), and O6 methylguanine-DNA methyltransferase (MGMT) [258].

In a cross-sectional human study, P.M. 2.5 from coke oven plant decreased DNA methylation and suppressed DNM T3B (DNA methyl transferase 3B) expression. Among the metals and PAH constituents characterized in the urinary sample of the exposed subjects, PAHs and Ni were associated with the DNA hypomethylation [259]. Similar decrease in H3K79 di-methylation among coke oven workers exposed to coke oven emissions, was reported, the methylation decreased by 29.3% relative to control subjects [257]. Decreased methylation of histone was related with severity of DNA damage in the subjects. In an *In-vitro* model, inhibition of H3k79 Histone methyltransferase Dot 1-like protein (DOTIL) resulted in the inhibition of H3K79 di-methylation in immortalized human bronchial epithelial cells after treatment with benzo[*a*] pyrene and consequently aggravated DNA damage [257].

(OUP-accepted manuscript) correlated the decrease in the methylation of long interspersed element-1 (LINE-1) and O6 methylguanine-DNA methyltransferase (MGMT) with the enhanced trimethylated Lys 36 of Histone H3 (H3k36me3) expression. The authors showed a synergy between Histone modification and DNA methylation in the induction of DNA damage.

On the contrary, hypermethylation of FMS related tyrosine kinase 1 (FLT1) is usually observed in many cancers [260] and increased hypermethylation of FLT1 in primary human lymphocytes upon treatment with benzo[*a*]pyrene and among workers exposed to coke oven emission (PAH) showed it possible involvement in PAH mediated malignant cell transformation. FLT1 is suspected to be a tumor suppressor, and it hypermethylation might result in loss of function [260].

Chromium equally crosslinks Histone deacetylase 1-DNA methyltransferase 1 (HDACI-DNMTI) complexes to CyPIA1 promoter chromatin as well as induced phosphorylation of Histone H3 Ser10 trimethylation of H3 Lys-4 and various acetylation marks in Histones H3

and H4 with consequent inhibition of RNA polymerase II recruitment [261]. The epigenetic changes due airborne particulate matter is reviewed in Sun et al. [262].

3. Conclusion

The present study is a detailed review of the metabolism and the toxicity mechanisms of environmental concern chemicals. Rather than exposure to single environmental concern chemicals, real life exposure is characterized by mixed composition of concern chemicals. This composition therefore defines the presence and severity of toxicity. The constituent of the chemical exposed to greatly influence their toxicity, for instance, the presence of nutritional essential elements such as zinc and selenium can lower the severity or even abolish the toxicity of toxic heavy metals, while the mixed composition of PAH might either increase or lower the severity of toxicity depending on the types and ratio of composition. From observation, environmental chemicals can be inert and may require metabolic activation to become toxic. Because mixed composition of PAH may result in competition for the binding site on Ah receptor; severity of high molecular weight PAH might be lowered by the low molecular weight PAH. In addition, multiple pathways activated during toxicity also reflect the multicomplex process of chemical toxicity effects of environmental concern chemicals.

It was evident from this study that environmental concern chemicals caused oxidative DNA modification to induce genotoxicity effects and at the same time alter the DNA repair mechanisms. It was also clear that the cross talk between the AhR and the NF- pathways is involved in the heavy metal and PAH induced inflammatory and oxidative stress process with consequent activation of diseases aetiology. In addition, mitochondria damage is a major effect of heavy metals and PAH exposure bringing about decreased energy metabolism and activation of cell death signals.

Finally in this review, it was clear that metal and PAH could alter gene expression via epigenetic mechanism. Different non-coding RNAs have been identified to be involved in disease pathophysiology either by their suppression or by up-regulation. Similarly, decrease DNA methylation and histone modification are major players in heavy metals and PAH mediated toxicity. While the suppression of some specific sRNAs has been reported in disease, up-regulation of some is reported in disease development. However, both the repression and up-regulation of some of the ncRNAs, depending on the tissue might result in disease development.

Authors contribution

Peter Adegbola; sourcing of material, writing of draft, Adewale Adetutu: reading of draft.

CRediT authorship contribution statement

Peter Adegbola: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Adewale Adetutu:** Writing – original draft, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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