Review Article
ISSN (Print): 0971-6580
ISSN (Online): 0976-5131
Journal of Endocrinology and Reproduction, *Vol 25(1), 1-21, June 2021, DOI: 10.18311/jer/2021/28038*

Alterations in the Epigenetic Landscape Underlying Later-Life Health Effects Due to In-utero Exposure to Endocrine Disrupting Chemicals: A Review of Outcomes from Mice to Men

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Abstract

Widespread persistence of Endocrine Disrupting Chemicals (EDCs) in the environment has mandated the need to study their potential long-term effects on human health, after acute as well aschronic exposures. The particular focus is on *in utero* exposure to EDCs in rodent models to look at altered epigenetic programming to result in transgenerational effects in later life of the offspring. This potentially contributes to reproductive and immune dysfunctions, obesity, cancer, and altered brain development and neurobehavioral outcomes. The literature to date establishes the transgenerational effects associated with *in utero* exposure to EDCs in rodent models. Hence, the aim of this review is to provide a comprehensive overview of epigenetic programming and its regulation in mammals, specially focussing on epigenetic plasticity and susceptibility to exogenous endocrine-active chemicals, EDCs, during the early developmental period, and carried forward to later life using rodent models. The available reports suggest that the key mechanism behind the long-term impact of EDCs is caused by alterations in the epigenetic programming machinery, leading to dysregulated gene expression during adult life. Studies have reported the effect of prenatal exposure to EDCs in the ovarian microRNA expression and function, highlighting ovary as an organ undergoing *in utero* programming. It ascertains the heightened sensitivity of the organ to exogenous hormone-active compounds, particularly during early development. In addition to this, another key aspect in this review is increased susceptibility of the brain when exposed to even minute quantities of EDCs during embryonic development, resulting in profound alterations in the structural organization of the brain and neurobehavior. Detailed analyses of variables such as folic acid and phytoestrogen content in maternal diet need to be considered as crucial factors while designing experiments and therapeutic interventions. Apart from this, appropriate animal handling during the experimental procedures to eliminate stress in animal models to ensure unbiased results is recommended.

Keywords: Adult Health, Endocrine Disrupting Chemicals (EDCs), Epigenetic Programming, Intrauterine Exposure

1. Introduction

As defined by the United States Environmental Protection Agency (US EPA, 1997), an endocrine disruptor refers to an "exogenous agent that interferes with the synthesis, secretion, transport, metabolism, binding action or elimination of natural blood-borne hormones present in the body responsible for homeostasis, reproduction and developmental processes". EDCs exert their effect through nuclear hormone receptors - estrogen, androgen, thyroid and retinoid receptors[1,2].

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The Medline (PubMed) Database (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2990277/) was used to generate a trend line for the number of papers published with a particular keyword during 2000-2017. A trend line was generated by entering the following keywords into the database- Environmental chemicals+epigenome, EDCs+methylation, Epigenetic disruption+EDCs and EDCs+miRNA. The papers with the specific keywords were retrieved and plotted in the form of a graph to interpret the trend in research over the past seventeen years. For better understanding, we analyzed the number of publications with the above-mentioned keywords from the year 2000, which generated interesting trend-lines. Currently, more than 45 published papers had investigated the effect of exposure to environmental chemicals on the epigenome, while close to 40 publications addressed the consequence of exposure to EDCs in bringing about altered methylation.

There is a steady increase in the number of papers (Figure 1) reporting the existence of epigenetic mechanisms behind the latent action of EDCs, which emphasizes the need to understand the impact of EDCs on biological processes, especially developmental, epigenetic programming and reprogramming events at work during early fetal development. Hence, the aim of this article is to provide a comprehensive overview of epigenetic programming and its regulation, focussing on the epigenetic plasticity and susceptibility to exogenous hormone-active chemicals during the early developmental period and to review the emerging literature reporting the latent effects of EDCs upon early developemental exposure, in rodent models.

2. EDCs as Emerging Epigenotoxicants

There is a growing body of literature in animals which supports the concept that both maternal and postnatal environmental factors such as maternal nutritional state[3-7], xenobiotic chemicals[8-9], behavioral cues[10] and low dose radiation[11] result in altered epigenetic reprogramming and increased disease susceptibility duringlater life. Further, epigenetic alterations can also be transmitted across generations through the germline, potentially affecting the health of successive progenies[12-14]. This process is referred to as 'transgenerational inheritance of disease[15]. Epigenotoxicants are chemicals that bring about an altered epigenetic state in the exposed organism. The two best characterized epigenetic modifications include DNA methylation and histone modifications[16]. Researchers in the field of endocrine disruption have begun to investigate the association between early developmental exposure to hormone-active compounds and their related later-

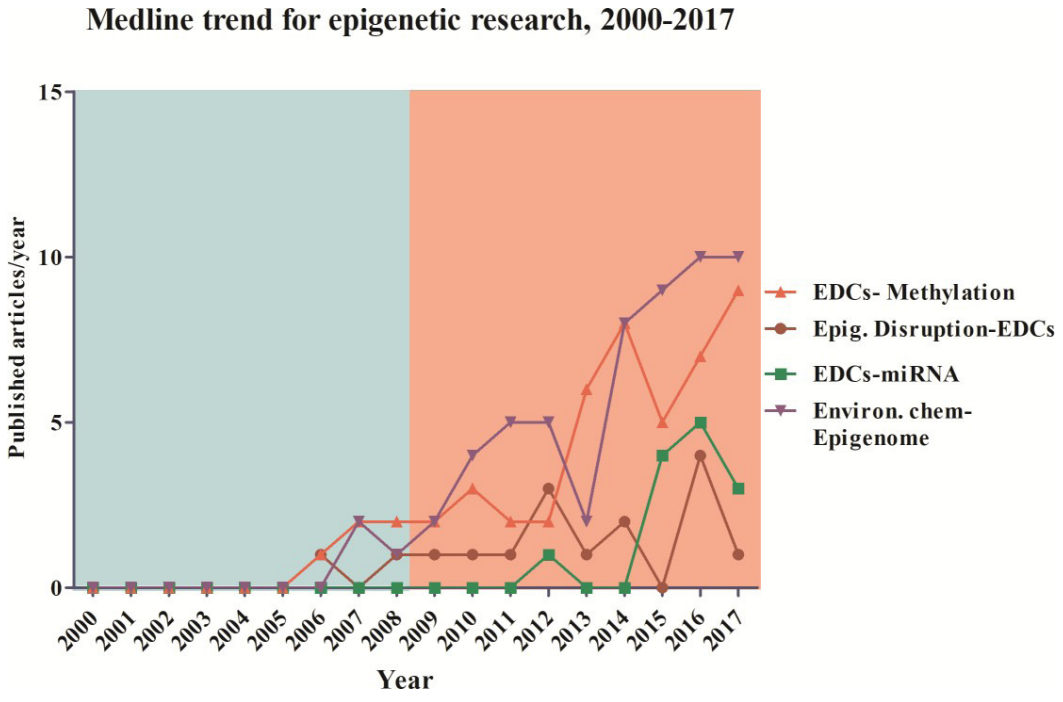

Figure 1. Trends in environmental epigenetic research publications from the year 2000-2017.

life health consequences. Experiments were designed to integrate the human observational studies with data from animal models to delineate the underlying biological mechanism.

3. Historical Perspectives

In 1938 the synthetic estrogen Di-Ethyl-Stilbestrol (DES) was prescribed to pregnant women for preventing miscarriage and premature births. However, during the fifties, it was found that the daughters of women who used DES were eventually diagnosed with clear-cell carcinoma, a rare form of cancer. Thus, in 1971, the Food and Drug Adminstration (FDA) of USA banned the prescription of DES. Over the subsequent years, research went on to reveal the possible links of DES with reproductive tract abnormalities and teratological malformation of limbs in DES sons and daughters (Giusti *et al*., 1995). To uncover the mechanism behind the latent action of these chemical, researchers started to explore DES-induced epigenetic alterations. In 1997, Li *et al.*[17] reported 9-fold increase of demethylation in 30 PND (postnatal day) old mature mice uteri, when neonatally exposed (PND 1-5) to DES. These findings prompted the development of the concept of early-life programming of adult disease. Later, studies were aimed at establishing the effects of other EDCs using gestating rodent models. Many studies have documented an array of EDCs which act as potential epigenotoxicants. EDCs, like vinclozolin and methoxychlor, when tested during the period of gonadal sex differentiation, were observed to reduce the spermatogenic capacity in four subsequent generations, consequent upon altered DNA methylation levels in the germ cells[18]. Particularly, vinclozolin was found to alter the DNA methylation pattern in the male germ line, which led to the onset of adult disease phenotypes such as spermatogenic defects, cancer, and prostate and kidney diseases[8]. To reveal the epigenotoxic capability, BPA was administered to transgenic gestating mice, which caused a shift in the coat color distribution of viable yellow agouti to yellow phenotype by hypomethylation of the CpG Island in an intracisternal-A particle retrotransposon upstream of the Agouti gene[19]. In a recent study, prenatal exposure to BPA was found to be associated with the development of liver tumor during adult life. The hypomethylation of Stat3 gene was later elucidated to be the reason for the tumor development[20]. Overall, the literature substantiates the ability of various environmental hormone-mimicking compounds to exert their effect at the epigenetic level. We have reviewed the published literature examining the association between developmental exposure of EDCs and altered epigenetic state when tested with gestating rodent models (Table 1).

Recent advances in the field of epigenetics, endocrinology and developemental biology have prompted the consideration of other factors in the hypothesis of fetal origin of adult disease[21] wherin disturbances that are caused during the embryonic development bynutritional, hormonal, and metabolic factors, and the presence of exogenous chemicals in the intra-uterine environment, would result in inappropriate programming of the epigenome and may lead to adult health outcomes. An environmental impact on the long-term health of an individual came to light during the Dutch famine in The Netherlands (1944-1945). During this period, people affected by the famine has to consume bread and potatoes as the major portion of their diet. Rations at the time were as low as 400-800 calories a day, which were less than a quarter of the recommended adult female intake of 2000 calories[22]. Gestating mothers, who were exposed to such conditions during the second and third trimesters gave birth to children with low birth weight and developed diabetes, cardiovascular disease, and metabolic and mental disorders during their post-natal life[23,24]. From this historical event, supported by epidemiological data, researchers were able to conceive the idea of intra-uterine programming of adult organs and the ontogeny of disease states arising due to disturbances during a critical period of early development. Another situation of interest is the human epidemiological study performed in Overkalix, Sweden, consisting of people born in the years 1890, 1905, and 1920. It was observed that drastic changes in a paternal grandmother's diet during her childhood, due to adverse conditions such as famine, increased the susceptibility of her grandchildren to cardiovascular disease in their adult life[14,25]. Similarly, during the Chinese famine of 1959-1961, women exposed to famine conditions during early pregnancy produced offspring with decreased BMI[26]. Thus, epidemiological studies highlight the importance of early environmental conditions that prevail during pregnancy and their role in increasing the susceptibility to disease states in later life of the offspring.

Chemical	Treatment Scheme	Animal model	Period of exposure	Time of study (of effects)	Dosage administered	Tissue/organ studied	Epigenetic factors studied	Technique employed	Gene studied	Conclusion	Refs
BPA	Oral	BALB/C mice	Gestational day 0-19	PND 30-70	2, 20, 200 ug/kg/day	Brain	DNA methylation	mRNA expression	Global brain tissue, Esr1	Induced epigenetic alteration in brain, especially in sexually dimorphic brain function and behaviou.	[138]
BPA	Oral	Wistr rats	Throughtout gestation and lactation	PND 21 and 147	50ug/kg/day	Liver	DNA methylation	Bisulphite-sequencing, Real-time PCR,Western blot analysis	Hepatic global DNA methylation and Gck gene	Abnormal DNA methylation in hepatic tissue preceded development of insulin resistance, indicating potential role of epigenetics in fetal reprogramming of metabolic disorders.	[139]
BPA	Intraperitoneal injection (IP)	CD-1 mice	9–16 days of gestation	PND 14-42	5mg/kg	Uterus.	DNA methylation	Bisulfite treatment, EMSA staining and chromatin immunoprecipitation, qRT-PCR	Homeobox gene Hoxa10 and ERE	Permanent epigenetic alteration of ERE sensitivity to estrogen may be a general mechanism through which endocrine disruptors exert their action.	[140]
BPA	Oral	SD rats	Gestational day 6-PND 21	PND 21	100µg/kg/day	Liver	Methylation, Histone marks	Methyl specific PCR, ChIP	Pparg1, Pparg2, Cebpa, Fasn, Igf1, Adipoq, Ppard, Fabp4, Lep, Cebpb, Irs1, Lpl, Ppara, Bmp2 and Bmp4, Stat1, Stat5a and Stat5b	Exposure decreased the adipocyte pool at birth, which initially increased adaptive adipocyte maturation and lipid accumulation, but led to adipose tissue dysfunction in adulthood, leading to systemic glucose intolerance.	[141]
BPA	Injection	CD-1 mice	PND 7-14, PND 5-20	PND 15, 21	0, 20 and 40 g/kg dissolved into physiological saline with0.1% DMSO	Ovary	DNA methy lation	Bisulphite sequencing, RT-PCR, Western blotting	Igf2r, Peg3 and estrogen receptor	Inhibits methylation of imprinted genes during oogenesis via the ER signaling pathway.	[142]
BPA	Feed	Non agouti wild type mice	14 days prior to mating	PND 280	50 ng, 50 µg, and 50 mg BPA/kg diet	Liver	DNA methylation	Enrichment of methylated DNA, qPCR, hybridization and array scanning	Jak-2, Rxr, Rfxap and Tmem238	DNA methylation of candidate genes was identified as a mediator in the mechanistic pathway leading to adult disease susceptibility.	[7]
BPA	Subcutaneous injection (SC)	SD rats	PND 1,3 and 5	1 year	0.1, 1.0, 10, 100 and 5,000 g BPA/kg body weight	Prostatic complex	DNA methylation	Histopathology, Immunohistochemistry, In situ apoptosis labelling, HPLC MS-MS, Steroid radioimmunoassays, Bisulphite PCR sequencing analysis	Creb3l4, Tpd52, Pitx3, Paqr4, and Sox2	Increased prostate cancer susceptibility in a complex dose- and lobe-specific manner.	[9]
BPA	Osmotic-pump	CD-1 mice	Day 9 of gestation	PND 14	5mg/kg/day BPA	Uterine tissue	DNA methylation	HPLC tandem-MS, gene expression microarray, qRT-PCR, methylated DNA immunoprecipitation	Tgfbi, Scd1, Ret, Fbln2, Muc1, Lcn2, Il1b, Mmp3, Mmp10, and S100A9	Selectively altered the normal developmental programming of estrogen-responsive genes via modification of the genes that bind ERa.	[140]

Chemical	Treatment Scheme	Animal model	Period of exposure	Time of study (of effects)	Dosage administered	Tissue/organ studied	Epigenetic factors studied	Technique employed	Gene studied	Conclusion	Refs
BPA	Water	Male Fischer 344 rats	75 days	PND 124	1,0.1 mg/kg/ day of BPA	Sperm and testes	microRNA global expression profile	Western blots, DNA microarrays and microRNA assays	Oct 4, alpha-SM actin/ calponin	Caused a moderate corporal veno-occlusive dysfunction (CVOD)• Altered the corporal tissue that pose gene transcriptional changes related to inflammation, fibrosis and epithelial/ mesenchymal transition (EMT).	[143]
BPA	SC injection	Holtzman strain rats	PND 1-5	PND 125	2.4 gof BPA/day	Testis	DNA methylation	Bisulfite sequencing, qRT-PCR, Western Blotting	CpG island region of ER-alpha and ER-beta	Led to aberrant DNA methylation in testis, indicating methylation mediated epigenetic changes as one of the possible mechanisms that induced adverse effects on spermatogenesis and fertility.	[144]
BPA, Genestein	Gavage	SD rats	PND 2-20	PND 100	250 µg BPA, 250 mg Genestein, 250 µg BPA+ 250 mg Genestein	The fourth abdominal mammary gland	DNA methylation	MBD Cap-Seq analysis	HPSE and RPS9	Identification of hypomethylation in mammary glands of rats exposed prepuberally to BPA+-Genestein led to reinforcement of cancer suppressive properties of Genistein.	[145]
DES, BPA	IP injection	CD-1 mice	9-26 days of gestation	PND 42	DES- 10 ug/ kgBPA- 5 mg/kg (mouse)	Mammary gland	Histone tail modification	Western blot, qRT-PCR	EZH2	Developmental programming of EZH2 is a novel mechanism by which in utero exposure to endocrine disruptors leads to epigenetic regulation of the mammary gland.	[146]
Methoxychlor (MXC)^^	IP injection	Fischer inbred rats	Embryonic day 19-PND 17 (Transient exposure)	PND 50-60	20ug/kgd or 100 mg/kgd	Ovary	Methylation	AP-PCR,B-SPCR,MSP-CR,RT-PCR	ER-ALPHA and ER-BETA promotor	Affects adult ovarian function via altered methylation patterns.	[147]
DES	IP injection	CD-1 mice	9-16 days of gestation	PND 14-42	10u g/kg	Uterus	DNA Methylation	BSP,MSP, RT-PCR	HOXA10	Hypermethylation is identified as a novel mechanism of exposure induced altered developmental programming.	[148]
DEHP*	Gavage	SD rats	7-19days	PND80	750mg/kg.bw. day	Testis	DNA methyl-transferase expression	Real Time-PCR, immune-histochemistry, western Blot, MeDIP-seq Data Analysis	DNA methyl-transferase expression	Led to methylation pattern changes which passed on to the next generation and eventually resulted in producing offspring with cryptorchidism.	[149]

Chemical	Treatment Scheme	Animal model	Period of exposure	Time of study (of effects)	Dosage administered	Tissue/organ studied	Epigenetic factors studied	Technique employed	Gene studied	Conclusion	Refs
Vinclozo-lin*, BPA, DEHP*	Oral gavage	Mice (JF1 females, OG2 males)	8.5 dpc to 12.5 days post coitum	13.5 dpc	Vinclozolin(VZ) at100 mg/kg/ day; di-(2-ethylhexyl) phthalate (DEHP) at750 mg/kg/ day; and BPA at 0.2 mg/ kg/ day.	Head, Heart, Liver, Lung, Placenta, Yolk sac, and Embryo carcass	Allele specific transcript-tion	multiplex RNA-single nucleotide primer extension (SNuPE) assay	allele-specific DMR methylation	EDCs exert direct epigenetic effects in exposed fetal germ cells, which are corrected by reprogramming events in the next generation. Avoiding transgenerational inheritance of environmentally-caused epigenetic aberrations may have played an evolutionary role in the development of dual waves of global epigenome reprogramming in mammals.	150
p-p'-DDE*	Gavage	SD rats	GD 8-15	PND 120	100 mg/kg of body-weight	Mature sperm and Testes	DNA methy-lation	RT-PCR, Bisulfite genomic sequencing	Igf2	Impaired male fertility with epigenetic alterations is transgenera-tionally inherited, posing significant implications in the etiology of male infertility.	151
DDT,BPA, MC	IP inject-tion	Wistar rats	Injected when female rats 150g	After72 hours of injection	50/75/75 mg/kg	Liver	miRNA expression	RT-PCR, Western Blotting	CYP1A1/2B1	Observed a potential involvement of miRNA in the post-transcriptional regulation of candidate genes in the livers and ovaries of exposed rats.	152
Estra-diol Benzoate	SC inject-tion	SD rats	PND 1-5	PND 6,30,90	0, 0.75, 1.25, 2.5, or 25 ug/d	Testes	microRNA and DNMT role on developmental effects of EB	TUNEL, Immunofluorescence, qRT-PCR, Western Blotting	DNMT1, DNMT3a, DNMT3b, Cdkn2a, miR-29a, miR-29b, miR-29c, L1td1 and Gstp1	Increased expression of the apoptomir that is involved in adult germ cell apoptosis.	153
Genestien	Diet	Agouti viable yellow (Avy) mouse model	PND 56-70	PND150	A modified control diet with corn oil subs-tituted for soybean oil, a modified diet containing 50 mg/kg BPA, a modified dietco-ntaining 50 mg/kg BPA and 250 mg/kg genistein, and amodi-fied diet contain-ing 50 mg/kg BPA and methyl donors	Hair follicle	DNA methy-lation	Sodium Bisulphate modification, PCR	Avy IAP	Affects gene expression and alters susceptibility to obesity in adulthood by permanently altering the epigenome.	154
Tributyltin	Gavage	C57BL/6J mice	E16.5	PND 56	TBT (0.1 mg/ kg), ROSI (1 mg/ kg) (Cayman Chemi-cal, Ann Arbor, MI)	Stromal stem cells from white epidi-dymal/ ovarian fat pads (WAT)	DNA methy lation	Proiferation assay, methylation sensitive enzyme digestion, qRT-PCR and flow cytometry	Fabp4 and PPARγ2	Multipotent stromal stem cells are sensitized to differentiate into adipocytes, an effect that increased adipose mass over time.	155

Chemical	Treatment Scheme	Animal model	Period of exposure	Time of study (of effects)	Dosage administered	Tissue/organ studied	Epigenetic factors studied	Technique employed	Gene studied	Conclusion	Refs
Estradiol, BPA	SC injection	SD rats	PND 1,3,5	PND 196	2,500 µg EB/kg body weight, 0.1 µg EB/kg body weight,10 µg BPA /kg body weight	Prostate tissues	DNA methylation	Bisulphite sequencing, methylation specific PCR, RT-PCR	Dgat and Agpat6, Fabp1, Lpl, Fasn, Cebpα, Cebpβ, Pck1, Acox1, Cybb, Cpt1a, Dnmt1, Dnmt3a, Dnmt3b, Hdac1, Hdac3, Ash1l, Kmt2b, Kmt2c, H3Me2K4, H3Me3K36, C/EBPβ, H4Ac and SREBP1	Affects prostate epigenome during development and promotes prostate disease with aging.	156
DES	Injection	CD-1 mice	PND 1-5, adult days 30-34	PND 17, 21 or 30, adult day 35	2 pg/ mouse/ day, in adult- 2 ug/kg of body weight/ day	Uterus	DNA methylation	Bisulphite sequencing, genomic southern hybridization	Five CpG sites -547,-533,-475,-464, and -454	Induced tumor formation as well as demethylation through a common cellular process.	17
DES, Methoxychlor	SC injection	CD-1 mice	Gestation days 12-18	PND 196	DES-0.1 µg/kg/ day, 100 µg/ kg/ day and MXC-10 µg/kg/ day, 10,000 µg/ kg/ day	Uterus	DNA methylation	Differential methylation hybridization analysis, Methylation analysis by Southern hybridization	Ribosomal 18S rDNA and 45S pre-rDNA	A monotonic dose-response relationship found for exposure on both liver weight and ribosomal DNA hypermethylation.	https://www.ncbi.nlm.nih.gov/pubmed/12217638 157
Coumestrol	Injection	SD rats	PND 1-10	PND 15	10 or 100 µg of coumestrol or equol	Pancreas	DNA methylation	methylation specific restriction enzymes	c-myc or c-fos	Equol may have anti-carcinogenic effectson some hormone-dependent cancers.	158
Vinclozolin*	Oral gavage	CD-1 mice	Gestational days 13-17	GD19	10 mg/kg dissolved in corn oil, 50 mg/ kg dissolved in corn oil	Genital tubercle	mRNA levels	qRT-PCR	ER, ERb, progesterone receptor and androgen receptor	Directly or indirectly affects progesterone receptor expression, also affects estrogen receptor expression in a sex-based manner. Hence, may also exert its effects by involving in additional steroid-signaling pathways.	159
Vinclozolin*	IP injection	CD-1 mice	E7–E13	PND 60-90	100 mg/kg· day	Testes, Epididymis, Prostate, Ovary and Kidney	DNA methylation	Tiling Array MeDIP-Chip Analysis and qPCR	Elf3 and Mro	Identified differential DNA methylation regions that can potentially be utilized as epigenetic biomarkers for transgenera-tional exposure and disease.	119

All chemicals estrogenic: *- Androgenic, ^- Anti androgenic, ^^- estrogenic, anti estrogenic & anti androgenic

4. *In Utero* Exposure to EDCs

The ubiquitous presence of a wide variety of EDCs in the environment and the products used in day-to-day life contribute to their exposure in human beings. The impact of EDCs on an organism's health has revealed to depend upon the following factors- windows of exposure[27,28], dosage[29,30], duration of exposure[31] and stages of development, thus making perinatal life the most sensitive and susceptible period for the action of EDCs. This is reflected in human biomonitoring studies, reporting the presence of detectable levels of EDCs from the human biological matrices *viz.,* blood[32], saliva[33], seminal plasma[33], serum[35,36] and urine[32,34]. In particular, EDCs have also been screened from pregnancy-associated fluids like maternal blood and serum[37-39], umbilical cord blood[40-42], amniotic fluid[43,44], breast milk[32,45,46], and placental tissue[38,47]. In addition to their presence in these matrices, a recent study has also revealed their ability to cross the protective placental barrier, enter the fetal compartment and come in contact with the developing fetus throughout pregnancy[43]. Together, the published literature uncovers the presence and distribution of EDCs in the feto-maternal unit. Reproductive tract formation and sex-specific organization of the brain can be influenced by the environment that prevails during pregnancy. Taking into consideration that early development is a hormone-dependent process, presence of untimely and irrelevant signals especially initiated by hormone-active chemicals, can alter the appropriate epigenetic programming required for reproductive fitness of the invidiual during adult life. This growing body of literature brings to light the *in utero* exposure of EDCs and warrants further study on the later-life health[48-50]. An emerging field of EDC research addresses the altered epigenetic state leading to dysregulated gene expression[8,51]. It is important to study such alterations in epigenetic programming owing to exposure of EDCs during the critical early developmental stages, which have profound effects in later years, leading to transgenerational inheritance of many disease phenotypes.

5. Epigenetics and Epigenetic Reprogramming

Understanding the mechanism of action of EDCs through epigenetic alterations first requires a proper understanding of the term 'epigenetics' and the research this field covers. Conrad Waddington coined the term 'epigenetics', defining it as "a branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being"[52]. Some of the well chraractersized epigenetic factors studied today include the covalent and non-covalent modifications of DNA and histone proteins, and the mechanisms through which these modifications influence the chromatin structure. Epigenetic reprogramming refers to any mitotic or meiotic alteration that does not change DNA sequence, but has a significant phenotypic impact on the organism[53]. Early embryonic cells contain identical genetic information; however, epigenetic factors regulate the process of differentiation and development. The specialized function taken up by each cell type occurs due to the specific expression of a subset of genes. The epigenetic regulation of gene expression has been demonstrated in the model organisms: mice, rats, flies and worms[54,55]. Genes are either activated or silenced through the epigenetic regulatory mechanism involving: 1. DNA methylation, 2. histone methylation and acetylation, 3. long non-coding RNA, 4. small non-coding RNA, and 5. chromatin modifications.

DNA methylation in mammals is a post-transcriptional modification, which involves the methylation of the 5′ -position of cytosine residues and results in the formation of 5-methyl cytosine (5mC). It is, by nature, a reversible covalent modification to DNA. The symmetric methylation of cytosine in the 5′ position in CpG dinucleotides is one of the most prominent forms of epigenetic alteration, often considered to play a crucial role in regulation of gene expression and structural integrity. The process of methylation is facilitated by a family of enzymes known as DNA Methyl-Transferases (DNMTs)[56]. At present, four types of DNMTs are known to be expressed in mammals: DNMT1, DNMT2, DNMT3a and DNMT3b[57]. These DNMTs are responsible for various functions in the body- DNMT1 aids to maintain the DNA methylation throughout the replication process, by copying the methylation pattern that occurs in the parent strand onto the newly synthesized DNA strand. DNMT2 has been reported to exhibit limited methylation activity *in vitro*[58]. *De novo* methylation involves DNMT3a and DNMT3b, which targets the unmethylated CpG dinucleotides[59,60]. DNMT3a and DNMT3b together with DNMT1 ensure copying of methylation patterns during the process of DNA replication[57].

6. Methylation as an Epigenetic Marker for Developmental Reprogramming Process

Mammalian development involves the occurrence of bimodal DNA methylation in two stages, i.e., - germ cell development and preimplantation period (Figure 2)[61]. While the Primordial Germ Cells (PGCs) arrive at the developing germinal ridge and begin differentiation and expansion, the highly methylated PGCs undergo genome-wide demethylation. Most of the methylation is lost by embryonic day 12.5 in mice[62]. At the same time, there occurs an erasure and resetting of parent-of-origin specific marks, namely DNA methylation, and imprint differentially methylated regions (DMRs) associated with allele-specific expression[63]. While the exact timing in which *de novo* methylation occurs has not yet been established in mammals, it appears to be initiated on 14.5 day post-coitum (dpc) in males, following that in females, such that the mature gametes of both sexes eventually become highly methylated[64].

DNA methylation represents an epigenetic mark in mammalian development that is erased when developmental potency has to be restored and subsequently re-established with the commitment to a particular cell fate. This first event occurs following fertilization, when the DNA methylation marks of the parental gametes are erased in two waves of demethylation process. In the first wave, the paternal pronucleus (shown in blue) undergoes rapid demethylation in the zygote, which is followed by a passive loss of DNA methylation marks in the maternal genome (shown in red). Following this, *de novo* DNA methylation occurs actively and passively in paternal and maternal pronuclei, respectively. Later, in the zygote stage and pre-implantation stage, the second cycle of demethylation of paternal and maternal pronuclei occurs simultaneously and passively. Following this, de-novo methylation occurs in the blastocyst (implanted embryo) ICM. As part of the continuous cycle of DNA methylation reprogramming, these epigenetic marks will be erased in the zygote of the next generation.

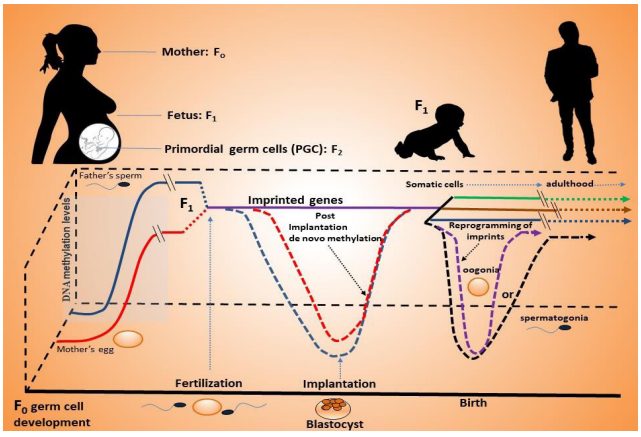

Figure 2. Major waves of DNA methylation during the life cycle of an individual.

During the period between fertilization and formation of the blastocyst, the second phase of methylation reprogramming occurs. Upon fertilization, a rapid paternal-specific asymmetric loss of methylation is observed[65,66]. This process, known as active demethylation, takes place in the absence of transcription or DNA replication. It involves a steady decline in methylation levels till the morula stage[67] which occurs in the absence of DNMT1 during DNA replication[68].

De novo methylation in the developing embryo is initiated prior to the fifth cell cycle and coincides with the first differentiation event. Another asymmetry of methylation is established during the formation of the Inner Cell Mass (ICM) and Troph-Ectoderm (TE). It has been observed that the ICM becomes hypermethylated whereas the trophectoderm is hypomethylated[67,69]. This difference in methylation is reflected in highly methylated somatic tissues and the hypomethylated extra-embryonic tissues of the placenta. The highly methylated PGCs, on day 7 in the extraembryonic mesoderm of the developing embryo, is amongst the somatic tissues derived from the ICM[70]. The cycle of epigenetic reprogramming is completed when these cells migrate *via* the allantois to the developing germinal ridges, where they eventually differentiate to form mature gametes. In case of somatic cells, the epigenetic changes are mitotically heritable, thus providing a potential mechanism by which disruption of the epigenome by environmental stressors can have long-lasting effects on the individual[71].

7. Regulation of Gene Expression by DNA Methylation

DNA methylation is associated with repression of gene expression. In general, there are two major mechanisms by which DNA methylation can bring about repression in the expression of a gene. A direct mechanism involves the alteration of transcription binding sites by the DNA methylation marks, which interferes with the binding

of transcription factors like E2F and CREB, preventing transcriptional activation[72-74]. Besides this, a more complex mechanism, which involves the recruitment of methyl-CpG binding proteins, is associated with chromatin modifiers to establish a repressive environment[75-79].

8. MicroRNA Biogenesis and Regulation

MicroRNAs are small non-protein coding RNAs of 20 nucleotides in length, responsible for the post-transcriptional regulation of gene expression, binding to the 3′ untranslated region (UTR) of the target mRNA. This results in the inhibition of protein translation or mRNA degradation[80,81]. Studies have reported the regulatory role of miRNAs in pathways of developmental programming, cell division and organogenesis[82-84]. The miRNA genes reside in the intergenic regions of a protein-coding gene constituting independent transcription units or are transcribed from the independent miRNA genes[85-87]. In the canonical mammalian miRNA biogenesis pathway, the miRNA genes are transcribed as long transcripts, known as pri-miRNAs (primary microRNAs) which are further processed into hairpin-shaped pre-miRNAs in an enzyme-mediated process catalyzed by the endonulease enzymes: nuclear RNase III Drosha (RN3) and Dicer[88-90]. Both Drosha and Dicer form a functional complex with the proteins having dsRNA-binding domains (dsRBDs). In *Drosophila melanogaster*, Drosha crops the pri-miRNA into hairpin-shaped miRNA, clubbing along with Pasha protein. However, the above-mentioned process in mammals is accomplished by partnering with the DiGeorge syndrome Critical Region gene 8 (DGCR8)[91]. The Drosha-DGCR8 complex results in a ~70- nucleotide long hairpin structure called precursor miRNA (pre-miRNA). Further, the pre-miRNAs are transported across the nucleus into the cytoplasm by the protein exportin[5]. Inside the cytoplasm, Dicer and TAR RNA Binding Protein (TRBP) cleave the pre-miRNA into a 20-bp miRNA duplex. One strand from the miRNA duplex functions as mature miRNA, which is assembled into the ribonucleoprotein, referred to as miRNA-induced silencing complex (miRISCs)[92]. The constituents of miRNPs are proteins from the Argonaute (AGO) family: AGO1-AGO4[93]. Argonaute proteins, in association with P-body components such as GW182 (Scaffold protein) and RCK/p54, interact with miRNPs that are involved in the miRNA-induced repression[94-96]. Binding to the specific mRNA target, mature miRNA is reported to engage in different kinds of mechanisms leading to translational repression or mRNA degradation. The mRNA degradation was shown to be mediated by initiating the endonuclease cleavage facilitated by mRNA decapping[97]. MicroRNAs interact with target mRNA by base-pairing and the perfect complementarity leads to endonucleolytic cleavage of the miRNA-mRNA duplex resulting in repression of the target gene (Figure 3).

9. Non-canonical MicroRNA Biogenesis

Besides the canonical miRNA biogenesis, there is another accessory mechanism in which microRNAs are synthesized. This pathway does not utilize the Drosha or microprocessor for microRNA biogenesis and is referred to as mirtron production. The Drosha-mediated process is bypassed by an alternating mechanism in which the small precursor strands are produced through mRNA splicing. The spliced transcripts separate and refold to form short stem-loops, reminiscent of pre-miRNA. Besides this, some microRNAs are synthesized from other small RNAs: tRNAs or tRNA-like precursors, small nucleolar RNAs (snoRNAs), or viral RNAs involving Drosha-independent processing. The non–canonical pathway of micro-RNA production is accomplished in cases where small RNAs are directly derived from the short hairpin RNAs (Figure 4)[98-100].

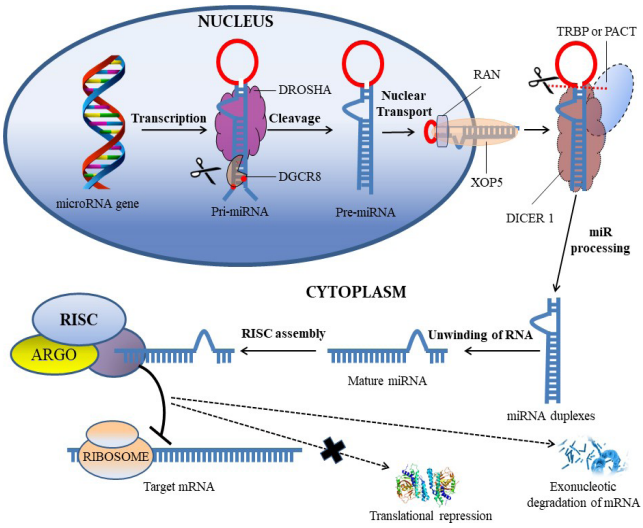

Figure 3. Canonical miRNA biogenesis pathway in mammals.

10. Epigenomic Plasticity during Early Developmental Windows of Exposure

When it comes to examining the toxicity of EDCs, adult exposure is important but it is not the sole factor to be taken into consideration. More emphasis needs to be given on fetal and/or prenatal exposure, particularly due to the increased sensitivity of the fetus to environmental perturbations, including concentrations much lower than what is considered to be safe[101,102]. This heightened sensitivity is due to the factors like less functional DNA repair mechanisms, incompetent immune system, underdeveloped liver metabolism and lack of a fully functional blood-brain barrier[102]. Prenatal exposure to environmental stressors can result in an altered trajectory of the developing organ system through the process of developmental programming, making individuals more susceptible to altered neurobehaviour, impaired immune function, reproductive abnormalities and cancer, later in life. The ability of a given genotype to produce different phenotypes in response to various environmental conditions is termed "plasticity," and is part of the organism's "adaptability" to environmental cues[103]. Changes in the epigenome due to environmental exposure to stressors can occur in both the embryonic and adult environment. Thus, epigenetic programming is now established as the key process that allows the environment to interact with the genotype during early development, resulting in the observed phenotype during adult life[104].

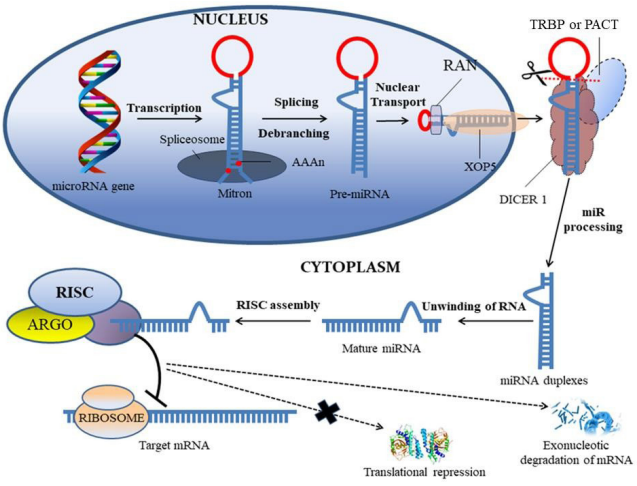

Figure 4. Non-canonical miRNA biogenesis pathway in mammals.

11. Influence of Maternal Behavior

Animal models have been used to study molecular mechanisms underlying the alterations in adult behavior as a result of early-life adversity or exposure. During the first week of life, offspring of mothers that exhibited higher levels of Licking/Grooming (LG) and Arched-Back Nursing (ABN) behavior, showed alterated DNA methylation patterns when compared to offspring of mothers that exhibited lower LG and ABN behavior[105]. It has also been reported that maternal care is directly related to cytosine methylation of the ER-1b promoter, providing a potential mechanism involved in programming individual differences in ER (estrogen receptor) expression and behavior of female offspring[106]. Together, the literature highlights the influence of maternal behavior on the offspring and its translational impact on altered neurobehavioral outcomes during its adult life[107] (For detailed review, refer ref. no. [108,109]).

12. Influence of Maternal Diet and Nutrition

Many studies highlighting the influence of maternal diet on the health status of the offspring in adult life have emerged. In a study where Avy mice were fed with high soy diet during gestation, it was observed that due to high levels of genistein (a phytoestrogen) intake, the coat color of viable yellow agouti offspring shifted to pseudoagouti. This shift in phenotype has been attributed to methylation in the transcription start site of the Agouti gene[110]. In-utero manipulation of maternal diet with a high-fat feed resulted in the loss of methylation at exon I of the ER gene, which later caused increased susceptibility to mammary tumorigenesis in aging rodents[111]. Thus, high fat intake by the mother during gestation can lead to hypomethylation similar to what is seen in individuals with cancer at adult stages. Besides this, folate content in dietary intake also plays an essential role in maintenance of methylation marks. The pre-pubertal transition period has been reported to be highly plastic to folate-induced epigenetic programming[112,113]. Altogether, maternal diet was found to play a crucial role in the epigenetic programming of the fetus, thus contributing to later-life health outcomes in the offspring. Hence, it is recommended that proper screening of constituents of maternal diet such as fat,

folate and phytoestrogens should be carried out to ensure unbiased results in experimental studies, and more so in real time life situation in the human.

13. Influence of Maternal Psychological Status on Epigenome

It has been reported that maternal stress during critical periods of fetal brain development contributes to increased incidence of disease development in adult life of the offspring. Stress during gestational days 12-18 led to altered brain miRNA profiles in the mother and the offspring. Maternal stress induced the expression miR-103, causing down regulation of its target gene PTPIB in the brains of the exposed offspring. In addition, miR-145, a marker for multiple sclerosis was also down regulated. This result throws light on the mechanism that may elucidate the link between exposure to environmental contaminants and the development of neurological disorders[114,115]. The research assessing the role of maternal psychology in shaping the epigenome is limited and, thus, further investigation will improve our understanding of the etiology of neurological disease and disorders.

14. Studies Addressing the Altered Epigenome Leading to Transgenerational Effect in the Offspring

Epigenetic transgenerational inheritance has been defined as "the germline (egg or sperm) transmission of epigenetic information between generations in the absence of any environmental exposure"[116,117]. It has been reported that transgenerational effects of EDCs like vinclozolin (an antiandrogenic fungicide) and methoxychlor (an estrogenic pesticide), when exposed during gestation, resulted in decreased spermatogenic capacity and increased incidence of male infertility in the exposed offspring. It was also found that these effects are transferred through the male germline till the F_4 generation, with no direct exposure to the test compound[118]. It was observed that these effects are due to altered DNA methylation in the sperm promoter epigenome[119]. Similar studies have also been carried out with chemicals- BPA[120] and dioxin[121]. Other factors such as maternal diet[6] and stress pathology[122] yielded similar results. When gestating females were exposed to vinclozolin during the critical period of embryonic development, various disease states such as tumors and hypercholesterolemia, prostate andk idney diseases, and compromised immune parameters and testicular function, were consistently observed in F_1-F_4 generations[123]. These results suggest that endocrine disruptors can induce transgenerational inheritance of disease. A behavioral investigation revealed that F_3 generation males showed a decrease in anxiety-like behavior whereas females showed an increase in anxiety-like behavior. These results indicate that embryonic exposure to environmental chemicals like vinclozolin alters the brain epigenome, leading to transgenerational sex-specific alterations in the brain transcriptome and behavior[124]. In a similar study, it was observed that F_1-F_3 generation females were diagnosed with uterine haemorrhage and/or anaemia at late pregnancy. Upon examination of kidney histology, severe glomerular abnormalities were found in F_2 and F_3 generation adult females. These observations testify that exposure to environmental chemicals like vinclozolin at critical periods of development can lead to pregnancy abnormalities and adult onset of diseases in female offspring[125].

Exposure to methoxychlor has been reported to induce kidney and ovary diseases and obesity with increased intensity from F_1 to F_4 generation[126]. A very recent study proved that maternal exposure to di (2-Ethyl-Hexyl) Phthalate (DEHP) at human exposure-relevant doses during the critical stage of gonadal sex determination perturbs the reproductive indices of female offspring in the subsequent generations (F_1-F_3)[127]. Yet another well established environmental endocrine disruptor, dioxin, has been reported to increase the incidence of premature birth and sensitivity to inflammation fertility and birth outcomes[121]. It can also aggravate prostate disease, ovarian primordial follicle loss and polycystic ovary disease in the F_1 generation of dioxin lineage[126] and in three subsequent generations, which is heritable due to differentially methylated DNA regions. Similarly, upon embryonic exposure of CD1 mice to phthalates (DEHP), disruption of testicular germ cell organization and spermatogonial stem cell function were observed to occur in a transgenerational manner through a decrease in sperm count and motility from F_1-F_4 generation offspring[128]. The well known plasticizer BPA, when given to pregnant rodents during critical stages of fetal gonadal sex determination,

caused an alteration in DNA methylation patterns leading to increased pubertal abnormalities, testicular disease, obesity, and ovarian disease (primary ovarian insufficiency and polycystic ovaries) in the F_3 generation animals[126]. It also affects the male germ line, leading to impairment in three subsequent generations[129]. Such exposure to BPA affects brain organization and behavior of subsequent generations which could be a consequence of its action as a steroid hormone antagonist, agonist or an epigenetic modifier[130]. To conclude, during the critical window of germ cell development and embryonic gonadal sex determination in mammals, environmental factors, toxicants or maternal behavior have been shown to influence epigenetic programming in the male or female germ line which becomes permanently programmed or imprinted, thus allowing transgenerational inheritance of disease phenotypes[131].

The process of fetal development in mammals can be visualized as a set of gears, with one factor driving the other. Alterations in one of the gears can result in severe disruption of subsequent factors, together leading to altered health state in the adult life of the exposed individual. The developing fetus is considerably influenced by maternal cues such as prevailing intrauterine environment, behavior, nutritional status and psychological state. In addition to this, circulating hormones in the uterine environment also play a major role in shaping the epigenetic programming of the fetus. Thus, the fetus is most susceptible to disturbances that arise during this sub-optimal period of development[132]. Therefore, the epigenetic plasticity is influenced by exposure to environmental toxicants during this critical developmental time point. Since early development is a hormone-dependent process, EDC-exposure even at low concentrations can result in functional changes in gene expression and, while not obvious in the form of any phenotypic change, can later contribute to increased occurrence of disease and dysfunctions[133]. Early-life exposure can result in problems associated with neurobehavioral[134], immune response[135], reproductive system[136] and brain development[137]. It has also been studied to be one of the possible causative agents for cancer.

15. Summary and Conclusion

The literature to date establishes the transgenerational effect of EDCs upon exposure during critical stages of development, resulting in profound later-life effects such as alterations in neurobehavior, reproduction and immune function. A review of the available reports suggests that the key mechanism behind the long-term impact of EDCs was studied to be involving altered epigenetic programming, leading to dysregulated gene expression during adult-life. Especially, recent reports have demonstrated the effect of prenatal exposure to EDCs on the ovarian microRNA machinery, highlighting it to be an essential organ undergoing *in utero* programming. It ascertains the heightened sensitivity of the organ to exogenous hormone-active compounds. In addition to this, another key exposition in this review is the increased susceptibility of the brain to developmental exposure to even minute concentrations of EDCs, resulting in profound alterations in brain structural organization and neurobehavior. Detailed analyses of variables such as folic acid and phytoestrogen content in maternal diet have to be considered as crucial factors while designing experiments. Apart from this, appropriate animal handling during the experimental procedures to eliminate stress in animal models to ensure unbiased results, is recommended. Further, this compelling evidence should urge scientists and policymakers to rethink and include the epigenetic paradigm while screening and assessing the effects of EDCs.

16. References

1. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, *et al*. Endocrine-disrupting chemicals: An Endocrine Society scientific statement. Endocrine Reviews. 2009; 30(4):293-342. https://doi.org/10.1210/er.2009-0002. PMid:19502515 PMCid:PMC2726844.
2. Shanle EK and Xu W. Endocrine disrupting chemicals targeting estrogen receptor signaling: identification and mechanisms of action. Chemical Research in Toxicology. 2010; 24(1):6-19. https://doi.org/10.1021/tx100231n. PMid:21053929 PMCid:PMC3119362.
3. Jones PL, Veenstra GCJ, Wade PA, *et al*. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nature Genetics. 1998; 19(2):187-91. https://doi.org/10.1038/561. PMid:9620779.
4. Cooney CA, Dave AA, Wolff GL. Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring. The Journal of Nutrition. 2002; 132(8): 2393S-2400S. https://doi.org/10.1093/jn/132.8.2393S. PMid:12163699.
5. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Molecular and Cellular Biology. 2003; 23(15):5293-5300.

https://doi.org/10.1128/MCB.23.15.5293-5300.2003. PMid:12861015 PMCid:PMC165709.

6. Burdge G, Slater-Jefferies J, Torrens C, *et al*. Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. British Journal of Nutrition. 2007; 97(03):435. https://doi.org/10.1017/S0007114507352392. PMid:17313703 PMCid:PMC2211514.
7. Anderson OS, Kim JH, Peterson KE, *et al*. Novel Epigenetic Biomarkers Mediating Bisphenol A Exposure and Metabolic Phenotypes in Female Mice. Endocrinology. 2016; 158(1): 31-40. https://doi.org/10.1210/en.2016-1441. PMid:27824486 PMCid:PMC5412976.
8. AnwayM, Skinner M. Epigenetic programming of the germ line: effects of endocrine disruptors on the development of transgenerational disease. Reproductive BioMedicine Online. 2008; 16(1):23-25. https://doi.org/10.1016/S1472-6483(10)60553-6.
9. Ho SM, Tang WY, De Frausto JB, Prins GS. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Research. 2006; 66(11): 5624-5632. https://doi.org/10.1158/0008-5472.CAN-06-0516. PMid:16740699 PMCid:PMC2276876.
10. Weaver IC, Champagne FA, Brown SE, *et al*. Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. Journal of Neuroscience. 2005; 25(47):11045-11054. https://doi.org/10.1523/JNEUROSCI.3652-05.2005. PMid:16306417 PMCid:PMC6725868.
11. Koturbash I, Baker M, Loree J, *et al*. Epigenetic dysregulation underlies radiation-induced transgenerational genome instability in vivo. International Journal of Radiation Oncology, Biology, Physics. 2006; 66(2):327-330. https://doi.org/10.1016/j.ijrobp.2006.06.012. PMid:16965987.
12. Morgan HD, Sutherland HG, Martin DI, Whitelaw E. Epigenetic inheritance at the agouti locus in the mouse. Nature Genetics. 1999: 23(3):314-318 https://doi.org/10.1038/15490. PMid:10545949.
13. Rakyan VK, Chong S, Champ ME, *et al*. Transgenerational inheritance of epigenetic states at the murine AxinFu allele occurs after maternal and paternal transmission. Proceedings of the National Academy of Sciences. 2003; 100(5):2538-2543. https://doi.org/10.1073/pnas.0436776100. PMid:12601169 PMCid:PMC151376.
14. Bygren LO, Tinghog P, Carstensen J, *et al*. Change in paternal grandmothers early food supply influenced cardiovascular mortality of the female grandchildren. BMC Genetics. 2014; 15(1):12. https://doi.org/10.1186/1471-2156-15-12. PMid:24552514 PMCid:PMC3929550.
15. Manikkam M, Haque M, Guerrero-Bosagna C, *et al*. Pesticide Methoxychlor Promotes the Epigenetic Transgenerational Inheritance of Adult-Onset Disease through the Female Germline. PLoS ONE. 2014; 9(7):e102091. https://doi.org/10.1371/journal.pone.0102091. PMid:25057798 PMCid:PMC4109920.
16. Tang WY, Ho SM. Epigenetic reprogramming and imprinting in origins of disease. Reviews in Endocrine and Metabolic Disorders. 2007; 8(2):173-182. https://doi.org/10.1007/s11154-007-9042-4. PMid:17638084 PMCid:PMC4056338.
17. Li S, Washburn KA, Moore R, *et al*. Developmental exposure to diethylstilbestrol elicits demethylation of estrogen-responsive lactoferrin gene in mouse uterus. Cancer Research. 1997; 57(19):4356-4359. https://doi.org/10.1002/mc.10015.
18. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 2005; 308(5727):1466-1469. https://doi.org/10.1126/science.1108190. PMid:15933200.
19. Dolinoy D, Huang D, Jirtle R. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proceedings of the National Academy of Sciences. 104(32):13056-13061. https://doi.org/10.1073/pnas.0703739104. PMid:17670942 PMCid:PMC1941790.
20. Weinhouse C, Bergin I, Harris C, Dolino, D. Stat3 is A candidate epigenetic biomarker of perinatal Bisphenol A exposure associated with murine hepatic tumors with implications for human health. Epigenetics. 2015; 10(12):1099-1110. https://doi.org/10.1080/15592294.2015.1107694. PMid:26542749 PMCid:PMC4844208.
21. Barker DJ,. The origins of the developmental origins theory. Journal of Internal Medicine. 2007; 261(5):412-417. https://doi.org/10.1111/j.1365-2796.2007.01809.x. PMid:17444880.
22. Roseboom T, de Rooij S., Painter R. The Dutch famine and its long-term consequences for adult health. Early Human Development. 2006; 82(8):485-491. https://doi.org/10.1016/j.earlhumdev.2006.07.001. PMid:16876341.
23. Hoek H, Brown A, Susser E. The Dutch Famine and schizophrenia spectrum disorders. Social Psychiatry and Psychiatric Epidemiology. 1998; 33(8):373-379. https://doi.org/10.1007/s001270050068. PMid:9708024.
24. Bhan Khanna S, Dash K, Dwivedee K..Fetal Origin of Adult Disease. JK Science. 2007; 9(4):206-210. https://doi.org/10.1016/j.cppeds.2011.01.001 .

25. Bygren LO, Edvinsson S, Brostrom G. Change in food availability during pregnancy: Is it related to adult sudden death from cerebro-and cardiovascular disease in offspring?. American Journal of Human Biology. 2000; 12(4):447-453. https://doi.org/10.1002/1520-6300(200007/08)12:4<447::AID-AJHB3>3.0.CO;2-M.
26. Huang C, Li Z, Wang M, Martorell R. Early life exposure to the 1959-1961 Chinese famine has long-term health consequences. The Journal of Nutrition. 2010; 140(10):1874-1878. https://doi.org/10.3945/jn.110.121293. PMid:20702751.
27. Bourguignon JP, Juul A, Franssen D, Fudvoye J, Pinson A, Parent AS. 2016. Contribution of the endocrine perspective in the evaluation of endocrine disrupting chemical effects: The case study of pubertal timing. Hormone Research in Paediatrics. 86(4), 221-232. https://doi.org/10.1159/000442748. PMid:26799415.
28. Palanza P, Nagel SC, Parmigiani S, vom Saal FS. Perinatal exposure to endocrine disruptors: Sex, timing and behavioral endpoints. Current Opinion in Behavioral Sciences. 2016; 7:69-75. https://doi.org/10.1016/j.cobeha.2015.11.017. PMid:27019862 PMCid:PMC4805122.
29. Inagaki T, Smith N, Lee EK, Ramakrishnan S. Low dose exposure to Bisphenol A alters development of gonadotropin-releasing hormone 3 neurons and larval locomotor behavior in Japanese Medaka. Neurotoxicology. 2016; 52:188-197. https://doi.org/10.1016/j.neuro.2015.12.003. PMid:26687398.
30. McLellan D. Discussion of bisphenol A as an environmental endocrine disruptor: The low dose effect and governmental regulations concerning its use and disposal: A literature review. Revue Interdisciplinaire Des Sciences De La Santé-Interdisciplinary Journal of Health Sciences. 2016; 1(1):54-59. https://doi.org/10.18192/riss-ijhs.v1i1.1535.
31. Wang Q, Lam JC, Han J, Wang X, Guo Y, Lam PK, Zhou B. Developmental exposure to the organophosphorus flame retardant tris (1, 3-dichloro-2-propyl) phosphate: Estrogenic activity, endocrine disruption and reproductive effects on zebrafish. Aquatic Toxicology. 2015; 160:163-171. https://doi.org/10.1016/j.aquatox.2015.01.014. PMid:25637911.
32. Azzouz A, Rascon AJ, Ballesteros E. Simultaneous determination of parabens, alkylphenols, phenylphenols, bisphenol A and triclosan in human urine, blood and breast milk by continuous solid-phase extraction and gas chromatography-mass spectrometry. Journal of Pharmaceutical and Biomedical Analysis. 2016; 119:16-26. https://doi.org/10.1016/j.jpba.2015.11.024. PMid:26637951.
33. Raghavan AS, Sathyanarayana HP, Kailasam V, Padmanabhan S. Comparative evaluation of salivary bisphenol A levels in patients wearing vacuum-formed and Hawley retainers: An in-vivo study. American Journal of Orthodontics and Dentofacial Orthopedics. 2017; 151(3):471-476. https://doi.org/10.1016/j.ajodo.2016.07.022. PMid:28257731.
34. Frederiksen H, Jorgensen N, Andersson AM. Parabens in urine, serum and seminal plasma from healthy Danish men determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Journal of Exposure Science and Environmental Epidemiology. 2011; 21(3):262-271. https://doi.org/10.1038/jes.2010.6. PMid:20216574.
35. Takeuchi T, Tsutsumi O, Ikezuki Y, TAKAI Y, TAKETANI Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. Endocrine Journal. 2004; 51(2):165-169. https://doi.org/10.1507/endocrj.51.165. PMid:15118266.
36. Szybiak A, Rutkowska A, Wilczewska K, Wasik A, Namiesnik J, Rachon D. Daily diet containing canned products significantly increases serum concentrations of endocrine disruptor bisphenol A in young women. Polish Archives of Internal Medicine. 2017; 127(4):278. https://doi.org/10.20452/pamw.4005. PMid:28436414.
37. Lathi RB, Liebert CA, Brookfield KF, Taylor JA, Vom Saal FS, Fujimoto VY, Baker VL. Conjugated bisphenol A in maternal serum in relation to miscarriage risk. Fertility and Sterility. 2014; 102(1):123-128. https://doi.org/10.1016/j.fertnstert.2014.03.024. PMid:24746738 PMCid:PMC4711263.
38. Tyagi V, Garg N, Mustafa MD, Banerjee BD, Guleria K. Organochlorine pesticide levels in maternal blood and placental tissue with reference to preterm birth: A recent trend in North Indian population. Environmental Monitoring and Assessment. 2015; 187(7):471. https://doi.org/10.1007/s10661-015-4369-x. PMid:26122123.
39. Lyall K, Croen LA, Sjodin A, Yoshida CK, Zerbo O, Kharrazi M, Windham GC. Polychlorinated biphenyl and organochlorine pesticide concentrations in maternal mid-pregnancy serum samples: association with autism spectrum disorder and intellectual disability. Environmental Health Perspectives. 2017; 125(3):474. https://doi.org/10.1289/EHP277. PMid:27548254 PMCid:PMC5332182.
40. Choi G, Kim S, Kim S, Kim S, Choi Y, Kim HJ, Lee JJ, Kim SY, Lee S, Moon HB, Choi S. Occurrences of major Poly-Brominated Diphenyl Ethers (PBDEs) in maternal and fetal cord blood sera in Korea. Science of the Total Environment. 2014; 491:219-226. https://doi.org/10.1016/j.scitotenv.2014.02.071. PMid:24636800.
41. Zhao Y, Liu P, Wang J, Xiao X, Meng X, Zhang Y. Umbilical cord blood PBDEs concentrations are associated with placental DNA methylation. Environment International. 2016; 97:1-6. https://doi.org/10.1016/j.envint.2016.10.014. PMid:27768956.

42. Luo D, Pu Y, Tian H, Cheng J, Zhou T, Tao Y, Yuan J, Sun X, Mei S. Concentrations of organochlorine pesticides in umbilical cord blood and related lifestyle and dietary intake factors among pregnant women of the Huaihe River Basin in China. Environment International. 2016; 92:276-283. https://doi.org/10.1016/j.envint.2016.04.017. PMid:27123771.
43. Sudhanshu Shekhar, Surbhi Sood, Sadiya Showkat, Christy Lite, Anjalakshi Chandrasekhar, Mariappanadar Vairamani, Barathi S, Winkins Santosh. Detection of phenolic Endocrine Disrupting Chemicals (EDCs) from maternal blood plasma and amniotic fluid in Indian population. General and Comparative Endocrinology. 2017; 241:100-107. https://doi.org/10.1016/j.ygcen.2016.05.025. PMid:27235644.
44. Pinney SE, Mesaros CA, Snyder NW, Busch CM, Xiao R, Aijaz S, Ijaz N, Blair IA, Manson JM. Second trimester amniotic fluid bisphenol A concentration is associated with decreased birth weight in term infants. Reproductive Toxicology. 2017; 67:1-9. https://doi.org/10.1016/j.reprotox.2016.11.007. PMid:27829162 PMCid:PMC5303174.
45. Sengul SISE, Cevdet UGUZ. Nonylphenol in Human Breast Milk in Relation to Sociodemographic Variables, Diet, Obstetrics Histories and Lifestyle Habits in a Turkish Population. Iranian Journal of Public Health. 2017; 46(4):491. PMID: 28540265.
46. Inthavong C, Hommet F, Bordet F, Rigourd V, Guerin T, Dragacci S. Simultaneous liquid chromatography-tandem mass spectrometry analysis of brominated flame retardants (tetrabromobisphenol A and hexabromocyclododecane diastereoisomers) in French breast milk. Chemosphere. 2017; 186:762-769. https://doi.org/10.1016/j.chemosphere.2017.08.020. PMid:28821000.
47. Fernandez MF, Arrebola JP, Jimenez-Diaz I, Saenz JM, Molina-Molina JM, Ballesteros O, Kortenkamp A, Olea N. Bisphenol A and other phenols in human placenta from children with cryptorchidism or hypospadias. Reproductive Toxicology. 2016; 59:89-95. https://doi.org/10.1016/j.reprotox.2015.11.002. PMid:26602963.
48. Sood S, Shekhar S, Santosh W. Dimorphic placental stress: A repercussion of interaction between Endocrine Disrupting Chemicals (EDCs) and fetal sex. Medical Hypotheses. 2017; 99:73-75. https://doi.org/10.1016/j.mehy.2017.01.002. PMid:28110704.
49. Skinner M. Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability. Epigenetics. 2011; 6(7):838-842. https://doi.org/10.4161/epi.6.7.16537. PMid:21637037 PMCid:PMC5703187.
50. Dambal VY, Selvan KP, Lite C, Barathi S, Santosh W. Developmental toxicity and induction of vitellogenin in embryo-larval stages of zebrafish (Daniorerio) exposed to methyl Paraben. Ecotoxicology and Environmental Safety. 2017; 141:113-118. https://doi.org/10.1016/j.ecoenv.2017.02.048. PMid:28324817.
51. Moral R, Wang R, Russo IH, Lamartiniere CA, Pereira J, Russo J. Effect of prenatal exposure to the endocrine disruptor bisphenol A on mammary gland morphology and gene expression signature. Journal of Endocrinology. 2008; 196(1):101-112. https://doi.org/10.1677/JOE-07-0056. PMid:18180321.
52. Waddington C. The epigenotype. Endeavour. 1942; 1:18-20. 10.1093/ije/dyr184.
53. Russo VE, Martienssen RA, Riggs AD. Epigenetic mechanisms of gene regulation. Cold Spring Harbor Laboratory Press. 1996. https://doi.org/10.1017/s0016672397229320.
54. Seki Y, Yamaji M, Yabuta Y, Sano M, Shigeta M, Matsui Y, Saga Y, Tachibana M, Shinkai Y, Saitou M. Cellular dynamics associated with the genome-wide epigenetic reprogramming in migrating primordial germ cells in mice. Development. 2007; 134(14):2627-2638. https://doi.org/10.1242/dev.005611. PMid:17567665.
55. Tarantino LM, Sullivan PF, Meltzer-Brody S. Using animal models to disentangle the role of genetic, epigenetic, and environmental influences on behavioral outcomes associated with maternal anxiety and depression. Frontiers in Psychiatry. 2011; 2:10. https://doi.org/10.3389/fpsyt.2011.00044. PMid:21811473 PMCid:PMC3141357.
56. Kim MS, Kondo T, Takada I, Youn MY, Yamamoto Y, Takahashi S, Matsumoto T, Fujiyama S, Shirode Y, Yamaoka I, Kitagawa H. DNA demethylation in hormone-induced transcriptional derepression. Nature. 2009; 461(7266):1007-1012. https://doi.org/10.1038/nature08456. PMid:19829383.
57. Weber M, Schubeler D. Genomic patterns of DNA methylation: targets and function of an epigenetic mark. Current Opinion in Cell Biology. 2007; 19(3):273-280. https://doi.org/10.1016/j.ceb.2007.04.011. PMid:17466503.
58. Goll MG, Kirpekar F, Maggert KA, Yoder JA, Hsieh CL, Zhang X, Golic KG, Jacobsen SE, Bestor TH. Methylation of tRNAAsp by the DNA methyltransferase homolog Dnmt2. Science. 2006; 311(5759):395-398. https://doi.org/10.1126/science.1120976. PMid:16424344.
59. Newell-Price J, Clark AJ, King P. DNA methylation and silencing of gene expression. Trends in Endocrinology and Metabolism. 2000; 11(4):142-148. https://doi.org/10.1016/S1043-2760(00)00248-4.
60. Hervouet E, Vallette FM, Cartron PF. Dnmt3/transcription factor interactions as crucial players in targeted DNA methylation. Epigenetics. 2009; 4(7):487-499. https://doi.org/10.4161/epi.4.7.9883. PMid:19786833.

61. Reik W, Walter J. Evolution of imprinting mechanisms: The battle of the sexes begins in the zygote. Nature Genetics. 2001a; 27(3):255-256. https://doi.org/10.1038/85804. PMid:11242103.
62. Reik W, Walter J. Genomic imprinting: parental influence on the genome. Nature Reviews Genetics. 2001b; 2(1):21-32. https://doi.org/10.1038/35047554. PMid:11253064.
63. Tucker KL, Beard C, Dausmann J, Jackson-Grusby L, Laird PW, Lei H, Li E, Jaenisch, R. Germ-line passage is required for establishment of methylation and expression patterns of imprinted but not of nonimprinted genes. Genes and development. 1996; 10(8):1008-1020. https://doi.org/10.1101/gad.10.8.1008. PMid:8608936.
64. Santos F, Dean W. Epigenetic reprogramming during early development in mammals. Reproduction. 2004; 127(6):643-651. https://doi.org/10.1530/rep.1.00221. PMid:15175501.
65. Mayer W, Niveleau A, Walter J, Fundele R, Haaf T. Embryogenesis: Demethylation of the zygotic paternal genome. Nature. 2000; 403(6769):501-502. https://doi.org/10.1038/35000656. PMid:10676950.
66. Dean W, Santos F, Reik W. February. Epigenetic Reprogramming in Early Mammalian Development and Following Somatic Nuclear Transfer. In: Seminars in Cell and Developmental Biology; 2003. 14(1), p. 93-100. https://doi.org/10.1016/S1084-9521(02)00141-6.
67. Dean W, Santos F, Stojkovic M, Zakhartchenko V, Walter J, Wolf E, Reik W. Conservation of methylation reprogramming in mammalian development: aberrant reprogramming in cloned embryos. Proceedings of the National Academy of Sciences. 2001; 98(24):13734-13738. https://doi.org/10.1073/pnas.241522698. PMid:11717434 PMCid:PMC61110.
68. Bestor TH. The DNA methyltransferases of mammals. Human Molecular Genetics. 2000; 9(16):2395-2402. https://doi.org/10.1093/hmg/9.16.2395. PMid:11005794.
69. Santos F, Hendrich B, Reik W, Dean W. Dynamic reprogramming of DNA methylation in the early mouse embryo. Developmental Biology. 2002; 241(1):172-182. https://doi.org/10.1006/dbio.2001.0501. PMid:11784103.
70. Ginsburg MALKA, Snow MH, McLaren ANNE. Primordial germ cells in the mouse embryo during gastrulation. Development. 1990; 110(2):521-528. https://doi.org/10.1242/dev.110.2.521. PMid:2133553.
71. Lees-Murdock DJ, Walsh CP. DNA methylation reprogramming in the germ line. Epigenetics. 2008; 3(1):5-13. https://doi.org/10.4161/epi.3.1.5553. PMid:18259118.
72. Iguchi-Ariga SM, Schaffner W. CpG methylation of the cAMP-responsive enhancer/promoter sequence TGACGTCA abolishes specific factor binding as well as transcriptional activation. Genes and Development. 1989; 3(5):612-619. https://doi.org/10.1101/gad.3.5.612. PMid:2545524.
73. Campanero MR, Armstrong MI, Flemington EK. CpG methylation as a mechanism for the regulation of E2F activity. Proceedings of the National Academy of Sciences. 2000; 97(12):6481-6486. https://doi.org/10.1073/pnas.100340697. PMid:10823896 PMCid:PMC18629.
74. Miranda TB, Jones PA. DNA methylation: the nuts and bolts of repression. Journal of Cellular Physiology. 2007; 213(2):384-390. https://doi.org/10.1002/jcp.21224. PMid:17708532.
75. Jones PL, Veenstra GCJ, Wade PA, Vermaak D, Kass SU, Landsberger N, Strouboulis J, Wolffe AP. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nature Genetics. 1998; 19(2):187-191. https://doi.org/10.1038/561. PMid:9620779.
76. Nan X, Ng HH, Johnson CA, Laherty CD, Turner BM, Eisenman RN, Bird A. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature. 1998; 393(6683):386-389. https://doi.org/10.1038/30764. PMid:9620804.
77. Wade PA, Gegonne A, Jones PL, Ballestar E, Aubry F, Wolffe AP. Mi-2 complex couples DNA methylation to chromatin remodelling and histone deacetylation. Nature Genetics. 1999; 23(1):62-66. https://doi.org/10.1038/12664. PMid:10471500.
78. Fuks F, Hurd PJ, Wolf D, Nan X, Bird AP, Kouzarides T. The methyl-CpG-binding protein MeCP2 links DNA methylation to histone methylation. Journal of Biological Chemistry. 2003; 278(6):4035-4040. https://doi.org/10.1074/jbc.M210256200. PMid:12427740.
79. Bogdanovic O, Veenstra GJC. DNA methylation and methyl-CpG binding proteins: Developmental requirements and function. Chromosoma. 2009; 118(5):549-565. https://doi.org/10.1007/s00412-009-0221-9. PMid:19506892 PMCid:PMC2729420.
80. Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell. 2004; 116(2):281-297. https://doi.org/10.1016/S0092-8674(04)00045-5.
81. Siomi H, Siomi MC. Posttranscriptional regulation of microRNA biogenesis in animals. Molecular Cell. 2010; 38(3):323-332. https://doi.org/10.1016/j.molcel.2010.03.013. PMid:20471939.
82. Carrington JC, Ambros V. Role of microRNAs in plant and animal development. Science. 2003; 301(5631):336-338. https://doi.org/10.1126/science.1085242. PMid:12869753.
83. Ambros V. The functions of animal microRNAs. Nature. 2004; 431(7006):350. https://doi.org/10.1038/nature02871. PMid:15372042.
84. Hatfield SD, Shcherbata HR, Fischer KA, Nakahara K. Stem cell division is regulated by the microRNA pathway. Nature. 2005; 435(7044):974. https://doi.org/10.1038/nature03816. PMid:15944714.

85. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. Science. 2001; 294(5543):853-858. https://doi.org/10.1126/science.1064921. PMid:11679670.
86. Lee Y, Jeon K, Lee JT, Kim S, Kim VN. MicroRNA maturation: stepwise processing and subcellular localization. The EMBO Journal. 2002; 21(17):4663-4670. https://doi.org/10.1093/emboj/cdf476. PMid:12198168 PMCid:PMC126204.
87. Mourelatos Z, Dostie J, Paushkin S, Sharma A, Charroux B, Abel L, Rappsilber J, Mann M, Dreyfuss G. miRNPs: a novel class of ribonucleoproteins containing numerous microRNAs. Genes and Development. 2002; 16(6):720-728. https://doi.org/10.1101/gad.974702. PMid:11914277 PMCid:PMC155365.
88. Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Radmark O, Kim S, Kim VN. The nuclear RNase III Drosha initiates microRNA processing. Nature. 2003; 425(6956):415-419. https://doi.org/10.1038/nature01957. PMid:14508493.
89. Han J, Lee Y, Yeom KH, Kim YK, Jin H, Kim VN. The Drosha-DGCR8 complex in primary microRNA processing. Genes and Development. 2004; 18(24):3016-3027. https://doi.org/10.1101/gad.1262504. PMid:15574589 PMCid:PMC535913.
90. Zeng Y, Yi R, and Cullen BR. Recognition and cleavage of primary microRNA precursors by the nuclear processing enzyme Drosha. The EMBO Journal. 2005; 24(1):138-148. https://doi.org/10.1038/sj.emboj.7600491. PMid:15565168 PMCid:PMC544904.
91. Martin R, Smibert P, Yalcin A, Tyler D.M, Schafer U, Tuschl T, Lai EC. A Drosophila pasha mutant distinguishes the canonical microRNA and mirtron pathways. Molecular and Cellular Biology. 2009; 29(3):861-870. https://doi.org/10.1128/MCB.01524-08. PMid:19047376 PMCid:PMC2630677.
92. Chendrimada TP, Gregory RI, Kumaraswamy E, Norman J, Cooch N, Nishikura K, Shiekhattar R. TRBP recruits the Dicer complex to Ago2 for microRNA processing and gene silencing. Nature. 2005; 436(7051):740-744. https://doi.org/10.1038/nature03868. PMid:15973356 PMCid:PMC2944926.
93. Peters L, Meister G. Argonaute proteins: Mediators of RNA silencing. Molecular cell. 2007; 26(5):611-623. https://doi.org/10.1016/j.molcel.2007.05.001. PMid:17560368.
94. Jakymiw A, Lian S, Eystathioy T, Li S, Satoh M, Hamel JC, Fritzler MJ, Chan EK. Disruption of GW bodies impairs mammalian RNA interference. Nature Cell Biology. 2005; 7(12):1267-1274. https://doi.org/10.1038/ncb1334. PMid:16284622.
95. Behm-Ansmant I, Rehwinkel J, Doerks T, Stark A, Bork P, Izaurralde E. mRNA degradation by miRNAs and GW182 requires both CCR4: NOT deadenylase and DCP1: DCP2 decapping complexes. Genes and Development. 2006; 20(14):1885-1898. https://doi.org/10.1101/gad.1424106. PMid:16815998 PMCid:PMC1522082.
96. Chu CY, Rana TM. Translation repression in human cells by microRNA-induced gene silencing requires RCK/p54. PLoS Biology. 2006; 4(7):e210. https://doi.org/10.1371/journal.pbio.0040210. PMid:16756390 PMCid:PMC1475773.
97. Winter J, Jung S, Keller S, Gregory RI, Diederichs S. Many roads to maturity: MicroRNA biogenesis pathways and their regulation. Nature Cell Biology. 2009; 11(3):228-234. https://doi.org/10.1038/ncb0309-228. PMid:19255566.
98. Ha M, Kim VN. Regulation of microRNA biogenesis. Nature Reviews Molecular Cell Biology. 2014; 15(8):509-524. https://doi.org/10.1038/nrm3838. PMid:25027649.
99. Abdelfattah AM, Park C, Choi MY. Update on non-canonical microRNAs. Biomolecular Concepts. 2014; 5(4):275-287. https://doi.org/10.1515/bmc-2014-0012. PMid:25372759 PMCid:PMC4343302.
100. Havens MA, Reich AA, Duelli DM, Hastings ML. Biogenesis of mammalian microRNAs by a non-canonical processing pathway. Nucleic Acids Research. 2012; 40(10):4626-4640. https://doi.org/10.1093/nar/gks026. PMid:22270084 PMCid:PMC3378869.
101. Newbold RR, Padilla-Banks E, Jefferson WN. Adverse effects of the model environmental estrogen diethylstilbestrol are transmitted to subsequent generations. Endocrinology. 2006; 147(6):s11-s17. https://doi.org/10.1210/en.2005-1164. PMid:16690809.
102. Newbold RR, Padilla-Banks E, Snyder RJ, Phillips TM, Jefferson WN. Developmental exposure to endocrine disruptors and the obesity epidemic. Reproductive Toxicology. 2007; 23(3):290-296. https://doi.org/10.1016/j.reprotox.2006.12.010. PMid:17321108 PMCid:PMC1931509.
103. Bateson P, Barker D, Clutton-Brock T, Deb D, Dudine B, Foley RA, Gluckman P, Godfrey K, Kirkwood T, Lahr MM, McNamara J. Developmental plasticity and human health. Nature. 2004; 430(6998):419-421. https://doi.org/10.1038/nature02725. PMid:15269759.
104. Warri A, Saarinen N, Makela S, Hilakivi-Clarke L. The role of early life genistein exposures in modifying breast cancer risk. British Journal of Cancer. 2008; 98(9):1485-1493. https://doi.org/10.1038/sj.bjc.6604321. PMid:18392054 PMCid:PMC2391102.
105. Weaver I, Cervoni N, Champagne F, Alessio AD, Sharma S, Seckl J, Dymov S, Szyf M, Meaney M. Epigenetic programming by maternal behavior. Nature Neuroscience.

2004; 7(8):847-854. https://doi.org/10.1038/nn1276. PMid:15220929.

106. Champagne FA, Weaver IC, Diorio J, Dymov S, Szyf M, Meaney MJ. Maternal care associated with methylation of the estrogen receptor-α1b promoter and estrogen receptor-α expression in the medial preoptic area of female offspring. Endocrinology. 2006; 147(6):2909-2915. https://doi.org/10.1210/en.2005-1119. PMid:16513834.
107. Meaney MJ Szyf M. Maternal care as a model for experience-dependent chromatin plasticity? Trends in Neurosciences. 2005; 28(9):456-463. https://doi.org/10.1016/j.tins.2005.07.006. PMid:16054244.
108. Beery AK, Francis DD. Adaptive significance of natural variations in maternal care in rats: A translational perspective. Neuroscience and Biobehavioral Reviews. 2011; 35(7):1552-1561. https://doi.org/10.1016/j.neubiorev.2011.03.012. PMid:21458485 PMCid:PMC3104121.
109. Curley JP, Champagne FA. Influence of maternal care on the developing brain: Mechanisms, temporal dynamics and sensitive periods. Frontiers in neuroendocrinology. 2016; 40:52-66. https://doi.org/10.1016/j.yfrne.2015.11.001. PMid:26616341 PMCid:PMC4783284.
110. Dolinoy DC. Weidman JR, Waterland RA, Jirtle RL. Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. Environmental Health Perspectives. 2006; 114(4):567. https://doi.org/10.1289/ehp.8700. PMid:16581547 PMCid: PMC1440782
111. Yenbutr P, Hilakivi-Clarke L, Passaniti A. Hypomethylation of an exon I estrogen receptor CpG island in spontaneous and carcinogen-induced mammary tumorigenesis in the rat. Mechanisms of Ageing and Development. 1998; 106(1-2):93-102. https://doi.org/10.1016/S0047-6374(98)00093-1
112. Keyes MK, Jang H, Mason JB, Liu Z, Crott JW, Smith DE, Friso S, Woon CS. Older age and dietary folate are determinants of genomic and p16-specific DNA methylation in mouse colon. The Journal of Nutrition Biochemical, Molecular, and Genetic Mechanisms. 2007; 1713-1717. https://doi. org/10.1017/s0007114510000322. PMid:17585020
113. Kotsopoulos J, Sohn KJ, Kim YI. Postweaning dietary folate deficiency provided through childhood to puberty permanently increases genomic DNA methylation in adult rat liver. The Journal of Nutrition. 2008. 138(4):703-709. 10.1093/carcin/24.1.81. https://doi.org/10.1093/jn/138.4.703. PMid:18356324.
114. Kinsella MT, Monk C. Impact of maternal stress, depression and anxiety on fetal neurobehavioral development. Clinical Obstetrics and Gynecology. 2009; 52(3):425. https://doi.org/10.1097/GRF.0b013e3181b52df1. PMid:19661759 PMCid:PMC3710585.
115. Zucchi FC, Yao Y, Ward ID, Ilnytskyy Y, Olson DM, Benzies K, Kovalchuk I, Kovalchuk O, Metz GA. Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. PloS one. 2013; 8(2):e56967. https://doi.org/10.1371/journal.pone.0056967. PMid:23451123 PMCid:PMC3579944.
116. Harper L. Epigenetic inheritance and the intergenerational transfer of experience. Psychological Bulletin. 2005; 131(3):340. https://doi.org/10.1037/0033-2909.131.3.340. PMid:15869332.
117. Skinner MK. Endocrine disruptor induction of epigenetic transgenerational inheritance of disease. Molecular and Cellular Endocrinology. 2014; 398(1):4-12. https://doi.org/10.1016/j.mce.2014.07.019. PMid:25088466 PMCid:PMC4262585.
118. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 2005; 308(5727):1466-1469. . https://doi.org/10.1126/science.1108190. PMid:15933200.
119. Guerrero-Bosagna C, Settles M, Lucker B. Skinner M. Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. PLoS ONE. 2010; 5(9):e13100. https://doi.org/10.1371/journal.pone.0013100. PMid:20927350 PMCid:PMC2948035
120. Salian S, Doshi T, Vanage G. Impairment in protein expression profile of testicular steroid receptor coregulators in male rat offspring perinatally exposed to Bisphenol A. Life Sciences. 2009a; 85(1-2):11-18. https://doi.org/10.1016/j.lfs.2009.04.005. PMid:19379760.
121. Bruner-Tran K, Osteen K. Developmental exposure to TCDD reduces fertility and negatively affects pregnancy outcomes across multiple generations. Reproductive Toxicology. 2011; 31(3):344-350. https://doi.org/10.1016/j.reprotox.2010.10.003. PMid:20955784 PMCid:PMC3044210.
122. Matthews S, Phillips D. Transgenerational inheritance of stress pathology. Experimental Neurology. 2012; 233(1):95-101. 10.1016/j.expneurol.2011.01.009. https://doi.org/10.1016/j.expneurol.2011.01.009. PMid:21281632.
123. Anway M, Leathers C, Skinner M. Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology. 2006; 147(12):5515-5523. https://doi.org/10.1210/en.2006-0640. PMid:16973726 PMCid:PMC5940332.
124. Anway MD, Skinner MK. Epigenetic programming of the germ line: Effects of endocrine disruptors on the development of transgenerational disease. Reproductive Biomedicine Online. 2008. 16(1):23-25. https://doi.org/10.1016/S1472-6483(10)60553-6.
125. Nilsson E, Anway M, Stanfield J, Skinner M. Transgenerational epigenetic effects of the endocrine

disruptor vinclozolin on pregnancies and female adult onset disease. Reproduction. 2008; 135(5):713-721. https://doi.org/10.1530/REP-07-0542. PMid:18304984 PMCid:PMC5703189.

126. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner M. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS ONE. 2013; 8(1):e55387. https://doi.org/10.1371/journal.pone.0055387. PMid:23359474 PMCid:PMC3554682.

127. Pocar P, Fiandanese N, Berrini A, Secchi C, Borromeo V. Maternal exposure to di (2-ethylhexyl)phthalate (DEHP) promotes the transgenerational inheritance of adult-onset reproductive dysfunctions through the female germline in mice. Toxicology and Applied Pharmacology. 2017; 322:113-121. https://doi.org/10.1016/j.taap.2017.03.008. PMid:28286118.

128. Doyle T, Bowman J, Windell V, McLean D, Kim K. Transgenerational effects of Di-(2-ethylhexyl) phthalate on testicular germ cell associations and spermatogonial stem cells in mice1. Biology of Reproduction. 2013; 88(5):10. https://doi.org/10.1095/biolreprod.112.106104. PMid:23536373 PMCid:PMC4013901.

129. Salian S, Doshi T, Vanage G. Perinatal exposure of rats to Bisphenol A affects the fertility of male offspring. Life Sciences. 2009b.; 85(21-22):742-752. https://doi.org/10.1016/j.lfs.2009.10.004. PMid:19837096.

130. Wolstenholme J, Edwards M, Shetty S, Gatewood J, Taylor J, Rissman E, Connelly J. Gestational exposure to bisphenol a produces transgenerational changes in behaviors and gene expression. Endocrinology. 2012; 153(8):3828-3838. https://doi.org/10.1210/en.2012-1195. PMid:22707478 PMCid:PMC3404345.

131. Skinner MK. Role of epigenetics in developmental biology and transgenerational inheritance. Birth Defects Research Part C: Embryo Today: Reviews. 2011; 93(1):51-55. https://doi.org/10.1002/bdrc.20199. PMid:21425441 PMCid:PMC5703206.

132. Grun F, Blumberg B. Endocrine disrupters as obesogens. Molecular and Cellular Endocrinology. 2009; 304(1):19-29. https://doi.org/10.1016/j.mce.2009.02.018. PMid:19433244 PMCid:PMC2713042.

133. Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: Implications for research and public health. Environmental Health. 2012; 11(1):42. https://doi.org/10.1186/1476-069X-11-42. PMid:22715989 PMCid:PMC3384466.

134. Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, Khoury J. Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. Neurotoxicology and teratology. 2011; 33(5):558-566. https://doi.org/10.1016/j.ntt.2011.08.003. PMid:21854843 PMCid:PMC3183357.

135. Rier SE, Zarmakoupis PN, Hu XIAOLING, Becker JL. Dysregulation of interleukin-6 responses in ectopic endometrial stromal cells: Correlation with decreased soluble receptor levels in peritoneal fluid of women with endometriosis. The Journal of Clinical Endocrinology and Metabolism. 1995; 80(4):1431-1437. https://doi.org/10.1210/jcem.80.4.7714120. PMid:7714120.

136. Boberg J, Mandrup KR, Jacobsen PR, Isling LK, Hadrup N, Berthelsen L, Elleby A, Kiersgaard M, Vinggaard AM, Hass U, Nellemann C. Endocrine disrupting effects in rats perinatally exposed to a dietary relevant mixture of phytoestrogens. Reproductive Toxicology. 2013; 40:41-51. https://doi.org/10.1016/j.reprotox.2013.05.014. PMid:23770295.

137. Masuo Y, Ishido M. Neurotoxicity of endocrine disruptors: Possible involvement in brain development and neurodegeneration. Journal of Toxicology and Environmental Health, Part B. 2011; 14(5-7):346-369. https://doi.org/10.1080/10937404.2011.578557. PMid:21790316.

138. Kundakovic M, Gudsnuk K, Franks B, *et al*. Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. Proceedings of the National Academy of Sciences. 2013; 110(24):9956-9961. https://doi.org/10.1073/pnas.1214056110. PMid:23716699 PMCid:PMC3683772.

139. Ma Y, Xia W, Wang DQ, *et al*. Hepatic DNA methylation modifications in early development of rats resulting from perinatal BPA exposure contribute to insulin resistance in adulthood. Diabetologia. 2013; 56(9):2059-2067. https://doi.org/10.1007/s00125-013-2944-7. PMid:23748860.

140. Bromer JG, Zhou Y, Taylor MB, *et al*. Bisphenol-A exposure in utero leads to epigenetic alterations in the developmental programming of uterine estrogen response. The FASEB Journal. 2010; 24(7):2273-2280. https://doi.org/10.1096/fj.09-140533. PMid:20181937 PMCid:PMC3230522.

141. Strakovsky RS, Wang H, Engeseth NJ, *et al*. Developmental Bisphenol A (BPA) exposure leads to sex-specific modification of hepatic gene expression and epigenome at birth that may exacerbate high-fat diet-induced hepatic steatosis. Toxicology and Applied Pharmacology. 2015; 284(2):101-112. https://doi.org/10.1016/j.taap.2015.02.021. PMid:25748669 PMCid:PMC4520316.

142. Chao HH, Zhang XF, Chen B, *et al*. Bisphenol A exposure modifies methylation of imprinted genes in mouse oocytes via the estrogen receptor signaling pathway. Histochemistry and Cell Biology. 2012; 137(2):249-259. https://doi.org/10.1007/s00418-011-0894-z. PMid:22131059.

143. Kovanecz I, Gelfand R, Masouminia M, *et al*. Oral Bisphenol A (BPA) given to rats at moderate doses is associated with erectile dysfunction, cavernosal lipofibrosis and alterations of global gene transcription. International Journal of Impotence Research. 2014; 26(2):67-75. https://doi.org/10.1038/ijir.2013.37. PMid:24305612 PMCid:PMC4098849.
144. Doshi T, Mehta SS, Dighe V, *et al*. Hypermethylation of estrogen receptor promoter region in adult testis of rats exposed neonatally to bisphenol A. Toxicology. 2011; 289(2):74-82. https://doi.org/10.1016/j.tox.2011.07.011. PMid:21827818.
145. Jadhav RR, Santucci-Pereira J, Wang YV, *et al*. DNA Methylation Targets Influenced by Bisphenol A and/or Genistein Are Associated with Survival Outcomes in Breast Cancer Patients. Genes (Basel). 2017; 8(5):144. https://doi.org/10.3390/genes8050144. PMid:28505145 PMCid:PMC5448018.
146. Doherty LF, Bromer JG, Zhou Y, *et al*. In utero exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) increases EZH2 expression in the mammary gland: An epigenetic mechanism linking endocrine disruptors to breast cancer. Hormones and Cancer. 2010; 1(3):146-155. https://doi.org/10.1007/s12672-010-0015-9. PMid:21761357 PMCid:PMC3140020.
147. Zama AM, Uzumcu M. Fetal and neonatal exposure to the endocrine disruptor methoxychlor causes epigenetic alterations in adult ovarian genes. Endocrinology. 2009; 2009(10):4681-91. https://doi.org/10.1210/en.2009-0499. PMid:19589859 PMCid:PMC2754680.
148. Bromer JG, Wu J, Zhou Y, Taylor HS. Hypermethylation of homeobox A10 by in utero diethylstilbestrol exposure: An epigenetic mechanism for altered developmental programming. Endocrinology. 2009; 150(7):3376-3382. https://doi.org/10.1210/en.2009-0071. PMid:19299448 PMCid:PMC2703508.
149. Chen J, Wu S, Wen S, *et al*. The mechanism of environmental endocrine disruptors (DEHP) induces epigenetic transgenerational inheritance of cryptorchidism. PloS One. 2015; 10.1371/journal.pone.0126403. https://doi.org/10.1371/journal.pone.0126403. PMid:26035430 PMCid:PMC4452760.
150. Iqbal K, Tran DA, Li AX, *et al*. Deleterious effects of endocrine disruptors arecorrected in the mammalian germline by epigenome reprogramming. Genome Biology. 2015; 16(1):59. https://doi.org/10.1186/s13059-015-0619-z. PMid:25853433 PMCid:PMC4376074.
151. Song Y, Wu N, Wang S, *et al*. Transgenerational impaired male fertility with an Igf2 epigenetic defect in the rat are induced by the endocrine disruptor p, p´-DDE. Human Reproduction. 2014; 29(11):2512-2521. . https://doi.org/10.1093/humrep/deu208. PMid:25187598.
152. Chanyshev MD, Kosorotikov NI, Titov SE, *et al*. Expression of microRNAs, CYP1A1 and CYP2B1 in the livers and ovaries of female rats treated with DDT and PAHs. Life Sciences. 2014; 103(2):95-100. https://doi.org/10.1016/j.lfs.2014.03.031. PMid:24727239.
153. Meunier L, Siddeek B, Vega A, *et al*. Perinatal programming of adult rat germ cell death after exposure to xenoestrogens: Role of microRNA miR-29 family in the down-regulation of DNA methyltransferases and Mcl-1. Endocrinology. 2012; 153(4):1936-1947. https://doi.org/10.1210/en.2011-1109. PMid:22334722.
154. Dolinoy DC, Weidman JR, Waterland RA, Jirtle RL. Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. Environmental Health Perspectives. 2006; 114(4):567. https://doi.org/10.1289/ehp.8700. PMid:16581547 PMCid:PMC1440782.
155. Kirchner S, Kieu T, Chow C, *et al*. Prenatal exposure to the environmental obesogentributyltin predisposes multipotent stem cells to become adipocytes. Molecular Endocrinology. 2010; 24(3):526-539. https://doi.org/10.1210/me.2009-0261. PMid:20160124 PMCid:PMC2840805.
156. Strakovsky RS, Lezmi S, Shkoda I, *et al*. In utero growth restriction and catch-up adipogenesis after developmental di (2-ethylhexyl) phthalate exposure cause glucose intolerance in adult male rats following a high-fat dietary challenge. The Journal of Nutritional Biochemistry. 2015; 26(11):1208-1220. https://doi.org/10.1016/j.jnutbio.2015.05.012. PMid:26188368 PMCid:PMC4631689.
157. Alworth LC, Howdeshell KL, Ruhlen RL, *et al*. Uterine responsiveness to estradiol and DNA methylation are altered by fetal exposure to diethylstilbestrol and methoxychlor in CD-1 mice: Effects of low versus high doses. Toxicology and Applied Pharmacology. 2002; 183(1):10-22. https://doi.org/10.1006/taap.2002.9459. PMid:12217638.
158. Lyn-Cook BD, Blann E, Payne PW, *et al*. Methylation profile and amplification of proto-oncogenes in rat pancreas induced with phytoestrogens. Proceedings of the Society for Experimental Biology and Medicine. 1995; 208(1):116-119. https://doi.org/10.3181/00379727-208-43842. PMid:7534422.
159. Buckley J, Willingham E, Agras K, Baskin LS. Embryonic exposure to the fungicide vinclozolin causes virilization of females and alteration of progesterone receptor expression in vivo: An experimental study in mice. Environmental Health. 2006; 5(1):4. https://doi.org/10.1186/1476-069X-5-4. PMid:16504050 PMCid:PMC1403752.