HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Environ Int. 2018 May ; 114: 77–86. doi:10.1016/j.envint.2018.02.014.

Epigenetics as a mechanism linking developmental exposures to long-term toxicity

R Barouki[1,2], **E Melén**[3,4], **Z Herceg**[5], **J Beckers**[6,7,8], **J Chen**[9], **M Karagas**[10], **A Puga**[11], **Y Xia**[11], **L Chadwick**[12], **W Yan**[13,14], **K Audouze**[15], **R Slama**[16], **J Heindel**[17], **P Grandjean**[18,19], **T Kawamoto**[20], and **K Nohara**[21]

[1]INSERM UMR-S 1124, Université Paris Descartes, Paris, France

[2]Service de Biochimie Métabolomique et Protéomique, Hôpital Necker Enfants Malades, AP-HP, Paris, France

[3]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[4]Sachs' Children and Youth Hospital, and Centre for Occupational and Environmental Medicine, Stockholm County Council, Sweden

[5]Epigenetics Group, International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, F-69008, Lyon, France

[6]Institute of Experimental Genetics, Helmholtz Zentrum München GmbH, 85764 Neuherberg, Germany

[7]Technische Universität München, Chair of Experimental Genetics, 85354 Freising, Germany

[8]German Center for Diabetes Research (DZD), 85764 Neuherberg, Germany

[9]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY 10029

[10]Department of Epidemiology, Children's Environmental Health and Disease Prevention Research Center at Dartmouth, Hanover, NH, USA

[11]Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio

[12]NIEHS, Research Triangle Park, NC

[13]Department of Physiology and Cell Biology, University of Nevada, Reno School of Medicine, 1664 North Virginia Street, Reno, NV 89557, USA MS575

[14]Department of Biology, University of Nevada, Reno, 1664 North Virginia Street, Reno, NV 89557, USA

[15]INSERM UMR-S973, Molécules Thérapeutiques in silico, University of Paris Diderot, Paris, France

[16]Institute for Advanced Biosciences, INSERM U1209, CNRS UMR 5309, University Grenoble Alpes, Grenoble, France

[17]Program in Endocrine Disruption Strategies, Commonweal, Bolinas CA

[18]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[19]Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark

[20]Department of Environmental Health, University of Occupational and Environmental Health, Kitakyushu 807-8555, Japan

[21]Center for Health and Environmental Risk Research, National Institute for Environmental Studies, Tsukuba 305-8506, Japan

Summary

A variety of experimental and epidemiological studies lend support to the Developmental Origin of Health and Disease (DOHaD) concept. Yet, the actual mechanisms accounting for mid- and long-term effects of early-life exposures remain unclear. Epigenetic alterations such as changes in DNA methylation, histone modifications and the expression of certain RNAs have been suggested as possible mediators of long-term health effects of environmental stressors.

This report captures discussions and conclusions debated during the last Prenatal Programming and Toxicity meeting held in Japan. Its first aim is to propose a number of criteria that are critical to support the primary contribution of epigenetics in DOHaD and intergenerational transmission of environmental stressors effects. The main criteria are the full characterization of the stressors, the actual window of exposure, the target tissue and function, the specificity of the epigenetic changes and the biological plausibility of the linkage between those changes and health outcomes. The second aim is to discuss long-term effects of a number of stressors such as smoking, air pollution and endocrine disruptors in order to identify the arguments supporting the involvement of an epigenetic mechanism. Based on the developed criteria, missing evidence and suggestions for future research will be identified. The third aim is to critically analyze the evidence supporting the involvement of epigenetic mechanisms in intergenerational and transgenerational effects of environmental exposure and to particularly discuss the role of placenta and sperm.

While the article is not a systematic review and is not meant to be exhaustive, it critically assesses the contribution of epigenetics in the long-term effects of environmental exposures as well as provides insight for future research.

Keywords

endocrine disrupting compounds; tobacco smoking; particulate matter; developmental vulnerability; mechanistic toxicology

Introduction

Non-communicable diseases (NCDs) have increased considerably during the last decades and have become the leading causes of death worldwide (Balbus et al., 2013; Bauer et al.,

2014). NCDs have increased at a pace that cannot be explained solely by factors like genetic drift, traditional occupational exposures or traditional smoking effects. Emerging hazards include a variety of factors i.e., sedentary lifestyle and/or lack of exercise, psycho-social stresses, unhealthy diet as well as exposure to environmental pollutants, such as endocrine disruptors (Barouki et al., 2012; Grandjean et al., 2015). Compelling new evidence highlights the early human development period as being particularly sensitive to chemicals and other stressors that can lead to adverse health effects later in life. This is in line with the Developmental Origin of Health and Disease (DOHaD) concept (Barouki et al., 2012; Heindel et al., 2015b, 2015a; Schug et al., 2013). In addition, these stressors may interact to exacerbate detrimental effects, for example when high fat diet is combined with toxic chemicals or when individuals with low socio-economic status are exposed to air pollution (Deguen et al., 2015; Duval et al., 2017). Presently, it is unclear whether different stressors can interfere with the same cellular or molecular targets or can affect different parts of the same pathway. Therefore, a more comprehensive approach highlighting the interactions between different stressors, as put forward by the exposome concept, is needed (Escher et al., 2017; Wild et al., 2013).

Epidemiological studies have provided evidence supporting the impact of exposure to chemicals on developmental programing (Grandjean et al., 2015) during the critical periods of *fetal and child* development. However, mechanistic insight is needed to more convincingly show that developmental exposure leads to toxic effects that appear later in life (Barouki et al., 2012). Epigenetics is such a potential mechanism. Indeed, the pattern of epigenetic markers such as DNA methylation, histone modification and non-coding RNAs, which ultimately regulate chromatin structure or gene activity, is influenced by a variety of exposures including those involving environmental toxicants (Faulk and Dolinoy, 2011). Moreover, epigenetic marks undergo profound changes during development with the establishment of the different cell lineages, and this phenomenon may account for the high vulnerability of this developmental period. Further, there is evidence that environmental stressors can modify epigenetic patterns leading to biological or adverse health outcomes (Barouki et al., 2012). Recent studies and concepts tend to support such a hypothesis. In a recent review, researchers developed the concept of epigenetic memory with both adaptive and toxic implications (Vineis et al., 2017). Furthermore, a recent study suggested that transmissible chromatin opening triggered by inflammatory stress acted as a memory accelerating the response to subsequent stressors (Naik et al., 2017). However, additional studies are required before epigenetic regulation is approved as a mechanism of developmentally-mediated adverse effects later on in life.

These and other fundamental issues have been discussed in the latest PPTOX V (Prenatal Programming and TOXicity V) meeting held in Kitakyushu, Japan (November 2016). This report summarizes questions and conclusions debated during that meeting on epigenetic alterations occurring during the period of developmental programming and their contribution to long-term adverse health consequences. We focus here on relatively stable epigenetic changes and do not discuss short-lived epigenetic modifications. We also take into consideration epigenetic changes occurring during development with possible long-term effects and not the rapidly changing epigenetic landscape that occurs at any stage of life. As

a first step, we list below the criteria that we believe are important to discuss in order to identify or support an epigenetic mechanism and its relevance to exposure-related diseases:

- *1. The stressor*. It is important to point out exactly which stressor or combinations of stressors are studied and their likely adverse effects. In some cases, different stressors may correlate with each other, for example lipophilic contaminants and high fat diets. The availability of both epidemiological data and experimental data is critical for causal attribution.
- *2. The window of exposure*. Since the regulation of epigenetic marks depends on the developmental period, the time at which the exposure takes place is important. In cases where exposure is long-lasting and consistent (e.g. exposure to persistent pollutants like POPs, air pollution or uninterrupted smoking for example), it may affect different targets at different developmental stages and the effects may be more complex.
- *3. The time course*. The time at which epigenetic markers are assessed may not reflect the timing of the exposure and the clinical or other adverse signs may develop much later. The time course is obviously an important issue to consider.
- *4. The target tissue*. In experimental studies, epigenetic regulation can be assessed in a variety of tissues including the suspected target tissue of relevance for each disease or condition. However in epidemiological studies, that is usually not possible. Blood, semen and placenta are the most widely studied and epigenetic changes in these fluids and tissues may not represent processes in the target tissue. Indeed, there is a lack of studies correlating epigenetic changes in blood with changes in target tissues. Thus, epigenetic changes in blood, while useful markers, may not be related to tissue dysfunctions that lead to disease. The heterogeneity of those fluids/tissues is also a concern for the interpretation of the data.
- *5. The specificity*. There are different levels at which specificity can be investigated. For example, if different stressors lead to the same epigenetic changes, this could be relevant in terms of toxicity despite the lack of specificity of the changes *per se*. Alternatively, a single stressor can lead to a wide variety of epigenetic effects. At the molecular level, specificity can refer to the selective epigenetic modification of a subset of genes in the genome. In many cases, enzymes involved in DNA or histone modification are targeted by a stressor, but why this leads to a modification of the epigenetic pattern of only certain genes remains elusive. It is conceivable that the combination of a generic mechanism with a specific window of exposure may account for the selective effect. In all cases, it is important to determine the specificity of the linkage associating exposure-epigenetic changes-health outcomes.
- *6. The biological plausibility of the linkage between epigenetic changes and health outcomes*. Showing that a specific modification of DNA methylation or histone post-translational regulation is causing a particular health effect remains extremely difficult. Nevertheless, when the target gene function is known, one

can assess the biological plausibility of such a presumably causal effect. For example, when obesity is the considered outcome, an altered methylation of a PPARγ target gene is in line with what is known about the function of this biological pathway. Another example is the correlation between behavioral effects and the regulation of stress genes of the Hypothalamic-Pituitary-Adrenal axis.

In light of the criteria listed above, we will discuss new developments in the field that elucidate the contributions of epigenetics to the DOHaD concept. Following some mechanistic insight, we will specifically address cases in which the contribution of epigenetics has been successfully explored. Our aim is not to be comprehensive but rather to critically assess the state of the science with regard to epigenetics and long-term environmental effects. We will illustrate some of the most prominent research developments with case studies that address the role of sperm and oocyte epigenetics, placental epigenetics, as well as smoking and exposure to chemicals during pregnancy.

General mechanistic aspects of environmental epigenetics and development

Environmental cues enable organisms to react and adapt to changing living conditions. More than a filter that selects potential phenotypic variations, the environment is itself the source of the variation. Environmental signals can modify preexisting genetic and epigenetic states and elicit changes in organisms that increase or decrease their fitness to that particular environment (West-Eberhard, 2005). Compelling epidemiologic evidence suggests that early-life conditions, such as maternal nutrition, stress, smoking and toxic chemical exposures, influence children growth and body composition, and later risk of chronic diseases (Heindel et al., 2017b). This phenomenon may be the consequence of the evolutionarily-derived developmental plasticity of a flexible developing program that can adjust the *in utero* environment for optimal survival, however, this has yet to be proven in the case of chemical toxicity.

As mentioned earlier, a number of epidemiological and animal studies have suggested that the fetal and early postnatal stages are particularly sensitive to the impact of environmental exposure, and that exposures during this critical developmental window may contribute to later onset disease (Grandjean et al., 2015; Heindel et al., 2017a). The mechanism underlying these latent effects is less clear, although a growing body of evidence suggests that epigenetics might play an important role. Epigenetic modifications,, render the underlying DNA sequence either more or less accessible to other components of the transcriptional machinery, and as such, help control gene expression. Epigenetics is an important component of the fundamental mechanism that controls normal development, from pluripotent stem cells, through lineage commitment and differentiation, to the generation of the more than two hundred different cell types that define the adult organism. During this process, epigenetic programing reinforces cell-fate decisions such that although the stem cells and their derivatives share identical genetic materials, they possess different epigenetic signatures, responsible for differential gene expression, distinct cellular activities and biological functions. As the epigenetic patterns of DNA methylation and histone

modification propagate through time and space across the whole organism, they provide a dynamic memory mechanism for gene expression regulation, insuring epigenetic inheritance.

Phenotypic plasticity is a critical feature of early development. Embryonic life is a period of extensive epigenetic programming and the time when the organism is most sensitive to environmental signals (Hanson and Gluckman, 2014; Yamazaki et al., 2003). Environmental exposures occurring during this sensitive window may alter these epigenetic programs, and lead to life-long, permanent changes in the pattern of gene expression (Faulk and Dolinoy, 2011). Through their impact on epigenetic programming, environmental factors can cause changes in gene expression that may affect cellular proliferation leading to altered numbers of cells as well as cell location metabolic activity and lineage differentiation with both short-term and long-term consequences. In this context, the epigenome serves as the interface between gene, environment and developmental outcomes. It is important to emphasize, however, that in most tissues, lifelong dynamic epigenetic modifications are commonplace, leading to alterations of the epigenetic landscape. Early-life epigenetic changes may persist in tissues with long half-lives, like neurons, germ cells or stem cells, but cells with continuous and rapid turnover times may quickly wash out any epigenetic modifications that took place during the exposure period. Hence, the target tissue may critically determine whether an epigenetic change is permanent and transmissible or diluted out by constant turnover.

Studies in animals and humans provide increasing evidence linking specific environmental exposure *in utero* with epigenetic changes in the progeny. One striking example of this phenomenon occurs in mice carrying the agouti viable yellow (Avy) allele, in which the availability of methyl donors in the diet of the dam affects methylation of a cryptic promoter that results in visible changes in coat color of the offspring (Dolinoy, 2008), the latter being a marker of increased susceptibility to disease. In addition to this genetic model, a number of animal studies have linked developmental exposures to methylation changes in endogenous loci. For example, developmental exposure to caffeine induces a cardiac phenotype that is associated with an altered DNA methylation pattern in the adult hearts (Rivkees and Wendler, 2017), and *in utero* exposure to PBDEs has been shown to change TNFα methylation (Dao et al., 2015). In addition, observational human studies have linked *in utero* exposure to famine in the Netherlands with distinct epigenetic changes in progeny 65 years later (Heijmans et al., 2008). It is important to remember that these observed epigenetic changes are a read-out of the actions of enzymes such as histone or DNA methyltransferases, and that these enzymes may be the direct target of environmental chemicals. Developmental exposure to the xenoestrogen diethylstilbestrol (DES) is associated with both an increased susceptibility to uterine leiomyoma, and a change in histone H3K27 trimethylation in a rat model. Later work established a direct link between these observed changes and phosphorylation of the histone methyltransferase EZH2 by phosphatidylinositol 3-kinase (PI3K) (Bredfeldt et al., 2010; Treviño et al., 2015a, 2015b). Notably, one of the best experimental examples to provide evidence for the epigenetic basis of DOHaD is the work of Zawia's group on developmental exposure to lead (Pb) and overexpression of genes related to neurodegenerative diseases in old age. Recent research by this group has shown that lead has the ability to alter DNA methylation, histone modifications, and miRNA

expression in experimental models and in humans, implicating epigenetics in lead induced toxicity and long term changes in individuals. Epigenetic modification could potentially provide a mechanism by which the environment, and toxic exposures contribute to the increased susceptibility of adult neurodegenerative disease (Eid and Zawia, 2016).

Despite these examples, the number of studies that show a causal link between exposure, epigenetic change and tissue function remain few, and there is a need to consider these findings in light of other potential mechanisms that may underlie the latent effects of early life exposures.

Correlating an environmental stressor and epigenetic marks: the case of tobacco smoke

Smoking during pregnancy remains a major public health challenge, despite well-known negative health effects in offspring. Epigenetics, in particular methylation changes, has been suggested as a potential mechanism involved in the pathogenesis of tobacco smoke related diseases. In one of the first epigenome-wide studies on cord blood methylation profiles associated with sustained maternal smoking (stressor) during pregnancy (window of exposure), differential methylation was identified in *AHRR, CYP1A1*, and *GFI1* (Joubert et al., 2012). The fact that *AHRR* (aryl hydrocarbon receptor repressor) and *CYP1A1* (cytochrome P450 family 1 subfamily A) play a key role in the detoxification processes of tobacco smoke components is particularly relevant and illustrates the biological plausibility criteria described above. In the largest study conducted to date, cord blood Illumina 450k data was meta-analyzed from almost 7,000 newborns across 13 cohorts and over 6,000 differentially methylated CpG sites were identified (lowest p-value 5×10^{-193} for *AHRR*) (Joubert et al., 2016). Methylation status at several of the identified CpGs were also shown to affect gene expression. A key issue has been whether methylation patterns early in life induced by environmental exposure may persist to older ages, and this study could convincingly show that identified DNA changes in blood seem to persist at least up to adolescence. Many of the identified genes are known to be associated with orofacial clefts, and cancer and asthma development. However, it is currently not known if the identified methylation changes and expression profiles related to maternal smoking are in the causal pathway towards disease development, or merely reliable biomarkers of exposure. In addition, most epidemiology studies of epigenetic markers have measured changes in accessible tissues or fluids like blood, and not always in disease-relevant target tissues. Since epigenetic markers can differ considerably according to the tested tissues, the correlation between epigenetic changes and health outcomes would be significantly strengthened if the former were observed in the disease-relevant target tissue. A recent study investigating the association between tobacco smoking and DNA methylation in lung tissue revealed that a limited number of loci previously identified as differentially methylated in smokers' blood were found differentially methylated in lung tissue of smokers (Stueve et al., 2017). These results are consistent with the notion that exposure-specific methylation markers identified in blood may, in some cases, reflect changes in the target tissue. When target tissue methylation changes cannot be assessed in human studies, the correlation between these

changes and toxic outcomes can be tested in experimental studies, in line with the criteria listed in the introduction.

Similarly to the studies on birth cohorts, a number of smoking-associated DNA methylation biomarkers have been identified using methylome-wide profiling of adult blood (Harlid et al., 2014; Markunas et al., 2014; Shenker et al., 2013). Among these markers, several loci (*F2RL3*, *AHRR*, 2q37.1 and 6p21.33) were common among most differentially methylated sites. A more recent study on a large prospective cohort combined dimension reduction and methylome variability (most variable probe [MVP]) analyses and longitudinal analysis of former smokers and revealed a marked reversibility of methylation changes after smoking cessation, although specific genes remained differentially methylated decades after smoking cessation (Ambatipudi et al., 2016). In addition, a meta-analysis of genome-wide DNA methylation on more than 15,000 subjects from 16 cohorts has comprehensively catalogued the smoking-associated DNA methylation alterations (Joehanes et al., 2016). Among the genes that are associated with differentially methylated CpGs in smokers there was an enrichment for the pathways associated with cancer, pulmonary function, inflammatory and cardiovascular diseases. Comparison of former and never smokers further confirmed the phenomenon of persistent aberrant methylation, which get attenuated after smoking cessation (Joehanes et al., 2016). These studies demonstrate that smoking has a broad impact on the methylome and that these altered methylation levels persist decades after smoking cessation. Although many of the differentially methylated genes suggest novel biologically relevant effects of smoking, the role of altered methylations in the causal pathways from smoking to the disease remains to be established. For example, the role of *AHRR* methylation in the causal pathway translating smoking exposure to lung cancer (as suggested by mediation analysis) (Fasanelli et al., 2015) has been challenged by a genomics-based Mendelian Randomization approach (Richmond et al., 2016).

Correlating an environmental stressor and epigenetic marks: the case of air pollution exposure

Ambient air pollution exposure has been associated with a number of different negative health effects, including adverse pregnancy outcomes, and methylation changes of genes related to oxidative stress, immunity and inflammatory responses have been suggested to be important mechanisms. Until recently, only candidate gene approaches (e.g. on T-cell regulatory genes such as *FOXP3*) (Nadeau et al., 2010) had been used to study air pollution–methylation associations. The first study evaluating prenatal air pollution exposure (using NO_2 as an indicator of traffic-related air pollution) on methylation levels across the genome in newborns (n=1,508) showed far less significant hits compared to the smoking studies, yet anti-oxidative defense genes (*CAT, TPO*) were highlighted, as well as genes related to mitochondria function (Gruzieva et al., 2017). Another study also analyzed global methylation in relation to air pollution and showed possible correlation with immune cell function (Plusquin et al., 2017). Additional large-scale analyses in this field are now warranted.

In the context of gene-environment interaction effects, epigenetic analyses may provide insight about disease-related pathways. A recent genome-wide interaction study on air pollution (NO_2) and childhood asthma identified and replicated four loci with evidence of interaction (Gref et al., 2017). Significant differential methylation following both short-term (in an experimental setting) and long-term (cohort analyses) air pollution exposure was seen for two of the genes, *DLG2* and *ADCY2* – both genes previously associated with COPD in adults which supports the relevance of those observations. Studies addressing epigenetic changes as causative factors for disease development are ongoing, and recent experimental studies lend support to this concept (Leclercq et al., 2017; Zhong et al., 2017)(Leclercq et al., 2017).

Correlating an environmental stressor and epigenetic marks: the case of Endocrine Disrupting Compounds (EDCs)

Recent reviews have focused on the large number of studies which have shown that developmental exposures to a variety of EDCS in animal (Gore et al., 2015; Grandjean et al., 2015; Heindel et al., 2015b, 2017a) or human studies (Braun, 2017; Heindel et al., 2017b) can result in altered programming that leads to increased disorders or disease risks across the lifespan. There are also numerous studies describing the changes in epigenetic marks due to exposure to EDCs during development. While both effects altered programming leading to increased susceptibility to diseases later in life and alterations in epigenetic regulation are widely accepted, more studies are needed to prove cause and effect. Two early studies that showed neonatal exposure to estrogenic chemicals in a fibroid (Walker and Ho, 2012) and a prostate cancer (Prins and Ho, 2010) animal models were related to epigenetic changes in the tissues. There are now numerous examples in animal models that developmental exposures to EDCs can cause changes in DNA methylation and/or histone marks or microRNAs (Derghal, Djelloul et al. 2016) that can be shown to be related to alterations in gene expression (reviewed in (Ankolkar and Balasinor, 2016; Baccarelli and Bollati, 2009; Casati et al., 2015; Desai et al., 2015; Walker, 2016) This includes BPA (Deb et al., 2016; Dhimolea et al., 2014) phthalates (Martinez-Arguelles and Papadopoulos, 2016), tributyl tin (Kirchner et al., 2010), dioxin (Bruner-Tran et al., 2012; Sofo et al., 2015), metals (Bommarito et al., 2017; Park et al., 2017) and PAHs (Hew et al., 2015). However, there are many effects of EDCs that have been linked to increased susceptibility, but the role of epigenetic modifications has not been examined. Thus this is an important mechanistic link that must be examined in more detail. Moreover, in humans, only few studies linked EDCs (phthalates, bisphenol A, persistent organic pollutants, etc.) exposure to epigenetic marks (Bommarito et al., 2017; Consales et al., 2016; Faulk et al., 2016; Huen et al., 2016; Solomon et al., 2017; Vilahur et al., 2016; Zheng et al., 2017). As noted in another section of this review, developmental exposures to some EDCs can lead to transgenerational inheritance, sometimes called epigenetic transgenerational inheritance because of data showing epigenetic changes across generations. While it seems likely that epigenetic changes play a role in transgenerational inheritance due to EDC exposures more data is needed to prove cause and effect and additionally there may be other mechanisms such as those related to copy number variations (Skinner et al., 2015).

Understanding prenatal effects: role of the placenta

The placenta is a “fetomaternal” organ with two components: the fetal (Chorion frondosum developed from the same blastocyst as the fetus) and the maternal (Decidua basalis developed from the maternal uterine tissue) placenta. It serves as the interface of maternal-fetal interactions and performs critical functions through signaling networks that include cytokines, growth factors and hormones to ensure sufficient transfer of gases and nutrients while also protecting the fetus from maternal reactivity. Thus, it is the primary regulator of intrauterine growth and development through which the developmental trajectory of the fetus may be altered in response to changes in the intrauterine environment. As a readily accessible tissue at birth, placental samples have been and will continue to be collected from several large birth cohort studies. With recent advances in high-throughput screening and integrative genomics, whole-genome characterization of placenta epigenome has been instrumental in our understanding of the developmental origin of human diseases. In the meantime, we have to acknowledge the fact that the placenta undergo rapid epigenomic changes throughout pregnancy, a termed placenta collected at birth may not reflect the dynamics of such changes.

Applying genome-wide DNA methylation array techniques has given rise to a new understanding of the molecular characteristics of the placenta that relates to both prenatal exposures and health outcomes (Everson et al., 2016). These studies further suggest sexually dimorphic patterns in DNA methylation profiles in the placenta that may elucidate differential responses to environmental stimuli and disease susceptibility (Martin et al., 2017). With the rapid expansion of genome-wide DNA methylation data across the globe, consortia analyses are beginning to develop (Joubert et al., 2016). Such efforts will help to ensure the robustness of emergent results.

Using RNAseq and high-density SNP array, expressional quantitative trait loci (eQTL) analysis and weighted gene co-expression network analysis (WGCNA) have been applied to placenta transcriptome and whole-genome SNP data to delineate functional gene networks and pathways that are driving placental processes. It has been shown that the placenta has an actively transcribed genome that is organized into 17 gene networks predominantly with functions such as growth, organ development, gas exchange and protein transport (Deyssenroth et al., 2017). In addition, there are >3000 eQTLs in placentas that strongly influence transcript abundance (Peng et al., 2017). Enrichment analyses of placental eQTLs leveraging GWAS hits suggest placental gene networks may influence postnatal risk of multiple human diseases including immunologic, metabolic and developmental diseases. Importantly, accumulating evidence suggests that environmental exposure, such as heavy metals, can disrupt the placental genome or epigenome leading to altered susceptibility to human diseases. Although other mechanisms are possible such as placental morphology, signaling or inflammatory response, disruption of these pathways may also partially go through changes in the placenta epigenome. Results provide key insight into intrauterine perturbations that result in abnormal birth and even adverse health outcomes later in life, lending support for the DOHaD.

Understanding epigenetic inheritance: the case of acquired metabolic diseases

There is increasing evidence, also in mammals, that specific parental epigenetic changes can persist throughout early embryonic reprogramming of the progeny (for review see, e.g., (Schaefer and Nadeau, 2015). Reported cases of epigenetic inheritance across generations, challenge the notion that phenotypes result exclusively from the inherited genotype and the individuals' exposure to the environment (Beckers et al., 2009). Accordingly, the suggestion that acquired metabolic traits such as obesity or diabetes could be epigenetically inherited has been controversially discussed (Heard and Martienssen, 2014). Previous studies conducted under conditions of natural reproduction in rodents have shown that paternal high fat-diets propagate obesity and glucose intolerance in their offspring (Borengasser et al., 2013; Fullston et al., 2013; Ng et al., 2010; Sasson et al., 2015; Shankar et al., 2008, 2010; Wei et al., 2014). Using an *in vitro*-fertilization approach from parental mice that either received a healthy diet or an energy dense high fat-diet, it was demonstrated that the susceptibility of the offspring to developing obesity and diabetes is inter-generationally transmitted by both parents in a gender- and parent-of-origin specific mode (Huypens et al., 2016). Since in vitro-fertilized zygotes in this experiment were carried out by healthy foster mothers, confounding factors such as effects in utero, during lactation, adoption of parental microbiomes as well as behavioral confounders were excluded. Interestingly, the observed metabolic phenotype in the progeny were consistent with epidemiological studies showing that an offspring's body mass index is significantly associated with the degree of parental obesity(Fox et al., 2014; Kivimäki et al., 2007; Lake et al., 1997), whereas impaired glucose tolerance was more prominently associated with maternal than with paternal impaired glycemic control (Meigs et al., 2000). Changes in the gametes' transcriptomes, proteomes, and metabolomes as well as characteristic marks in histones or genomic methylomes are potential candidates for the epigenomic information that transmit the acquired metabolic phenotype. Recent studies have shown that microinjection of specific sperm-derived small RNAs into zygotes are sufficient to trigger gene transcriptional effects and contribute to the metabolic phenotype in the offspring generation (Chen et al., 2016a; Grandjean et al., 2015; Sharma et al., 2016). One of the interesting questions stemming from these observations is, how changes in the epigenomic signatures of gametes may affect zygotic gene activation and epigenomic reprogramming in the pre-implantation embryo and how these signatures evolve during embryogenesis.

Understanding intergenerational and transgenerational effects: role of sperm epigenome

Since the first report on epigenetic transgenerational inheritance of vinclozolin-induced disease phenotype in rats (Anway et al., 2005), the number of publications on similar findings has increased exponentially over the past decade. Numerous animal and human studies have shown that males can pass their phenotypes or traits gained during their life time due to dietary changes, chemical exposure, stress, or trauma, onto their offspring (Chen et al., 2016b). For example, F1 and F2 generation offspring of male mice subjected to odor fear conditioning before conception display increased behavioral sensitivity to the F0-

conditioning odor rather than other odors (Dias and Ressler, 2014). Offspring of male mice with enhanced hepatic wound-healing response show similar capability (Zeybel et al., 2012). As described above, high fat diet-induced obesity and metabolic disorders can be inherited to the offspring in both mice and humans (Chen et al., 2016a; Donkin et al., 2016; Huypens et al., 2016; Sharma et al., 2016). Given that the penetrance of the phenotypes does not follow the Mendelian Law, epigenetic alterations (i.e., epimutations) are the most likely causes of the phenotypes. Transmission of the epimutations from the father to offspring must be mediated by sperm. Indeed, specific changes in sperm DNA methylation patterns, retained histone profiles, and small noncoding RNA transcriptomes have been identified in those animal models of epigenetic transgenerational inheritance (Chen et al., 2016b).

The idea of DNA methylation marks as the carrier of epigenetic memory has long been proposed, but remains highly debatable. Indeed, data published so far have been contradictory, and many believe that DNA methylation epimutations cannot be memorized in the germline because of the two waves of reprograming during development, one occurring post fertilization and the other during primordial germ cell development, which would erase and reset the vast majority of the DNA methylation marks (McCarrey, 2014). However, it has been demonstrated that many regions/loci, especially repetitive elements, e.g. IAP and subgroups of LINE1, appear to be resistant to the reprogramming in both mice and humans (Smith and Meissner, 2013). Therefore, the idea that environmentally induced DNA methylation epimutations may gain the capability of resisting reprogramming and thus, can be transmitted across multiple generations, remains a valid hypothesis.

Mammalian sperm retain a small amount of histones with various modifications, and disruptions of histone methylation cause transgenerational inheritance of phenotypes in mice (Siklenka et al., 2015). Although studies conducted so far remain highly correlative and the cause-effect relationship between sperm histones and paternal phenotypes needs to be further demonstrated experimentally, the hypothesis that sperm-borne histone marks act as the carrier of epigenetic memory remains highly appealing. Furthermore, sperm small RNAs have been shown to be capable of inducing paternal phenotypes in offspring (Chen et al., 2016b). When total or small RNAs isolated from males with environmentally induced phenotypes or a *Kit* paramutation are introduced into wild-type zygotes through microinjection, a significant proportion of the offspring display the paternal phenotypes (Chen et al., 2016a; Rassoulzadegan et al., 2006; Rodgers et al., 2015; Sharma et al., 2016; Yuan et al., 2015). Moreover, injection of a specific set of miRNAs dysregulated in male mice subjected to stress, or sperm tRNA-derived small RNAs (tsRNAs) from fathers with high fat diet-induced obesity (as shown above) into wild-type zygotes leads to offspring displaying stress and metabolic disorders, respectively (Chen et al., 2016a; Rodgers et al., 2015; Sharma et al., 2016). This suggests that sperm-borne miRNAs and tsRNAs are the likely carriers of the paternal epigenetic memory. While these observations are fascinating, the underlying molecular mechanisms remain elusive.

Given that both maternal and paternal RNAs are largely eliminated by the two-cell stage during early embryonic development, the sperm-borne small RNAs have to act rather quickly to induce epigenetic changes that can affect specific genes or gene networks responsible for the paternal phenotypes in offspring. Based on the known functions of small

RNAs, it is possible to hypothesize that the sperm small RNAs may act at the posttranscriptional and/or transcriptional levels (Yan, 2014). As post-transcriptional regulators, sperm small RNA, e.g., miRNAs or endo-siRNAs, may act on maternal, or even early zygotic transcripts, some of which may be involved in the setup of zygotic epigenome. Alternatively, sperm small RNAs, e.g., tsRNAs, may serve as a sequence guide that directs the DNA methylation and histone modification machineries to specific loci to generate specific methylation or histone marks that can recapitulate the paternal phenotype. Although hypothetical, these ideas are worth testing.

Another big gap in our understanding of sperm RNA-mediated transmission of epigenetic information is the origin of those paternal phenotype-inducing sperm RNAs. Are they formed during spermatogenesis, or acquired from their microenvironments during sperm transit through the male and the female reproductive tracts? If those specific RNAs are generated during spermatogenesis, then how are the spermatogenic cells informed and programed to produce specific sets of small RNAs that can be packed into spermatozoa and induce the paternal phenotypes with such a high precision (e.g., specific odor response)? If sperm cells acquire those small RNAs during their transit through the male reproductive tract during maturation and/or through the female reproductive tract after mating, then how do those small RNAs get into or onto sperm and how are they reliably delivered into the oocytes? As a first answer, a recent study has suggested that epididymal sperm appear to be able to gain tsRNAs from epididymosomes, the exosomes secreted by the epithelial cells of the epididymis (Sharma et al., 2016) These questions are critical to understand how paternal phenotypes are memorized in sperm as epigenetic information and how the specific epigenetic information gets transmitted to the subsequent generations in a faithful manner (Skinner, 2014). With next-generation sequencing and a better understanding of genome/epigenome editing, as well with the development of single cell technologies, the underlying mechanism through which sperm-mediated epigenetic inheritance will be elucidated in the near future.

Conclusion

The mechanisms of long-term effects of exposure to contaminants remain elusive to a large extent. Yet, epigenetic regulation is still a likely and highly relevant mechanism whether exposure occurs prenatally, pre-conceptionally, or even at any other time of life. While this report has focused on certain windows of vulnerability, there are others such as puberty and adolescence as well as older age. Progress has clearly been made on an emblematic stressor, cigarette smoking. In this case, lasting effects on gene methylation are observed in humans with a certain level of reversibility following smoking cessation, which is characteristic of epigenetic regulation. Furthermore, although there is yet no proof that those regulations are responsible for the pathologies induced by smoking, at least there is a clear biological plausibility. Evidence is also accumulating for air pollution, diet imbalance and certain endocrine disruptors such as bisphenol A, phthalates and persistent organic pollutants among others. In addition, there has been progress on the role of placenta in prenatal programming and this has been a relatively neglected mechanism until lately. Concerning intergenerational and transgenerational effects, the contribution of small regulatory RNAs has been supported

by recent data, but in general much work needs to be done to support a contribution of epigenetic mechanism to those effects.

In addition to epidemiological and experimental approaches, this field is likely to benefit from the very significant progress in systems biology. For example, specific methods use reconstituted metabolic networks to assist in metabolomic data (Jourdan et al., 2010). Efforts in network-based modeling have led to the development of integrative systems biology models using functional pathways annotation, high confidence human interactome and toxicogenomics data, multiple phenotype data (Ghiassian et al., 2016), to mention but a few sources, to predict potential adverse effects of chemicals (Audouze and Grandjean, 2011; Guney et al., 2016; Taboureau and Audouze, 2017). Association between gene-environment interactions and disease modeling allowed to predict novel environmental links with human disorders (Patel and Butte, 2010). The interaction of environmental exposure and epigenetic marks has been shown to affect transcriptional regulation (Feil and Fraga, 2012; Smith and Meissner, 2013) and could lead to biomarker identification. Biological networks associated to such integrative models (methylome and transcriptome, metabolome and proteome) but also computational methods based on multi omics layers (Uppal et al., 2017) help in understanding and elucidating the roles of the molecular entities individually and jointly, meaning that interacting partners of the epigenetically modified genes may be explored to decipher novel patterns not visible by analyzing epigenetics data alone. Such integrative systems biology approaches can therefore offer promising guidance for future research related to public health risk assessment in regard to the etiology and pathogenesis of complex diseases and dysfunctions.

Despite uncertainties, it seems reasonable to start drawing public health implications from the recent progress made on the role of epigenetics.

- First, studies that provide mechanistic evidence for the DOHaD and prenatal programming concepts should be considered as highly relevant since they strengthen the link between early life exposure and later health outcomes. Decision makers should take into consideration those long-term programming effects and should focus not only on the prenatal period, but also on the preconceptional period which covers a much larger part of the population. In fact, it seems reasonable to extend preventive and precautionary decisions to all the population.
- A targeted effort should be made to demonstrate whether some alterations in gene methylation are actual predictors of later diseases. Among the pathways that should be considered, are the AHRR pathway, oxidative stress and inflammation pathways as well as the hypothalamo-hypophyseal axis pathway.
- Even if epigenetic marks are not predictors of effect, they could prove to be good markers of current or past exposure. Again, research should attempt to prove the specificity of these markers with respect to timing and dose of exposure, as well as tissue and cell specificity.

Today, epigenetics is one of the most exciting fields of biological sciences. Epigenetics is very likely involved in environmental exposure-related programming and intergenerational

effects. Future research should delineate the actual contribution of epigenetic regulation and underline its mechanistic input as well as its public health implications.

Acknowledgments

RB is supported by grants from Inserm, Université Paris Descartes, ANR, ANSES, EU FP6 (Heals project), EU H2020 (HBM4EU). KA is supported by grants from Inserm, Université Paris Diderot. JB is supported by grants from the Helmholtz Portfolio Theme 'Metabolic Dysfunction and Common Disease', the Helmholtz Alliance 'Imaging and Curing Environmental Metabolic Diseases' (ICEMED) and the German Federal Ministry of Education and Research, INFRAFRONTIER grant 01KX1012. EM is supported by grants from the Swedish Research Council, the Swedish Heart-Lung Foundation and the Strategic Research Programme (SFO) in Epidemiology at Karolinska Institutet. PG is supported by the National Institute of Environmental Health Sciences, NIH (P42ES027706). KN is supported by Grant-in-Aid for Scientific Research (17H04139) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. WY is supported by grants from the NIH (HD071736 and HD085506) and the Templeton Foundation (PID: 50183)

References

Ambatipudi S, Cuenin C, Hernandez-Vargas H, Ghantous A, Le Calvez-Kelm F, Kaaks R, Barrdahl M, Boeing H, Aleksandrova K, Trichopoulou A, Lagiou P, Naska A, Palli D, Krogh V, Polidoro S, Tumino R, Panico S, Bueno-de-Mesquita B, Peeters PH, Quirós JR, Navarro C, Ardanaz E, Dorronsoro M, Key T, Vineis P, Murphy N, Riboli E, Romieu I, Herceg Z. Tobacco smoking-associated genome-wide DNA methylation changes in the EPIC study. Epigenomics. 2016; 8:599–618. https://doi.org/10.2217/epi-2016-0001. [PubMed: 26864933]

Ankolkar M, Balasinor NH. Endocrine control of epigenetic mechanisms in male reproduction. Horm Mol Biol Clin Investig. 2016; 25:65–70. https://doi.org/10.1515/hmbci-2016-0007.

Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 2005; 308:1466–1469. https://doi.org/10.1126/science.1108190. [PubMed: 15933200]

Audouze K, Grandjean P. Application of computational systems biology to explore environmental toxicity hazards. Environ Health Perspect. 2011; 119:1754–1759. https://doi.org/10.1289/ehp.1103533. [PubMed: 21846611]

Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Curr Opin Pediatr. 2009; 21:243–251. [PubMed: 19663042]

Balbus JM, Barouki R, Birnbaum LS, Etzel RA, Gluckman PD, Grandjean P, Hancock C, Hanson MA, Heindel JJ, Hoffman K, Jensen GK, Keeling A, Neira M, Rabadán-Diehl C, Ralston J, Tang KC. Early-life prevention of non-communicable diseases. Lancet Lond Engl. 2013; 381:3–4. https://doi.org/10.1016/S0140-6736(12)61609-2.

Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: implications for research and public health. Environ Health Glob Access Sci Source. 2012; 11:42. https://doi.org/10.1186/1476-069X-11-42.

Bauer UE, Briss PA, Goodman RA, Bowman BA. Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. Lancet Lond Engl. 2014; 384:45–52. https://doi.org/10.1016/S0140-6736(14)60648-6.

Beckers J, Wurst W, de Angelis MH. Towards better mouse models: enhanced genotypes, systemic phenotyping and envirotype modelling. Nat Rev Genet. 2009; 10:371–380. https://doi.org/10.1038/nrg2578. [PubMed: 19434078]

Bommarito PA, Martin E, Fry RC. Effects of prenatal exposure to endocrine disruptors and toxic metals on the fetal epigenome. Epigenomics. 2017; 9:333–350. https://doi.org/10.2217/epi-2016-0112. [PubMed: 28234024]

Borengasser SJ, Zhong Y, Kang P, Lindsey F, Ronis MJJ, Badger TM, Gomez-Acevedo H, Shankar K. Maternal obesity enhances white adipose tissue differentiation and alters genome-scale DNA methylation in male rat offspring. Endocrinology. 2013; 154:4113–4125. https://doi.org/10.1210/en.2012-2255. [PubMed: 23959936]

Braun JM. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. Nat Rev Endocrinol. 2017; 13:161–173. https://doi.org/10.1038/nrendo.2016.186. [PubMed: 27857130]

Bredfeldt TG, Greathouse KL, Safe SH, Hung MC, Bedford MT, Walker CL. Xenoestrogen-induced regulation of EZH2 and histone methylation via estrogen receptor signaling to PI3K/AKT. Mol Endocrinol Baltim Md. 2010; 24:993–1006. https://doi.org/10.1210/me.2009-0438.

Bruner-Tran KL, Resuehr D, Ding T, Lucas JA, Osteen KG. The Role of Endocrine Disruptors in the Epigenetics of Reproductive Disease and Dysfunction: Potential Relevance to Humans. Curr Obstet Gynecol Rep. 2012; 1:116–123. https://doi.org/10.1007/s13669-012-0014-7. [PubMed: 24932427]

Casati L, Sendra R, Sibilia V, Celotti F. Endocrine disrupters: the new players able to affect the epigenome. Front Cell Dev Biol. 2015; 3:37. https://doi.org/10.3389/fcell.2015.00037. [PubMed: 26151052]

Chen Q, Yan M, Cao Z, Li X, Zhang Y, Shi J, Feng G, Peng H, Zhang X, Zhang Y, Qian J, Duan E, Zhai Q, Zhou Q. Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. Science. 2016a; 351:397–400. https://doi.org/10.1126/science.aad7977. [PubMed: 26721680]

Chen Q, Yan W, Duan E. Epigenetic inheritance of acquired traits through sperm RNAs and sperm RNA modifications. Nat Rev Genet. 2016b; 17:733–743. https://doi.org/10.1038/nrg.2016.106. [PubMed: 27694809]

Consales C, Toft G, Leter G, Bonde JPE, Uccelli R, Pacchierotti F, Eleuteri P, Jönsson BAG, Giwercman A, Pedersen HS, Struciński P, Góralczyk K, Zviezdai V, Spanò M. Exposure to persistent organic pollutants and sperm DNA methylation changes in Arctic and European populations. Environ Mol Mutagen. 2016; 57:200–209. https://doi.org/10.1002/em.21994. [PubMed: 26801515]

Dao T, Hong X, Wang X, Tang WY. Aberrant 5′-CpG Methylation of Cord Blood TNFα Associated with Maternal Exposure to Polybrominated Diphenyl Ethers. PloS One. 2015; 10:e0138815. https://doi.org/10.1371/journal.pone.0138815. [PubMed: 26406892]

Deb P, Bhan A, Hussain I, Ansari KI, Bobzean SA, Pandita TK, Perrotti LI, Mandal SS. Endocrine disrupting chemical, bisphenol-A, induces breast cancer associated gene HOXB9 expression in vitro and in vivo. Gene. 2016; 590:234–243. https://doi.org/10.1016/j.gene.2016.05.009. [PubMed: 27182052]

Deguen S, Petit C, Delbarre A, Kihal W, Padilla C, Benmarhnia T, Lapostolle A, Chauvin P, Zmirou-Navier D. Neighbourhood Characteristics and Long-Term Air Pollution Levels Modify the Association between the Short-Term Nitrogen Dioxide Concentrations and All-Cause Mortality in Paris. PloS One. 2015; 10:e0131463. https://doi.org/10.1371/journal.pone.0131463. [PubMed: 26197409]

Desai M, Jellyman JK, Ross MG. Epigenomics, gestational programming and risk of metabolic syndrome. Int J Obes 2005. 2015; 39:633–641. https://doi.org/10.1038/ijo.2015.13.

Deyssenroth MA, Peng S, Hao K, Lambertini L, Marsit CJ, Chen J. Whole-transcriptome analysis delineates the human placenta gene network and its associations with fetal growth. BMC Genomics. 2017; 18:520. https://doi.org/10.1186/s12864-017-3878-0. [PubMed: 28693416]

Dhimolea E, Wadia PR, Murray TJ, Settles ML, Treitman JD, Sonnenschein C, Shioda T, Soto AM. Prenatal exposure to BPA alters the epigenome of the rat mammary gland and increases the propensity to neoplastic development. PloS One. 2014; 9:e99800. https://doi.org/10.1371/journal.pone.0099800. [PubMed: 24988533]

Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. Nat Neurosci. 2014; 17:89–96. https://doi.org/10.1038/nn.3594. [PubMed: 24292232]

Dolinoy DC. The agouti mouse model: an epigenetic biosensor for nutritional and environmental alterations on the fetal epigenome. Nutr Rev. 2008; 66(Suppl 1):S7–11. https://doi.org/10.1111/j.1753-4887.2008.00056.x. [PubMed: 18673496]

Donkin I, Versteyhe S, Ingerslev LR, Qian K, Mechta M, Nordkap L, Mortensen B, Appel EVR, Jørgensen N, Kristiansen VB, Hansen T, Workman CT, Zierath JR, Barrès R. Obesity and Bariatric Surgery Drive Epigenetic Variation of Spermatozoa in Humans. Cell Metab. 2016; 23:369–378. https://doi.org/10.1016/j.cmet.2015.11.004. [PubMed: 26669700]

Duval C, Teixeira-Clerc F, Leblanc AF, Touch S, Emond C, Guerre-Millo M, Lotersztajn S, Barouki R, Aggerbeck M, Coumoul X. Chronic Exposure to Low Doses of Dioxin Promotes Liver Fibrosis Development in the C57BL/6J Diet-Induced Obesity Mouse Model. Environ Health Perspect. 2017; 125:428–436. https://doi.org/10.1289/EHP316. [PubMed: 27713108]

Eid A, Zawia N. Consequences of lead exposure, and it's emerging role as an epigenetic modifier in the aging brain. Neurotoxicology. 2016; 56:254–261. https://doi.org/10.1016/j.neuro.2016.04.006. [PubMed: 27066759]

Escher BI, Hackermüller J, Polte T, Scholz S, Aigner A, Altenburger R, Böhme A, Bopp SK, Brack W, Busch W, Chadeau-Hyam M, Covaci A, Eisenträger A, Galligan JJ, Garcia-Reyero N, Hartung T, Hein M, Herberth G, Jahnke A, Kleinjans J, Klüver N, Krauss M, Lamoree M, Lehmann I, Luckenbach T, Miller GW, Müller A, Phillips DH, Reemtsma T, Rolle-Kampczyk U, Schüürmann G, Schwikowski B, Tan YM, Trump S, Walter-Rohde S, Wambaugh JF. From the exposome to mechanistic understanding of chemical-induced adverse effects. Environ Int. 2017; 99:97–106. https://doi.org/10.1016/j.envint.2016.11.029. [PubMed: 27939949]

Everson TM, Armstrong DA, Jackson BP, Green BB, Karagas MR, Marsit CJ. Maternal cadmium, placental PCDHAC1, and fetal development. Reprod Toxicol Elmsford N. 2016; 65:263–271. https://doi.org/10.1016/j.reprotox.2016.08.011.

Fasanelli F, Baglietto L, Ponzi E, Guida F, Campanella G, Johansson M, Grankvist K, Johansson M, Assumma MB, Naccarati A, Chadeau-Hyam M, Ala U, Faltus C, Kaaks R, Risch A, De Stavola B, Hodge A, Giles GG, Southey MC, Relton CL, Haycock PC, Lund E, Polidoro S, Sandanger TM, Severi G, Vineis P. Hypomethylation of smoking-related genes is associated with future lung cancer in four prospective cohorts. Nat Commun. 2015; 6:10192. https://doi.org/10.1038/ncomms10192. [PubMed: 26667048]

Faulk C, Dolinoy DC. Timing is everything: the when and how of environmentally induced changes in the epigenome of animals. Epigenetics. 2011; 6:791–797. [PubMed: 21636976]

Faulk C, Kim JH, Anderson OS, Nahar MS, Jones TR, Sartor MA, Dolinoy DC. Detection of differential DNA methylation in repetitive DNA of mice and humans perinatally exposed to bisphenol A. Epigenetics. 2016; 11:489–500. https://doi.org/10.1080/15592294.2016.1183856. [PubMed: 27267941]

Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications. Nat Rev Genet. 2012; 13:97–109. https://doi.org/10.1038/nrg3142. [PubMed: 22215131]

Fox CS, Pencina MJ, Heard-Costa NL, Shrader P, Jaquish C, O'Donnell CJ, Vasan RS, Cupples LA, D'Agostino RB. Trends in the association of parental history of obesity over 60 years. Obes Silver Spring Md. 2014; 22:919–924. https://doi.org/10.1002/oby.20564.

Fullston T, Ohlsson Teague EMC, Palmer NO, DeBlasio MJ, Mitchell M, Corbett M, Print CG, Owens JA, Lane M. Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content. FASEB J Off Publ Fed Am Soc Exp Biol. 2013; 27:4226–4243. https://doi.org/10.1096/fj.12-224048.

Ghiassian SD, Menche J, Chasman DI, Giulianini F, Wang R, Ricchiuto P, Aikawa M, Iwata H, Müller C, Zeller T, Sharma A, Wild P, Lackner K, Singh S, Ridker PM, Blankenberg S, Barabási AL, Loscalzo J. Endophenotype Network Models: Common Core of Complex Diseases. Sci Rep. 2016; 6:27414. https://doi.org/10.1038/srep27414. [PubMed: 27278246]

Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev. 2015; 36:E1–E150. https://doi.org/10.1210/er.2015-1010. [PubMed: 26544531]

Grandjean P, Barouki R, Bellinger DC, Casteleyn L, Chadwick LH, Cordier S, Etzel RA, Gray KA, Ha EH, Junien C, Karagas M, Kawamoto T, Paige Lawrence B, Perera FP, Prins GS, Puga A, Rosenfeld CS, Sherr DH, Sly PD, Suk W, Sun Q, Toppari J, van den Hazel P, Walker CL, Heindel JJ. Life-Long Implications of Developmental Exposure to Environmental Stressors: New Perspectives. Endocrinology. 2015; 156:3408–3415. https://doi.org/10.1210/EN.2015-1350. [PubMed: 26241067]

Gref A, Merid SK, Gruzieva O, Ballereau S, Becker A, Bellander T, Bergström A, Bossé Y, Bottai M, Chan-Yeung M, Fuertes E, Ierodiakonou D, Jiang R, Joly S, Jones M, Kobor MS, Korek M, Kozyrskyj AL, Kumar A, Lemonnier N, MacIntyre E, Ménard C, Nickle D, Obeidat M'en, Pellet

J, Standl M, Sääf A, Söderhäll C, Tiesler CMT, van den Berge M, Vonk JM, Vora H, Xu CJ, Antó JM, Auffray C, Brauer M, Bousquet J, Brunekreef B, Gauderman WJ, Heinrich J, Kere J, Koppelman GH, Postma D, Carlsten C, Pershagen G, Melén E. Genome-Wide Interaction Analysis of Air Pollution Exposure and Childhood Asthma with Functional Follow-up. Am J Respir Crit Care Med. 2017; 195:1373–1383. https://doi.org/10.1164/rccm.201605-1026OC. [PubMed: 27901618]

Gruzieva O, Xu CJ, Breton CV, Annesi-Maesano I, Antó JM, Auffray C, Ballereau S, Bellander T, Bousquet J, Bustamante M, Charles MA, de Kluizenaar Y, den Dekker HT, Duijts L, Felix JF, Gehring U, Guxens M, Jaddoe VVW, Jankipersadsing SA, Merid SK, Kere J, Kumar A, Lemonnier N, Lepeule J, Nystad W, Page CM, Panasevich S, Postma D, Slama R, Sunyer J, Söderhäll C, Yao J, London SJ, Pershagen G, Koppelman GH, Melén E. Epigenome-Wide Meta-Analysis of Methylation in Children Related to Prenatal NO2 Air Pollution Exposure. Environ Health Perspect. 2017; 125:104–110. https://doi.org/10.1289/EHP36. [PubMed: 27448387]

Guney E, Menche J, Vidal M, Barábasi AL. Network-based in silico drug efficacy screening. Nat Commun. 2016; 7:10331. https://doi.org/10.1038/ncomms10331. [PubMed: 26831545]

Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev. 2014; 94:1027–1076. https://doi.org/10.1152/physrev.00029.2013. [PubMed: 25287859]

Harlid S, Xu Z, Panduri V, Sandler DP, Taylor JA. CpG sites associated with cigarette smoking: analysis of epigenome-wide data from the Sister Study. Environ Health Perspect. 2014; 122:673–678. https://doi.org/10.1289/ehp.1307480. [PubMed: 24704585]

Heard E, Martienssen RA. Transgenerational epigenetic inheritance: myths and mechanisms. Cell. 2014; 157:95–109. https://doi.org/10.1016/j.cell.2014.02.045. [PubMed: 24679529]

Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008; 105:17046–17049. https://doi.org/10.1073/pnas.0806560105. [PubMed: 18955703]

Heindel JJ, Balbus J, Birnbaum L, Brune-Drisse MN, Grandjean P, Gray K, Landrigan PJ, Sly PD, Suk W, Cory Slechta D, Thompson C, Hanson M. Developmental Origins of Health and Disease: Integrating Environmental Influences. Endocrinology. 2015a; 156:3416–3421. https://doi.org/10.1210/EN.2015-1394. [PubMed: 26241070]

Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, Vandenberg LN, Vom Saal F. Metabolism disrupting chemicals and metabolic disorders. Reprod Toxicol Elmsford N. 2017a; 68:3–33. https://doi.org/10.1016/j.reprotox.2016.10.001.

Heindel JJ, Newbold R, Schug TT. Endocrine disruptors and obesity. Nat Rev Endocrinol. 2015b; 11:653–661. https://doi.org/10.1038/nrendo.2015.163. [PubMed: 26391979]

Heindel JJ, Skalla LA, Joubert BR, Dilworth CH, Gray KA. Review of developmental origins of health and disease publications in environmental epidemiology. Reprod Toxicol Elmsford N. 2017b; 68:34–48. https://doi.org/10.1016/j.reprotox.2016.11.011.

Hew KM, Walker AI, Kohli A, Garcia M, Syed A, McDonald-Hyman C, Noth EM, Mann JK, Pratt B, Balmes J, Hammond SK, Eisen EA, Nadeau KC. Childhood exposure to ambient polycyclic aromatic hydrocarbons is linked to epigenetic modifications and impaired systemic immunity in T cells. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2015; 45:238–248. https://doi.org/10.1111/cea.12377.

Huen K, Calafat AM, Bradman A, Yousefi P, Eskenazi B, Holland N. Maternal phthalate exposure during pregnancy is associated with DNA methylation of LINE-1 and Alu repetitive elements in Mexican-American children. Environ Res. 2016; 148:55–62. https://doi.org/10.1016/j.envres.2016.03.025. [PubMed: 27019040]

Huypens P, Sass S, Wu M, Dyckhoff D, Tschöp M, Theis F, Marschall S, Hrabě de Angelis M, Beckers J. Epigenetic germline inheritance of diet-induced obesity and insulin resistance. Nat Genet. 2016; 48:497–499. https://doi.org/10.1038/ng.3527. [PubMed: 26974008]

Joehanes R, Just AC, Marioni RE, Pilling LC, Reynolds LM, Mandaviya PR, Guan W, Xu T, Elks CE, Aslibekyan S, Moreno-Macias H, Smith JA, Brody JA, Dhingra R, Yousefi P, Pankow JS, Kunze S, Shah SH, McRae AF, Lohman K, Sha J, Absher DM, Ferrucci L, Zhao W, Demerath EW, Bressler

J, Grove ML, Huan T, Liu C, Mendelson MM, Yao C, Kiel DP, Peters A, Wang-Sattler R, Visscher PM, Wray NR, Starr JM, Ding J, Rodriguez CJ, Wareham NJ, Irvin MR, Zhi D, Barrdahl M, Vineis P, Ambatipudi S, Uitterlinden AG, Hofman A, Schwartz J, Colicino E, Hou L, Vokonas PS, Hernandez DG, Singleton AB, Bandinelli S, Turner ST, Ware EB, Smith AK, Klengel T, Binder EB, Psaty BM, Taylor KD, Gharib SA, Swenson BR, Liang L, DeMeo DL, O'Connor GT, Herceg Z, Ressler KJ, Conneely KN, Sotoodehnia N, Kardia SLR, Melzer D, Baccarelli AA, van Meurs JBJ, Romieu I, Arnett DK, Ong KK, Liu Y, Waldenberger M, Deary IJ, Fornage M, Levy D, London SJ. Epigenetic Signatures of Cigarette Smoking. Circ Cardiovasc Genet. 2016; 9:436–447. https://doi.org/10.1161/CIRCGENETICS.116.001506. [PubMed: 27651444]

Joubert BR, Felix JF, Yousefi P, Bakulski KM, Just AC, Breton C, Reese SE, Markunas CA, Richmond RC, Xu CJ, Küpers LK, Oh SS, Hoyo C, Gruzieva O, Söderhäll C, Salas LA, Baïz N, Zhang H, Lepeule J, Ruiz C, Ligthart S, Wang T, Taylor JA, Duijts L, Sharp GC, Jankipersadsing SA, Nilsen RM, Vaez A, Fallin MD, Hu D, Litonjua AA, Fuemmeler BF, Huen K, Kere J, Kull I, Munthe-Kaas MC, Gehring U, Bustamante M, Saurel-Coubizolles MJ, Quraishi BM, Ren J, Tost J, Gonzalez JR, Peters MJ, Håberg SE, Xu Z, van Meurs JB, Gaunt TR, Kerkhof M, Corpeleijn E, Feinberg AP, Eng C, Baccarelli AA, Benjamin Neelon SE, Bradman A, Merid SK, Bergström A, Herceg Z, Hernandez-Vargas H, Brunekreef B, Pinart M, Heude B, Ewart S, Yao J, Lemonnier N, Franco OH, Wu MC, Hofman A, McArdle W, Van der Vlies P, Falahi F, Gillman MW, Barcellos LF, Kumar A, Wickman M, Guerra S, Charles MA, Holloway J, Auffray C, Tiemeier HW, Smith GD, Postma D, Hivert MF, Eskenazi B, Vrijheid M, Arshad H, Antó JM, Dehghan A, Karmaus W, Annesi-Maesano I, Sunyer J, Ghantous A, Pershagen G, Holland N, Murphy SK, DeMeo DL, Burchard EG, Ladd-Acosta C, Snieder H, Nystad W, Koppelman GH, Relton CL, Jaddoe VWV, Wilcox A, Melén E, London SJ. DNA Methylation in Newborns and Maternal Smoking in Pregnancy: Genome-wide Consortium Meta-analysis. Am J Hum Genet. 2016; 98:680–696. https://doi.org/10.1016/j.ajhg.2016.02.019. [PubMed: 27040690]

Joubert BR, Håberg SE, Nilsen RM, Wang X, Vollset SE, Murphy SK, Huang Z, Hoyo C, Midttun Ø, Cupul-Uicab LA, Ueland PM, Wu MC, Nystad W, Bell DA, Peddada SD, London SJ. 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. Environ Health Perspect. 2012; 120:1425–1431. https://doi.org/10.1289/ehp.1205412. [PubMed: 22851337]

Jourdan F, Cottret L, Huc L, Wildridge D, Scheltema R, Hillenweck A, Barrett MP, Zalko D, Watson DG, Debrauwer L. Use of reconstituted metabolic networks to assist in metabolomic data visualization and mining. Metabolomics Off J Metabolomic Soc. 2010; 6:312–321. https://doi.org/10.1007/s11306-009-0196-9.

Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. Mol Endocrinol Baltim Md. 2010; 24:526–539. https://doi.org/10.1210/me.2009-0261.

Kivimäki M, Lawlor DA, Smith GD, Elovainio M, Jokela M, Keltikangas-Järvinen L, Viikari JS, Raitakari OT. Substantial intergenerational increases in body mass index are not explained by the fetal overnutrition hypothesis: the Cardiovascular Risk in Young Finns Study. Am J Clin Nutr. 2007; 86:1509–1514. [PubMed: 17991666]

Lake JK, Power C, Cole TJ. Child to adult body mass index in the 1958 British birth cohort: associations with parental obesity. Arch Dis Child. 1997; 77:376–381. [PubMed: 9487953]

Leclercq B, Platel A, Antherieu S, Alleman LY, Hardy EM, Perdrix E, Grova N, Riffault V, Appenzeller BM, Happillon M, Nesslany F, Coddeville P, Lo-Guidice JM, Garçon G. Genetic and epigenetic alterations in normal and sensitive COPD-diseased human bronchial epithelial cells repeatedly exposed to air pollution-derived PM2.5. Environ Pollut Barking Essex 1987. 2017; 230:163–177. https://doi.org/10.1016/j.envpol.2017.06.028.

Markunas CA, Xu Z, Harlid S, Wade PA, Lie RT, Taylor JA, Wilcox AJ. Identification of DNA methylation changes in newborns related to maternal smoking during pregnancy. Environ Health Perspect. 2014; 122:1147–1153. https://doi.org/10.1289/ehp.1307892. [PubMed: 24906187]

Martin E, Smeester L, Bommarito PA, Grace MR, Boggess K, Kuban K, Karagas MR, Marsit CJ, O'Shea TM, Fry RC. Sexual epigenetic dimorphism in the human placenta: implications for susceptibility during the prenatal period. Epigenomics. 2017; 9:267–278. https://doi.org/10.2217/epi-2016-0132. [PubMed: 28234023]

Martinez-Arguelles DB, Papadopoulos V. Prenatal phthalate exposure: epigenetic changes leading to lifelong impact on steroid formation. Andrology. 2016; 4:573–584. https://doi.org/10.1111/andr.12175. [PubMed: 27044004]

McCarrey JR. Distinctions between transgenerational and non-transgenerational epimutations. Mol Cell Endocrinol. 2014; 398:13–23. https://doi.org/10.1016/j.mce.2014.07.016. [PubMed: 25079508]

Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. Diabetes. 2000; 49:2201–2207. [PubMed: 11118026]

Nadeau K, McDonald-Hyman C, Noth EM, Pratt B, Hammond SK, Balmes J, Tager I. Ambient air pollution impairs regulatory T-cell function in asthma. J Allergy Clin Immunol. 2010; 126:845–852.e10. https://doi.org/10.1016/j.jaci.2010.08.008. [PubMed: 20920773]

Naik S, Larsen SB, Gomez NC, Alaverdyan K, Sendoel A, Yuan S, Polak L, Kulukian A, Chai S, Fuchs E. Inflammatory memory sensitizes skin epithelial stem cells to tissue damage. Nature. 2017; 550:475–480. https://doi.org/10.1038/nature24271. [PubMed: 29045388]

Ng SF, Lin RCY, Laybutt DR, Barres R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring. Nature. 2010; 467:963–966. https://doi.org/10.1038/nature09491. [PubMed: 20962845]

Park SS, Skaar DA, Jirtle RL, Hoyo C. Epigenetics, obesity and early-life cadmium or lead exposure. Epigenomics. 2017; 9:57–75. https://doi.org/10.2217/epi-2016-0047. [PubMed: 27981852]

Patel CJ, Butte AJ. Predicting environmental chemical factors associated with disease-related gene expression data. BMC Med Genomics. 2010; 3 https://doi.org/10.1186/1755-8794-3-17.

Peng S, Deyssenroth MA, Di Narzo AF, Lambertini L, Marsit CJ, Chen J, Hao K. Expression quantitative trait loci (eQTLs) in human placentas suggest developmental origins of complex diseases. Hum Mol Genet. 2017; 26:3432–3441. https://doi.org/10.1093/hmg/ddx265. [PubMed: 28854703]

Plusquin M, Guida F, Polidoro S, Vermeulen R, Raaschou-Nielsen O, Campanella G, Hoek G, Kyrtopoulos SA, Georgiadis P, Naccarati A, Sacerdote C, Krogh V, Bas Bueno-de-Mesquita H, Monique Verschuren WM, Sayols-Baixeras S, Panni T, Peters A, Hebels DGAJ, Kleinjans J, Vineis P, Chadeau-Hyam M. DNA methylation and exposure to ambient air pollution in two prospective cohorts. Environ Int. 2017; 108:127–136. https://doi.org/10.1016/j.envint.2017.08.006. [PubMed: 28843141]

Prins GS, Ho SM. Early-life estrogens and prostate cancer in an animal model. J Dev Orig Health Dis. 2010; 1:365–370. https://doi.org/10.1017/S2040174410000577. [PubMed: 24795802]

Rassoulzadegan M, Grandjean V, Gounon P, Vincent S, Gillot I, Cuzin F. RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse. Nature. 2006; 441:469–474. https://doi.org/10.1038/nature04674. [PubMed: 16724059]

Richmond RC, Hemani G, Tilling K, Davey Smith G, Relton CL. Challenges and novel approaches for investigating molecular mediation. Hum Mol Genet. 2016; 25:R149–R156. https://doi.org/10.1093/hmg/ddw197. [PubMed: 27439390]

Rivkees SA, Wendler CC. Long-term consequences of disrupting adenosine signaling during embryonic development. Mol Aspects Med. 2017; 55:110–117. https://doi.org/10.1016/j.mam.2017.02.001. [PubMed: 28202385]

Rodgers AB, Morgan CP, Leu NA, Bale TL. Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress. Proc Natl Acad Sci U S A. 2015; 112:13699–13704. https://doi.org/10.1073/pnas.1508347112. [PubMed: 26483456]

Sasson IE, Vitins AP, Mainigi MA, Moley KH, Simmons RA. Pre-gestational vs gestational exposure to maternal obesity differentially programs the offspring in mice. Diabetologia. 2015; 58:615–624. https://doi.org/10.1007/s00125-014-3466-7. [PubMed: 25608625]

Schaefer S, Nadeau JH. THE GENETICS OF EPIGENETIC INHERITANCE: MODES, MOLECULES, AND MECHANISMS. Q Rev Biol. 2015; 90:381–415. [PubMed: 26714351]

Schug TT, Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. PPTOX III: environmental stressors in the developmental origins of disease–evidence and mechanisms. Toxicol Sci Off J Soc Toxicol. 2013; 131:343–350. https://doi.org/10.1093/toxsci/kfs267.

Shankar K, Harrell A, Liu X, Gilchrist JM, Ronis MJJ, Badger TM. Maternal obesity at conception programs obesity in the offspring. Am J Physiol Regul Integr Comp Physiol. 2008; 294:R528–538. https://doi.org/10.1152/ajpregu.00316.2007. [PubMed: 18032473]

Shankar K, Kang P, Harrell A, Zhong Y, Marecki JC, Ronis MJJ, Badger TM. Maternal overweight programs insulin and adiponectin signaling in the offspring. Endocrinology. 2010; 151:2577–2589. https://doi.org/10.1210/en.2010-0017. [PubMed: 20371699]

Sharma U, Conine CC, Shea JM, Boskovic A, Derr AG, Bing XY, Belleannee C, Kucukural A, Serra RW, Sun F, Song L, Carone BR, Ricci EP, Li XZ, Fauquier L, Moore MJ, Sullivan R, Mello CC, Garber M, Rando OJ. Biogenesis and function of tRNA fragments during sperm maturation and fertilization in mammals. Science. 2016; 351:391–396. https://doi.org/10.1126/science.aad6780. [PubMed: 26721685]

Shenker NS, Polidoro S, van Veldhoven K, Sacerdote C, Ricceri F, Birrell MA, Belvisi MG, Brown R, Vineis P, Flanagan JM. Epigenome-wide association study in the European Prospective Investigation into Cancer and Nutrition (EPIC-Turin) identifies novel genetic loci associated with smoking. Hum Mol Genet. 2013; 22:843–851. https://doi.org/10.1093/hmg/dds488. [PubMed: 23175441]

Siklenka K, Erkek S, Godmann M, Lambrot R, McGraw S, Lafleur C, Cohen T, Xia J, Suderman M, Hallett M, Trasler J, Peters AHFM, Kimmins S. Disruption of histone methylation in developing sperm impairs offspring health transgenerationally. Science. 2015; 350:aab2006. https://doi.org/10.1126/science.aab2006. [PubMed: 26449473]

Skinner MK. Environmental stress and epigenetic transgenerational inheritance. BMC Med. 2014; 12:153. https://doi.org/10.1186/s12916-014-0153-y. [PubMed: 25259699]

Skinner MK, Guerrero-Bosagna C, Haque MM. Environmentally induced epigenetic transgenerational inheritance of sperm epimutations promote genetic mutations. Epigenetics. 2015; 10:762–771. https://doi.org/10.1080/15592294.2015.1062207. [PubMed: 26237076]

Smith ZD, Meissner A. DNA methylation: roles in mammalian development. Nat Rev Genet. 2013; 14:204–220. https://doi.org/10.1038/nrg3354. [PubMed: 23400093]

Sofo V, Götte M, Laganà AS, Salmeri FM, Triolo O, Sturlese E, Retto G, Alfa M, Granese R, Abrão MS. Correlation between dioxin and endometriosis: an epigenetic route to unravel the pathogenesis of the disease. Arch Gynecol Obstet. 2015; 292:973–986. https://doi.org/10.1007/s00404-015-3739-5. [PubMed: 25920525]

Solomon O, Yousefi P, Huen K, Gunier RB, Escudero-Fung M, Barcellos LF, Eskenazi B, Holland N. Prenatal phthalate exposure and altered patterns of DNA methylation in cord blood. Environ Mol Mutagen. 2017; 58:398–410. https://doi.org/10.1002/em.22095. [PubMed: 28556291]

Stueve TR, Li WQ, Shi J, Marconett CN, Zhang T, Yang C, Mullen D, Yan C, Wheeler W, Hua X, Zhou B, Borok Z, Caporaso NE, Pesatori AC, Duan J, Laird-Offringa IA, Landi MT. Epigenome-wide analysis of DNA methylation in lung tissue shows concordance with blood studies and identifies tobacco smoke-inducible enhancers. Hum Mol Genet. 2017; 26:3014–3027. https://doi.org/10.1093/hmg/ddx188. [PubMed: 28854564]

Taboureau O, Audouze K. Human Environmental Disease Network: A computational model to assess toxicology of contaminants. ALTEX. 2017; 34:289–300. https://doi.org/10.14573/altex.1607201. [PubMed: 27768803]

Treviño LS, Wang Q, Walker CL. Hypothesis: Activation of rapid signaling by environmental estrogens and epigenetic reprogramming in breast cancer. Reprod Toxicol Elmsford N. 2015a; 54:136–140. https://doi.org/10.1016/j.reprotox.2014.12.014.

Treviño LS, Wang Q, Walker CL. Phosphorylation of epigenetic “readers, writers and erasers”: Implications for developmental reprogramming and the epigenetic basis for health and disease. Prog Biophys Mol Biol. 2015b; 118:8–13. https://doi.org/10.1016/j.pbiomolbio.2015.02.013. [PubMed: 25841987]

Uppal, K., Ma, C., Go, YM., Jones, DP. xMWAS: a data-driven integration and differential network analysis tool. Bioinformatics. 2017. https://doi.org/10.1093/bioinformatics/btx656

Vilahur N, Bustamante M, Morales E, Motta V, Fernandez MF, Salas LA, Escaramis G, Ballester F, Murcia M, Tardon A, Riaño I, Santa-Marina L, Ibarluzea J, Arrebola JP, Estivill X, Bollati V, Sunyer J, Olea N. Prenatal exposure to mixtures of xenoestrogens and genome-wide DNA

methylation in human placenta. Epigenomics. 2016; 8:43–54. https://doi.org/10.2217/epi.15.91. [PubMed: 26679211]

Vineis P, Chatziioannou A, Cunliffe VT, Flanagan JM, Hanson M, Kirsch-Volders M, Kyrtopoulos S. Epigenetic memory in response to environmental stressors. FASEB J Off Publ Fed Am Soc Exp Biol. 2017; 31:2241–2251. https://doi.org/10.1096/fj.201601059RR.

Walker CL. Minireview: Epigenomic Plasticity and Vulnerability to EDC Exposures. Mol Endocrinol Baltim Md. 2016; 30:848–855. https://doi.org/10.1210/me.2016-1086.

Walker CL, Ho S. Developmental reprogramming of cancer susceptibility. Nat Rev Cancer. 2012; 12:479–486. https://doi.org/10.1038/nrc3220. [PubMed: 22695395]

Wei Y, Yang CR, Wei YP, Zhao ZA, Hou Y, Schatten H, Sun QY. Paternally induced transgenerational inheritance of susceptibility to diabetes in mammals. Proc Natl Acad Sci U S A. 2014; 111:1873–1878. https://doi.org/10.1073/pnas.1321195111. [PubMed: 24449870]

West-Eberhard MJ. Developmental plasticity and the origin of species differences. Proc Natl Acad Sci U S A. 2005; 102(Suppl 1):6543–6549. https://doi.org/10.1073/pnas.0501844102. [PubMed: 15851679]

Wild CP, Scalbert A, Herceg Z. Measuring the exposome: a powerful basis for evaluating environmental exposures and cancer risk. Environ Mol Mutagen. 2013; 54:480–499. https://doi.org/10.1002/em.21777. [PubMed: 23681765]

Yamazaki Y, Mann MRW, Lee SS, Marh J, McCarrey JR, Yanagimachi R, Bartolomei MS. Reprogramming of primordial germ cells begins before migration into the genital ridge, making these cells inadequate donors for reproductive cloning. Proc Natl Acad Sci U S A. 2003; 100:12207–12212. https://doi.org/10.1073/pnas.2035119100. [PubMed: 14506296]

Yan W. Potential roles of noncoding RNAs in environmental epigenetic transgenerational inheritance. Mol Cell Endocrinol. 2014; 398:24–30. https://doi.org/10.1016/j.mce.2014.09.008. [PubMed: 25224488]

Yuan S, Oliver D, Schuster A, Zheng H, Yan W. Breeding scheme and maternal small RNAs affect the efficiency of transgenerational inheritance of a paramutation in mice. Sci Rep. 2015; 5:9266. https://doi.org/10.1038/srep09266. [PubMed: 25783852]

Zeybel M, Hardy T, Wong YK, Mathers JC, Fox CR, Gackowska A, Oakley F, Burt AD, Wilson CL, Anstee QM, Barter MJ, Masson S, Elsharkawy AM, Mann DA, Mann J. Multigenerational epigenetic adaptation of the hepatic wound-healing response. Nat Med. 2012; 18:1369–1377. https://doi.org/10.1038/nm.2893. [PubMed: 22941276]

Zheng H, Zhou X, Li DK, Yang F, Pan H, Li T, Miao M, Li R, Yuan W. Genome-wide alteration in DNA hydroxymethylation in the sperm from bisphenol A-exposed men. PloS One. 2017; 12:e0178535. https://doi.org/10.1371/journal.pone.0178535. [PubMed: 28582417]

Zhong J, Karlsson O, Wang G, Li J, Guo Y, Lin X, Zemplenyi M, Sanchez-Guerra M, Trevisi L, Urch B, Speck M, Liang L, Coull BA, Koutrakis P, Silverman F, Gold DR, Wu T, Baccarelli AA. B vitamins attenuate the epigenetic effects of ambient fine particles in a pilot human intervention trial. Proc Natl Acad Sci U S A. 2017; 114:3503–3508. https://doi.org/10.1073/pnas.1618545114. [PubMed: 28289216]

Highlights

- Epigenetic alterations could account for long-term health effects of environmental stressors
- A set of criteria has been developed to support epigenetic mechanisms of stressors effects
- Strongest evidence comes from work on smoking, air pollution, chemicals such as endocrine disruptors
- Epigenetic changes in germ cells and placenta could account for intergenerational effects

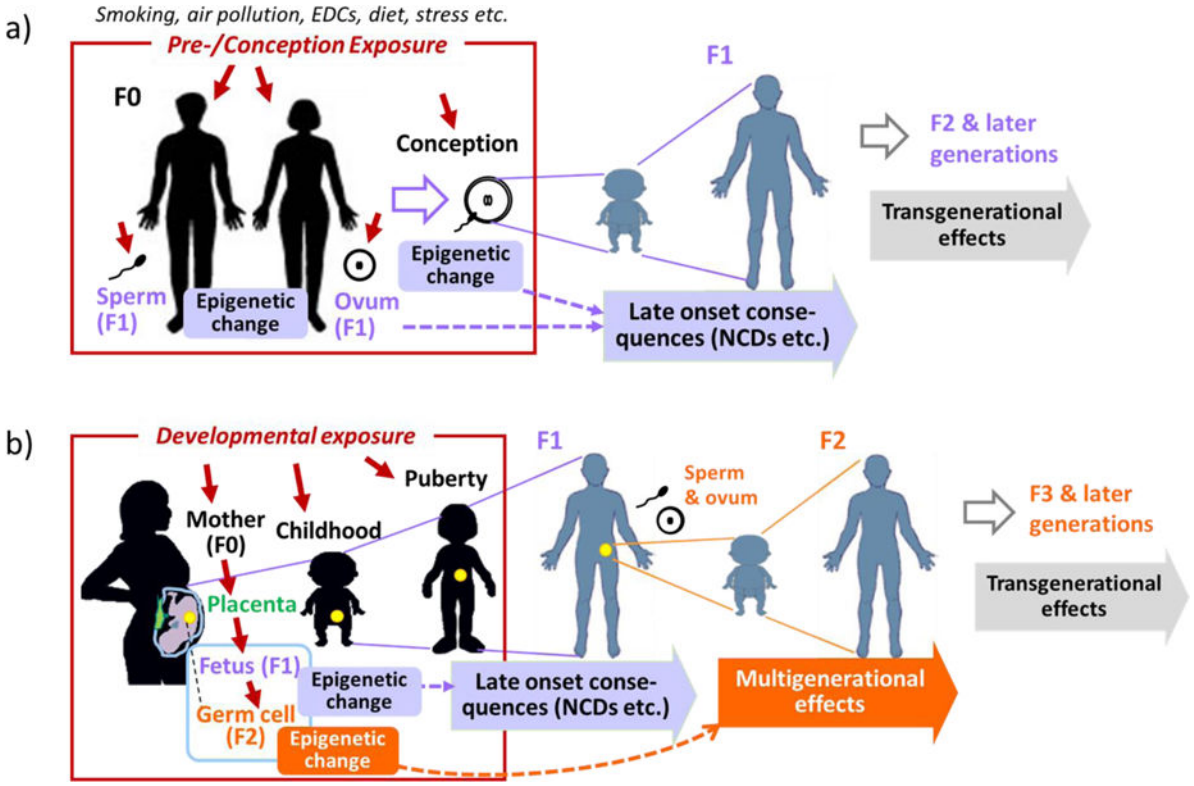

Figure.

Epigenetic changes caused by developmental environment exposure are implicated in the long-term/late-onset health effects. Development is vulnerable to environmental insults. The critical periods include pre-conception and conception (a) and in utero, childhood and puberty (b). Epigenetic alterations, such as changes in DNA methylation, histone modification and non-cording RNAs expression act through regulation of cell-type specific and time-dependent gene expression. Disturbance of such epigenetic marks by environmental stressors may bring about long-term and late-onset health effects, including NCDs. It can further lead to intergenerational effects, such as multigenerational and transgenerational effects, via epigenetic inheritance maintained in the germ cell genome.