Molecular Mechanism of Early-Life Chemical Exposure-Induced Harmful Effects

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1 Introduction

Early developmental stages are more sensitive to environmental chemicals, such as nicotine, ethanol, heavy metals, endocrine disruptors, pesticides, and so on [1]. Accumulating data have demonstrated that exposure to environmental chemicals in early life produces short-term and long-term harmful effects, such as metabolic diseases, neurodevelopmental defects, male infertility, etc. [2–4]. Other works further identified intergenerational and transgenerational effects of environmental chemicals [2, 5]. On one hand, some chemicals enter fetuses and neonates across either placental or blood milk barriers and directly impair fetal and neonatal development. On the other hand, early-life chemical exposure causes indirectly toxic effects via impairing placenta or germlines. In the past decade, great progress has been made in molecular mechanisms by which early-life chemical exposure induces adverse health outcomes later in life. This chapter will summarize the role of genetic mutation, epigenetic alterations, oxidative stress, inflammation, and glucocorticoid on the latent effects of early-life exposure.

2 Genetic Mutation

Genetic mutation refers to the processes that chemical agents alter genetic information. There is more and more evidence indicating that early-life exposure to chemicals can induce genetic mutation. An epidemiological study showed that higher arsenic exposure elevated micronucleus content in peripheral blood

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Y. Xia (ed.), *Early-life Environmental Exposure and Disease*,
https://doi.org/10.1007/978-981-15-3797-4_13

lymphocytes from children [6]. Another study found that maternal smoking during pregnancy was positively associated with DNA damage in lymphocytes of their newborns [7]. Later animal experiment demonstrated that early-life exposure to cadmium induced DNA damage in embryos of terrestrial snails [8]. A recent experiment found that early-life exposure to dichlorobenzoquinone elevated the level of 8-hydroxydeoxyguanosine in zebrafish [9].

Genetic mutation plays a key role in chemical-induced developmental toxicity. According to a recent study, gestational exposure to ethanol caused deficits of bone development mainly through osteoblast DNA injury and micronucleus formation in neonatal rats [10]. Moreover, prenatal co-exposure to copper and cadmium induced embryo spinal and cardiovascular deformities in *Oryzias latipes*, which was correlated with the increased DNA damage [11]. Another recent study found that developmental exposure to diethylstilbestrol elevated the incidence of uterine fibroids through altering DNA repair in myometrial stem cells [12]. An earlier research reported that ascorbic acid protected against cyclophosphamide-induced embryonic resorptions via inhibiting structural chromosomal aberrations in mice [13]. In addition, *N*-acetylcysteine alleviated cadmium-induced embryonic lethality through rescuing DNA mismatch repair in zebrafish embryos [14].

3 Epigenetic Alterations

Epigenetics was defined as heritable alterations in gene expression without underlying changes in DNA sequence. Increasing evidence has demonstrated that epigenetic modifications, such as DNA methylation, histone modification and noncoding RNA, play key roles in controlling gene expression through time- and space-dependent manner. Indeed, embryonic stem cells and their differentiated cells owned different biological functions due to selective gene expression affected by epigenetic modifications. During the embryonic development, cell differentiation and lineage commitment are determined by epigenetic reprogramming. Early-life exposure to toxic chemicals may disrupt epigenetic reprograming and cause persistent changes and even transgenerational impacts [15]. The Norwegian Mother and Child Cohort Study ($n = 1062$) showed that maternal smoking during pregnancy was associated with the differential methylation in AHRR, CYP1A1, and GFI1 in neonatal cord blood [16]. The Genome-wide Consortium Meta-analysis including 13 cohorts ($n = 6685$) found that over 6000 CpGs were differentially methylated in blood from newborns or older children whose mothers smoked during pregnancy [17]. An earlier animal experiment showed that perinatal nicotine exposure enhanced the susceptibility of HI-induced brain injury via DNA methylation of the AT2R gene in neonatal male rats [18]. Indeed, Pb-induced neurodevelopmental toxicity and subsequent epigenetic alterations was also a good example. This study found that early postnatal exposure to Pb markedly reduced the levels of DNMT1 and MECP2 in mouse cerebral cortex across life span [19]. In line with above data, an in vitro experiment showed that Pb altered the global DNA methylation profile in

human embryonic stem cells and subsequently impaired neuronal differentiation [20]. According to an observational study, gestational Pb exposure altered the DNA methylation profiles in fetal germ cells and persistently modified DNA methylation status in grandchildren's neonatal blood [21]. This group also found that Pb exposure in infancy upregulated H3K9Ac and H3K4me2 proteins (marks for gene activation) but downregulated H3K27me3 (marks for gene repression) in older primate and mouse brains [19, 22]. Additional study reported that miR-106b, which targeted the APP mRNA, was significantly reduced in the brain of mice whose mothers were exposed to Pb during lactation [23].

Epigenetic alterations in the germline, including sperm and egg, were essential for transmitting transgenerational effects. Numerous studies found that exposure to environmental chemicals in early life caused intergenerational and transgenerational effects, which was associated with epigenetic alterations in germlines [2, 24]. The earliest study reported that prenatal exposure to vinclozolin and methoxychlor, two environment endocrine disruptors, induced transgenerational actions of male fertility through altering sperm DNA methylation [5]. Consistent with alteration of sperm DNA methylation, Dnmt3a and Dnmt3l were altered in the testes of fetal rats (F1–F3) whose mothers were exposed to vinclozolin during pregnancy [25]. Further work found that alteration of sperm noncoding RNA, such as piRNAs, miRNAs and lncRNAs, and histone H3K27me3 methylation were observed in vinclozolin-induced epigenetic transgenerational inheritance of phenotypes [26, 27]. Recently, several studies demonstrated that sperm transfer RNA-derived small RNAs (tsRNAs) were involved in environment chemical-induced intergenerational inheritance of acquired metabolic disorders [4, 28].

4 Oxidative Stress

Oxidative stress results from imbalance between reactive oxygen species (ROS) overproduction and endogenous antioxidants. Excessive ROS causes oxidative injury to intracellular macromolecules, such as DNA, lipids and proteins. Accumulating evidence has demonstrated that early-life exposure to toxic chemicals triggers oxidative stress and even oxidative damage of intracellular macromolecules. An early report showed that urinary 8-hydroxydeoxyguanosine (8-OHdG) in infants was positively linked with cadmium level in both urine and breast milk [29]. Several animal experiments found that early-life exposure to dichlorobenzoquinone and cyhalofop-butyl triggered excess ROS production, upregulated activity of superoxide dismutase (SOD), and elevated the levels of 8-OHdG and malondialdehyde (MDA) in zebrafish [9, 30]. A recent study indicated that paternal arsenic exposure elevated MDA/GSH ratio in hypothalamic-pituitary-gonadal (HPG) axis of adolescent male mouse offspring [31].

Numerous studies have demonstrated that exposure to toxic chemicals induces oxidative stress in adult offspring. An early report showed that prenatal ethanol exposure caused hypothalamic oxidative stress and neuroendocrine alterations in

adult rat offspring [32]. Another early study indicated that prenatal co-exposure to ethanol and smoking impaired learning and memory abilities, which was associated with oxidative stress in cerebral cortex of adult offspring [33]. Moreover, antenatal nicotine exposure caused vascular dysfunction and enhanced oxidative stress in adult offspring [34]. Pretreatment with apocynin, an NAPDH oxidase inhibitor, and tempol, an SOD mimetic, improved vascular contractions in adult offspring whose mothers were exposed to nicotine in pregnancy [34]. Additionally, supplementation with MitoQ, a mitochondria-targeted antioxidant, protected against chronic kidney disease in adult mouse offspring whose mothers were exposed to smoking [35]. The modulatory subunit of glutamate cysteine ligase (GCLM) is the key enzyme of GSH synthesis. A recent study showed that Gclm KO mice were more sensitive to pharmacological stimuli as compared with WT mice [36]. Oxidative stress triggered by pharmacological stimuli in preweaning or pubertal Gclm KO mice reduced the number of parvalbumin-immunoreactive interneurons, but not in adult Gclm KO mice [36]. Further observation found that pretreatment with *N*-acetylcysteine reversed early-life stimuli-impaired parvalbumin interneurons via inhibiting oxidative stress in Gclm KO mice [36].

5 Inflammation

Inflammation is a biological response of immune system upon pathogens, damaged cells, or chemicals. The inflammatory process mainly includes vascular permeability changes, leukocyte recruitment, the release of inflammatory cytokines, the resolution of inflammation, and organ-specific inflammatory response [37, 38]. In response to inflammatory stimuli, acute or chronic inflammation occurs in target organs, potentially resulting in tissue injury and diseases [39]. Increasing data demonstrate that early-life exposure to chemicals triggers inflammation. A recent population study found that systemic inflammatory response of schoolchildren was associated with chronic exposure to air pollution [40]. Another population study reported that early gestational co-exposure to the mixture of phenols, phthalates, and metals was linked with altered inflammatory cytokines in maternal and neonatal blood [41]. Several earlier studies indicated that early-life exposure to endocrine-disrupting chemicals, including bisphenol A, caused inflammatory response in different target tissues [42, 43]. Later animal experiments demonstrated that early-life exposure to acetaminophen or 1-nitropyrene increased airway inflammation and susceptibility of allergic asthma in adult offspring [44, 45]. The NF-κB and MAPK are the key signaling pathways for modulating inflammatory mediators and cytokines in inflammatory cells [39]. A recent study indicated that prenatal LPS exposure caused activation of NF-κB signaling, resulting in prenatally programmed hypertension in adult offspring [46]. Moreover, maternal inflammation-mediated p38 MAPK activation predisposes offspring to heart injury caused by isoproterenol via augmenting ROS generation [47].

Various experimental studies have demonstrated that inflammation mediates the harmful effects induced by early-life exposure to chemicals. Maternal dioctyl sodium sulfosuccinate (DOSS) exposure during pregnancy elevated the circulating level of IL-6 and increased susceptibility of adiposity, metabolic disorders, and dyslipidemia in adult male offspring [48]. In utero exposure to lipopolysaccharide (LPS) increased the level of pro-inflammatory cytokines in the postnatal brain and caused the alteration of the glial cells in the developing amygdala [49]. Melatonin, an anti-inflammatory agent, protected mice from placental insufficiency and fetal cardiovascular compromise via downregulating IL-1β and TNF-α [50]. Supplementation with vitamin D3 inhibited IFN-γ production, thereby improving alveolar development in LPS-induced bronchopulmonary dysplasia (BPD) in rats [51].

6 Glucocorticoid Overexposure

Glucocorticoid (GC) is an adrenal steroid hormone that controls a variety of physiological processes such as development, metabolism, immune response, cardiovascular activity and brain function [52–54]. However, excessive GC exposure during pregnancy impairs fetal development. Indeed, increasing evidence has demonstrated that early-life chemical exposure may cause active GC overexposure. According to a birth cohort study in Chile, maternal urinary arsenic concentration during gestation was positively associated with the level of salivary cortisol in infants [55]. Several animal experiments demonstrated that prenatal exposure to caffeine or cadmium (Cd) caused fetal overexposure to active GC [56, 57]. An in vitro study confirmed that Cd downregulated expression of 11β-HSD2 and inhibited 11β-HSD2 promoter activity in human placental trophoblasts [58].

Numerous studies reported that early-life exposure to chemical caused abnormality in adult period maybe through excess exposure to active GC. Several studies showed that prenatal caffeine exposure increased circulatory GC level, changed peripheral glucose and lipid metabolic pathways, and caused hypercholesterolemia and osteoporosis in adult offspring [56, 59, 60]. Gestational ethanol exposure enhanced the susceptibility of offspring rats to glomerulosclerosis and hypercholesterolemia via programming glucocorticoid-insulin-like growth factor 1 (GC-IGF1) axis [61–63]. The Comparative Genomic Enrichment Method (CGEM) found that prenatal co-exposure to arsenic and cadmium altered the expression of glucocorticoid receptor (GR)-regulated target genes related to infectious disease [64]. Additional study found that cortexolone, a GR inhibitor, protected against arsenic-induced neural tube defects [65]. However, postnatal or perinatal exposure to toxic chemicals inhibits GC/GR signaling. According to a recent report, cigarette smoke during lactation lowered glucocorticoid level in male adult offspring [66]. Moreover, both perinatal exposure to arsenic and lactational exposure to benzpyrene reduced the level of serum GR in offspring [67, 68]. Indeed, GC reduction impairs the function of hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-adrenal (HPA) function, whereas the latter is the cause of

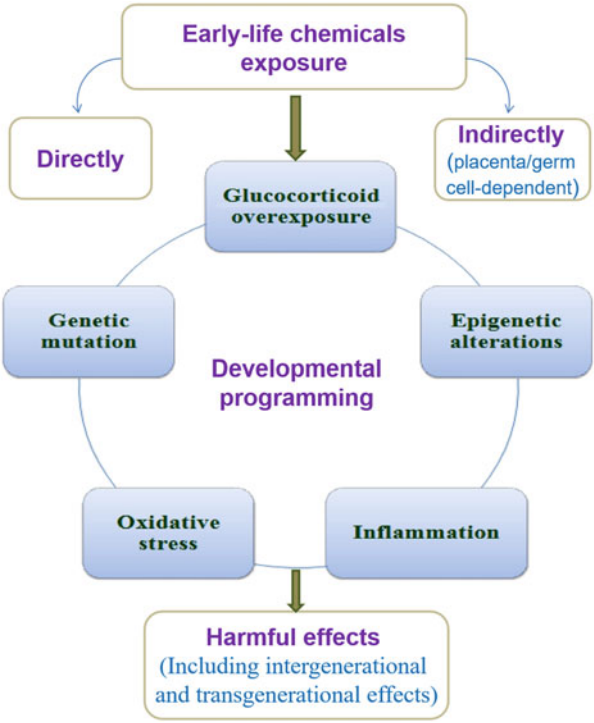

Fig. 1 Molecular mechanism of early-life chemical exposure-induced harmful effects

behavior alteration in rat offspring [69, 70]. Interestingly, gestational supplementation with betaine attenuates GC-induced hepatic lipid accumulation and activation of lipolytic genes in adipose tissue through epigenetic modification in adult offspring rats. In addition, postnatal supplementation with omega-3 fatty acid reversed GC-programmed adiposity, hypertension, and hyperlipidemia in high-fat diet-fed male offspring [71–73].

7 Conclusions and Future Prospect

The molecular mechanisms, such as genetic mutation, epigenetic alterations, oxidative stress, inflammation, and glucocorticoid overexposure, are involved in the harmful effects of early-life chemical exposure (Fig. 1). Although great progress has been made in the molecular mechanisms of early-life chemical exposure-induced harmful effects in adult period, further work is needed to elucidate following issues:

(1) The interaction among genetic mutation, epimutation, and other molecular mechanisms remains elusive, (2) the exact mechanism by which early-life chemical exposure induces intergenerational and transgenerational effects needs to be determined, (3) the mechanisms underlying enhanced disease susceptibility of offspring

to the second hit remain unclear, and (4) how to transform the molecular mechanisms into the predictive biomarkers remains uncertain. As above, additional work is required to explore the novel molecular mechanisms by which exposure to toxic chemicals in early life induces harmful effects in later life.

Acknowledgments This work was supported by National Natural Science Foundation of China (81930093, 81973079 and 81473016).

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