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Review

Can epigenetics translate environmental cues into phenotypes?

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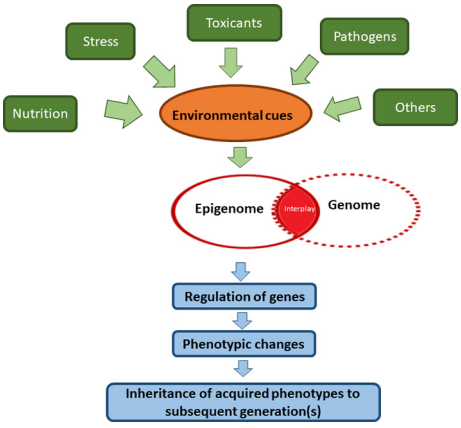
HIGHLIGHTS

- Comprehensive and readable review of environmental cues and epigenetic inheritance
- Discuss findings on inheritance of environmentally-induced phenotypes in organisms
- Underlining information gaps and further research directions

GRAPHICAL ABSTRACT



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ABSTRACT

Living organisms are constantly exposed to wide ranges of environmental cues. They react to these cues by undergoing a battery of phenotypic responses, such as by altering their physiological and behavioral traits, in order to adapt and survive in the changed environments. The adaptive response of a species induced by environmental cues is typically thought to be associated with its genetic diversity such that higher genetic diversity provides increased adaptive potential. This originates from the general consensus that phenotypic traits have a genetic basis and are subject to Darwinian natural selection and Mendelian inheritance. There is no doubt about the validity of these principles, supported by the successful introgression of specific traits during (selective) breeding. However, a range of recent studies provided fascinating evidences suggesting that environmental effects experienced by an organism during its lifetime can have marked influences on its phenotype, and additionally the organism can pass on the acquired phenotypes to its subsequent generations through non-genetic mechanisms (also termed as epigenetic mechanism) – a notion that dates back to Lamarck and has been controversial ever since. In this review, we describe how the epigenetics has reshaped our long perception about the inheritance/development of phenotypes within organisms, contrasting with the classical gene-based view of inheritance. We particularly highlighted recent developments in our understanding of inheritance of parental environmental induced phenotypic traits in multicellular organisms under different environmental conditions, and discuss how modifications of the epigenome contribute to the determination of the adult phenotype of future generations.

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1. Introduction

In the past centuries, our understanding of evolution has mostly been based on the theory of 'Modern Synthesis' focusing solely on the role of natural selection on the amount and structure of genetic variation (Laland et al., 2014; Paun et al., 2010). While there is no doubt about the validity of this neo-Darwinian evolutionary theory, more recently, several lines of studies have suggested that environmental effects experienced by an organism during its lifetime can have marked influences on its phenotype, and these acquired phenotypes can get transmitted to subsequent generations through non-genetic mechanisms, also termed as epigenetic mechanism (Kishimoto et al., 2017; Norouzitallab et al., 2014, 2016; Stadlbauer, 2017). The notion that acquired traits induced by environmental cues could become heritable dates back to Lamarck and has been controversial ever since (Jablonka and Lamb, 2002; Holliday, 2006). In this review, we describe how the field of epigenetics has reshaped our long perception about the inheritance/development of phenotypes within (some) organisms. In particular, we will highlight recent developments in our understanding of inheritance of parental environment induced phenotypic traits in multicellular organisms under different environmental conditions, and discuss how modifications of the epigenome might contribute to the determination of the adult phenotype of future generations. Recent advances in our ability to study the integrity of the genome will help to identify true epigenetic phenomena.

2. Epigenetics - a historical perspective

2.1. Epigenetics theory - development and evolution

Epigenetics has become one of the buzz words of biology in recent years. Despite being a fashionable topic in modern biology, the term 'epigenetics' is old and has a complex history. In fact, the adjective 'epigenetic' existed many centuries before the noun 'epigenetics'. It was, however, linked, to "epigenesis" and not "epigenetics." The term "epigenesis" was coined by the physician and physiologist William Harvey around 1650 for the conception of development as a gradual process of increasing complexity from initially homogeneous material in the egg or spore, a concept that was originally proposed by Aristotle in the 3rd Century BC. In the year 1942, the developmental biologist and evolutionist Conrad H. Waddington introduced the word 'epigenetics' to the lexicon by combining the words genetics with epigenesis (Jamniczky et al., 2010), and he used it to describe the influence of environmental cues on the development of specific phenotypes through genotype-environment interactions. In his characterization of the "epigenotype" he speculated about a biological system in which concatenations of processes are linked together in a network, so that a disturbance at an early stage may gradually cause more and more far-reaching alterations in many different organs and tissues (Waddington, 1957). His often-cited model of an "epigenetic landscape", describing the various developmental pathways a cell might take during differentiation, attributes a major role to the genes which underlie the landscape, acting to structure it. That is to say, according to Waddington, the expression or repression of particular genes, presence or absence of particular environmental clues and genotype-environment interactions determines which path the cell will follow from a certain point of divergence. Waddington's epigenetic landscape is a metaphor for how gene regulation modulates phenotypic development as a consequence of environmental variation. Waddington proposed 'genetic assimilation' as a mechanism that allows certain acquired characteristics to become heritable (Noble et al., 2014; Pigliucci et al., 2006). Genetic assimilation is a process during which environmentally induced phenotypic variation becomes constitutive and is maintained in absence of the initial environmental signal. This view was broadened by Nanney (1958), who defined epigenetic as the causes of heritable differences that are not dependent on changes in DNA sequence.

2.2. Modern epigenetics - the definition

In the modern aspects, "an epigenetic trait has been defined as a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" - a definition that was formulated in 2008 at a Cold Spring Harbor meeting (Berger et al., 2009). Owing to the fact that "epigenetics" has a complex history, the term is therefore often employed loosely and inconsistently, and is sometimes used as a synonym for "epigenetic inheritance". To avoid misinterpretations, we describe the term 'epigenetic inheritance' in this review as a mechanism that permits the stable transmission of parental environment-induced phenotypic traits to a subsequent generation or generations without any alteration in the DNA sequence (Kelly et al., 2010). Three main types of epigenetic inheritance have been proposed (Moshe Szyf, 2015a; T. Wang et al., 2017, Y. Wang et al., 2017) and these include: (i) intergenerational or cross-generational effects, such as the impact of *in utero* or paternal exposure to particular environmental cues (e.g. nutrition, stress) on the developing embryo and its germline (only the F1 generation) (Radford et al., 2014); (ii) multigenerational effects

(from the F1 to the F2 generation) (Dias and Ressler, 2014); and (iii) transgenerational effects that are found in more than three generations (Anway et al., 2005; Greer et al., 2016; Norouzitallab et al., 2014, 2015, 2016; Rechavi et al., 2011).

3. Mechanisms underlying epigenetic modifications

Numerous mechanisms for epigenetic modifications have been identified in vertebrates and invertebrates, and new mechanisms are likely to emerge. Key mechanisms underlying epigenetic modifications include: chromatin remodeling, methylation of cytosine in CpG dinucleotides (often referred to as DNA methylation), histone tail N-terminal modification, and post-translational modification of genes regulation by non-coding/small RNA (ncRNA/sRNA). Collectively, these processes and the components upon which they act constitute the epigenome. Individually or in concert, they play a key role in turning gene expression on or off, thus facilitating or inhibiting the production of specific proteins. The in-depth detailed description of these processes is beyond the scope of this review. However, a brief overview of the epigenetic factors and processes is presented in the subsequent sections, and a glossary of terminologies is provided to assist the reader. For further details, the reader is referred to the original studies describing the epigenome function (for reference see Table 1).

3.1. DNA methylation

The first evidence for the possible role of DNA methylation or demethylation as an important biological process was described by Griffith and Mahler (1969). Currently, DNA methylation is the most studied epigenetic mechanism. It involves the modification of a DNA base, most often at the fifth carbon atom of cytosine (or at the sixth nitrogen atom of adenine), with the enzymatic addition of a methyl (CH_3) group from S-adenosyl-L-methionine (SAM) in the presence of DNA methyl transferase (Métivier et al., 2008). This affects the coiling of DNA around histones and changes the potential binding of the transcriptional factors. DNA methylation is widespread in plants and animals, and functions to generally suppress gene transcription or maintain it at a silenced state through methylation of CpG islands, mostly near promoters of genes (Jones, 2012). Studies have also shown that DNA methylation is found throughout genes, and not just in promoter regions (Feng et al., 2010; Sarda et al., 2012; Zemach et al., 2010). At present, little is known about the influence of the environmental cues on genome-wide methylation patterns (Asselman et al., 2017).

The position of DNA methylation relative to the gene (i.e., intron, exon, transcriptional start site, or promoter) determines how gene expression is influenced by methylation. For example, gene body methylation has multiple functions, that include suppressing intragenic promoter activity (Maunakea et al., 2010), alternative splicing (Sati et al., 2012) and controlling transcriptional elongation (Lorincz et al., 2004) ensuring that the first and last exons are included in a transcript (Sati et al., 2012), while DNA methylation at the 5′ end of the gene was linked with gene silencing (Brenet et al., 2011).

The DNA methylation machinery is relatively conserved within an organism (Hernando-Herraez et al., 2015). However, the absolute levels and patterns of DNA methylation may vary substantially between different tissues, developmental stages, species and can be directly modulated by extrinsic environmental cues (Bocklandt et al., 2011; Fritsche et al., 2013; Hannum et al., 2013). For instance, in some invertebrates, methylated DNA was found primarily within the coding regions and its pattern was closely associated with gene function (Roberts and Gavery, 2012). The methylation level of DNA cytosine in the invertebrate can be 0% like in the nematode worm *Caenorhabditis elegans* (Greer et al., 2015) or very low (between 0.1 and 0.4% of the DNA cytosine) like in the fruit fly *Drosophila melanogaster* (Boffelli et al., 2014). A similar value of 0.4% was recorded in the aquatic invertebrate *Artemia* (Norouzitallab et al., 2014) for the proportion of cytosines that was hypermethylated throughout the DNA. In the genome of honey bee *Apis mellifera* and the wasp *Nasonia vitripennis*, all the three orthologous of DNMTs are found and CpG methylation has been observed in several genes, with the global DNA methylation level of about 1.5% of total cytosine (Rasmussen and Amdam, 2015). Vertebrates, in contrast, have relatively higher levels of DNA methylation. For example, in mammalian somatic tissues the genomic DNA is hypermethylated at 70–80% of all CpG sites across the genome (Li and Zhang, 2014). This methylation can occur evenly throughout the entire genome (for more details, see reviews (Feng et al., 2010; Varriale, 2014).Variations in the methylation levels across species suggest that DNA methylation may have different functions in different organisms. Notably, the heritability of DNA methylation has marked it as an attractive feature in the study of epigenetic inheritance. Specifically, during DNA replication, DNA methylation of newly generated CpG sequences occurs across from a methylated CpG in the parental strand, thus representing a biochemical mechanism for replicating an epigenetic mark (Law and Jacobsen, 2010). The potential of DNA methylation to act as a heritable epigenetic mark has been demonstrated in a few studies (Lämke and Bäurle, 2017; Stadlbauer, 2017; Zheng et al., 2017). However, whether the same mechanism of heritability during DNA replication can be extended to meiosis to enable non-genetic inheritance across generations remains to be established.

It is also interesting to mention that the occurrence of DNA modification is not limited to 5mC residue. In fact, some studies revealed the biological importance of methylation on other nucleotides, such as N6-methyladenine (m6A). For instance, adenine methylation was found to be essential for the viability of several bacteria (Reisenauer and Shapiro, 2002) and fungi (Mondo et al., 2017) and fungi (Mondo et al., 2017). Similarly, the occurrence of m6A has also been reported in eukaryotic cells, such as *Arabidopsis thaliana* (Lianga et al., 2017), *C. elegans* (Greer et al., 2016) and even mammalian cells (Wu et al., 2016). However, the significance of m6A in the transmission and expression of modified phenotypes across generations remains unclear.

3.2. Histone modifications or histone code

One of the primary roles of histone is to coil the DNA into a smaller volume for fitting in the nucleus of the cell in form of a nucleosome. Nucleosomes contain 147 base pairs, coiled twice around an octamer of histone (H) proteins (two molecules of H2A, H2B, H3 and H4). The linker histone protein H1 at the outside of the nucleosome further compact the chromatin.

Till the 1990s, DNA packing was the only role considered for histone proteins. However, in the past three decades, accumulating evidences suggested that these proteins play significant roles in: 1) the regulation of gene expression, 2) DNA damage repair, 3) DNA replication and recombination, and 4) heritable epigenetic regulation (Lennartsson and Ekwall, 2009; Leroux et al., 2017; Parisa Norouzitallab et al., 2014; Siklenka et al., 2015). Apart from the small globular structure, histones contain a more flexible and charged NH2-terminus named 'histone lysine tail (K)' that protrudes from the nucleosome and contains 25–30 basic amino acids rich residues (Jenuwein and Allis, 2001). The affinity of the histones for each other, for DNA and for other chromatin associated proteins is determined by post-translational modifications of their protruding amino-terminal tails (Araki and Mimura, 2017; Jih et al., 2017; Munshi et al., 2009). The covalent modifications (acetylation, phosphorylation, methylation or ubiquitination) on the histone tail can exhibit exquisite variations which in turn regulates the chromatin remodeling and different contacts with the underlying DNA. Addition or removal of histone modifications at specific points on the tails can readily condense or relax the chromatin resulting in causing reduction or facilitation of transcription.

The distinct histone tail modifications can occur sequentially or in combination, to create a histone code that is read by other proteins to bring about downstream effects (Fig. 1; Gardner et al., 2011). Also

Table 1
Effect of environmental cues on the induction of epigenetic inheritence of phenotypes.

Environmental cue	Epigenetic modification	Model	Target organ/gene	Manipulation	Phenotype	Transmission	References
Contaminants	DNA methylation	Rat	Germline	Endocrine disruption (vinclozolin methoxychlor	Decrease in sperm count and reduction in sperm motility.	F1	Anway et al. (2005)
			Granulosa cells	Pesticide mixture (permethrin and insect repellant)	Promotes early-onset of female puberty, apoptosis of Spermatogenic cell Decrease in ovarian primordial follicle pool size	F1, F2, F3	Manikkam et al. (2012)
				Plastic mixture (bisphenol A and phthalates)	Increased cysts resembling human polycystic ovarian disease, Decreased in the ovarian primordial follicle pool size resembling primary ovarian insufficiency	F1, F3	Nilsson et al. (2012)
				Jet fuel Fungicide Ioxin and a hydrocarbon mixture			
	H3K27me3	Human	Plasma	Contaminated drinking water with arsenic	Higher chances for having infants with myelomeningocele (bifidia)	F1	Tauheed et al. (2017)
	H3K27me3, H3K36me3, H3K9ac, H3K9ac, H3K9me3, H3K27me3	Human	Blood leukocytes	Air pollution, with black carbon (BC), and elemental components (potassium, sulfur, iron, silicon, aluminum, zinc, calcium, and titanium).	Sex-stratified analyses showed that associations between H3K9ac, and between BC and H3K9me3, were stronger in female truck drivers than in male truck drivers	F0	Zhenga et al. (2017)
Behavior	DNA methylation and histone acetylation	Rat	Hippocampus	Poor maternal care	Central infusion of a histone deacetylase inhibitor removed the DNA methylation	F1	Weaver et al. (2004), Weaver (2007)
	DNA methylation and Histone modification	Mice	Brain	Nicotine exposure	Nicotine addiction	F0, F1	Yohn et al. (2016); Jung et al. (2016)

Environmental cue	Epigenetic modification	Model	Target organ/gene	Manipulation	Phenotype	Transmission	Reference
Heat stress	DNA methylation and histone acetylation	Parthenogenetic *Artemia*	Entire body	Elevated temperature	Increased animal's robustness against biotic and abiotic stressors	F1, F2, F3	Norouzitallab et al. (2014)
	Chromatin remodeling though stress induced dATF2 phosphorylation and H3K9Me3	*Drosophila*	*drosophila* activation transcription factor 2 (dATF-2)	Elevated temperature	Eye pigmentation and wing notches	F1	Seong et al. (2011)
Predator	DNA methylation	Aphid	Entire body	Predator presence or crowding stressor in parental generation	Production of winged animals	F1	Walsh et al. (2010)
	Not well determined	*Daphnia*	Entire body	Exposure to predator	Long pointy helmets, tail spikes and neck teeth	F1	Feil and Fraga (2011)

Environmental cue	Epigenetic modification	Model	Target organ/gene	Manipulation	Phenotype	Transmission	References
Nutrition	Not determined	hamster	Phenotype	Malnutrition	More female offspring, low weight of progenies	F1, F2	Huck et al. (1987)
	DNA methylation	Agouti mice	Augouti gene	Inclusion of folic acid, cobalamin, choline, and betaine in the diet	A in the coat color	F1	Dolinoy (2008); Lillycrop and Burdge (2015)
		Apis mellifora	Dissected gland-free brains of egg-laying queens and 8-d-old workers	Feeding on royal jelly	Development of queens	F0	Lyko et al. (2010)
		Human	IGF2	Dutch Hunger Winter	Male offsprings whose mothers were exposed to famine during the last trimester of pregnancy were less obese than controls, whereas exposure in the first half of pregnancy resulted in higher obesity rates	F1	Ravelli et al. (1976), Heijmans et al. (2008), and Veenendaal et al. (2013)

Environmental cue	Epigenetic modification	Model	Target organ/gene	Manipulation	Phenotype	Transmission	References
Biotic stressors	Not determined	Crickets	Entire animal	Exposure to pathogen or pathogen cell wall	Increased reproduction	F0	Adamo (1998)
	Histone acetylation H3K4Me3, HMGB1	*Artemia*	Entire animal	Parental exposure to pathogenic *Vibrio*	Increased animals resistance against the same pathogen and increased animals reproduction	F0, F1, F2, F3	Norouzitallab et al. 2015, 2016

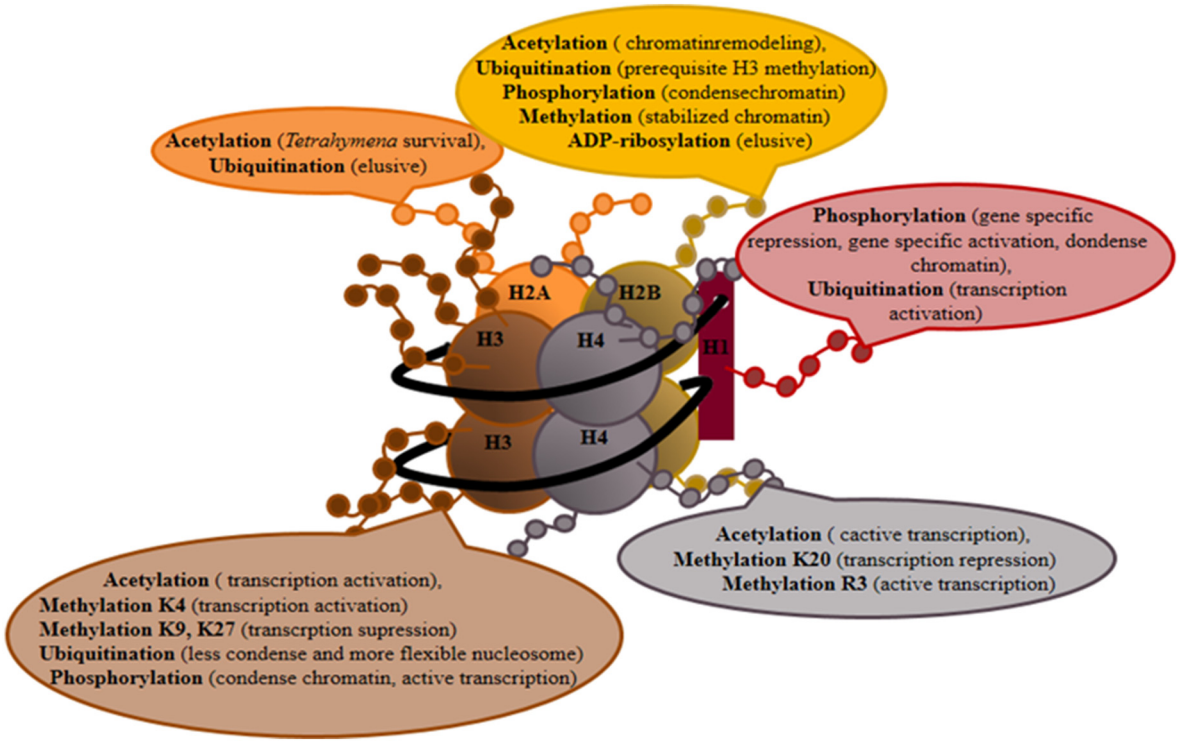

Fig. 1. Histone tails modifications. Histones post-translational modifications (PTM) are the covalent addition of marks that can regulate gene expression through forming active regions (euchromatin formation), or inactive regions (heterochromatin formation. A pictorial representation of PTMs on histones and their biological roles.

histone codes can occur differently on different histones and may be transiently altered by the cell environment (Bird, 2007; Gonzales-cope et al., 2016; Kishimoto et al., 2017). Highly specific enzymes are responsible for the histone tails modification (Barnetova et al., 2012). There are many detected residuals of the histones where the modifications can take place and yet more are expected to be discovered. This infinite enzymatically regulated array of modifications results in enormous plasticity for functional responses. For example, methylation at lysines or arginines may be in one of three different forms: mono-, di-, or trimethyl for lysines and mono- or di- (asymmetric or symmetric) for arginines (Kouzarides, 2007). For example, acetylation of histones or di/tri methylation of H3K4 leads to euchromatin (decondensed chromatin) formations, creating conditions for higher gene transcription. Conversely, condensed heterochromatin lacks this histone acetylation and is enriched in methylated H3K9 and H3K27 (Mattout et al., 2015).

It has been reported that histone methylations are regulated by two key enzymes: histone lysine methyltransferases (KMTs) and histone lysine demethylases (KDMs) (Nottke et al., 2009, 2011). KDMs have a catalytically active site named 'Jumonji' domain (JmjC). The demethylation occurs when JmjC utilizes multiple cofactors to remove the methyl group through hydroxylation. The demethylation by JmjC can be on any of the mono-, di-, and tri-methylated substrates. For other histone modifications, two important types of proteins are responsible: trithorax group proteins and polycomb (family of proteins that can remodel chromatin) group proteins, which are associated with transcriptionally active euchromatin and transcriptionally silent heterochromatin, respectively (Schuettengruber et al., 2007).

Histone modification and DNA methylation require different sets of enzymes and are carried out by different chemical and biochemical reactions. However, there is increasing evidence of cross-talk between the two processes (Cedar and Bergman, 2009; Lan et al., 2017; Spruijt and Vermeulen, 2014), suggesting that these mechanisms act together in modulating gene expression programming within organisms (Champagne, 2016). It is not known how cross-talk between these two systems is mediated, but data implies that, in at least some circumstances, changes to histone modifications may be induced prior to methylation changes that then serve as more stable epigenetic marks (Park et al., 2008). In plants, such as *Arabidopsis* and also in the invertebrate *Artemia* sp., inheritance of acquired phenotypes were reported to be mediated by altered DNA methylation levels and histone modification (Holeski et al., 2012; Norouzitallab et al., 2014; Springer and Schmitz, 2017). Additionally, in species, such as *C. elegans* and *D. melanogaster* (Ciabrelli et al., 2017; Greer et al., 2014; Norouzitallab et al., 2016), histone methylations were shown to play a key role in the inheritance of acquired phenotypes. These results suggest that histone modifications have the ability, along with DNA methylation, to serve as an epigenetic memory from one generation to the next.

3.3. Non-coding RNA

Small non-coding RNAs (ncRNAs) are RNA molecules that do not directly code for a protein. These small molecules of about 20–30 nucleotides with a two-base overhang at the 3′ end, have emerged as powerful regulators of gene expression and genome stability (Moazed, 2009). In fact, ncRNAs have been claimed to be responsible for regulating the expression of about 50% of the genes in a cell at the post-transcriptional level (Goldstein et al., 2017). Members of the regulatory small RNAs include short interfering RNAs (siRNAs), microRNAs (miRNAs) and piwi-interacting RNAs (piRNAs) (Carthew and Sontheimer, 2009). siRNAs are 21–22 nucleotides in length and are produced from endogenous double stranded RNA. They can silence their encoding DNA and are considered as defender of genome integrity in response to foreign or invasive nucleic acids, such as viruses, transposons, and transgenes (Anwar et al., 2017; Carthew and Sontheimer, 2009; Wan et al., 2014). The vast majority of miRNAs, on the contrary, exerts heterotypic silencing and is regulators of endogenous genes (Carthew and Sontheimer, 2009). Compared to siRNAs, piRNAs are larger (23–29 nucleotides) and are produced by a different mechanism (reviewed in (Castel and Martienssen, 2013). piRNAs were initially discovered in germ-line cells, but are now known to be widely distributed throughout somatic tissues (Zheng et al., 2017). In the germ-line, piRNAs mediate

transposon silencing via chromatin remodeling (Brower-toland et al., 2009; Elgin and Reuter, 2013; Wang and Elgin, 2011).

In addition to the classical 'epigenetic systems' as described in the above sections, ncRNA were also reported to possess epigenetic potential. It has been proposed that certain environmental cues can alter the expression of genes through expression of new or removal of old ncRNAs (Carthew and Sontheimer, 2009). Additionally, there are conclusive evidences for the direct involvement of ncRNAs in parental environment-induced epigenetic inheritance (Buckley et al., 2012; Larriba and Mazo, 2016; Rechavi et al., 2014). By means of deep sequencing, a large number of RNAs of all classes have been identified in growing oocytes (Barnetova et al., 2012; Svoboda and Flemr, 2010). Although spermatozoa have a highly condensed nucleus and contain little cytoplasm, a large portion of the RNA population has been detected in sperm (Chen et al., 2016; Peng et al., 2012; Sharma et al., 2016), indicating that RNAs may be involved in the inheritance of acquired phenotypes.

Furthermore, it was recently shown that tRNA-derived small RNA fragments in sperm represent a paternal epigenetic factor and contribute to intergenerational inheritance of paternal high-fat or low-protein diet-induced metabolic disorders, suggesting roles for these epigenetic marks in transmitting metabolic disorders across generations (Chen et al., 2016; Sharma et al., 2016).

4. Sustained epigenetic modifications during cell proliferation and diversification

In multicellular organisms, the germline is described as diploid cells that are highly specialized to form gametes and are responsible to pass the genetic information from parents to the progenies (Hill et al., 2018). In adults, the germline cells develop into haploid reproductive (gamete) cells by meiotic divisions in the process of gametogenesis (Hill et al., 2018; Maamar et al., 2018). Most complex organisms develop from these very specialized reproductive cells. In bisexual organisms, once the sperm penetrates the egg, the single diploid totipotent zygote cell is formed (Condic, 2014). The totipotent cells are capable to differentiate into all the other possible forms of cells required in an adult organism (Mitalipov and Wolf, 2009). Upon fertilization, a series of epigenetic modifications take place in the parental pronuclei which results in the removal of the gamete-specific modifications to facilitate the ability of embryonic development towards birth (Rivera and Ross, 2013). For this purpose the gamete cells epigenome is erased through a process called 'reprogramming' in order to return the cells to a genetic 'blank state' in which new epigenetic marks determine the fate of the cells (Fig. 2; Aguilera et al., 2010). For example, in mammals, DNA is progressively demethylated during the pre-implantation states, after which the DNA is re-methylated (Bocock and Aagaard-Tillery, 2009). Still, a very small percentage of genes keep their epigenetic marks during this process and pass unchanged from parents to progenies through the mechanism of self-sustaining feedback loop that was first described in *Escherichia coli* (Jablonka and Raz, 2009).

Dynamic regulation of the oocyte genome is essential for programming the embryo for achieving temporally required developmental landmarks. In the first few days (4 days in human) of embryonic development, more totipotent stem cells are produced by mitotic division of the zygote after which the cells begin to specialize into pluripotent cells. (Aguilera et al., 2010; Condic, 2014). Interestingly, embryonic stem cells achieve their pluripotent status by locking important regulator genes for future expression, using a polycomb group-mediated repressive histone lock which prevents precocious expression of genes that initiates the differentiation of cells along specific differentiation (Szyf, 2015b) pathways, but also allows the same genes to be primed for future expression (Spivakov and Fisher, 2007).

The pluripotent cells then differentiated into multipotent cells, which subsequently develop into progenitor cells that are programmed to differentiate into multiple, but limited cell types through specific gene activation. Therefore, the embryonic stem cells regeneration homeostasis and differentiation require selective activation or suppression of specific transcription programs (Zhou et al., 2011). Thus, synchronized epigenomic modifications are essential for lineage specification and maintenance of cellular identity (Gifford et al., 2014; Smith and Meissner, 2013; Zhou et al., 2011).

Despite the developmental stability maintained by the stem cells through genetic and epigenetic information, the embryo is highly influenced by the external environment of the parental generation (Spannhoff et al., 2011). A growing body of evidence shows that there are critical time points during the process of embryogenesis and primordial germ cells specification in which the epigenome is sensitive

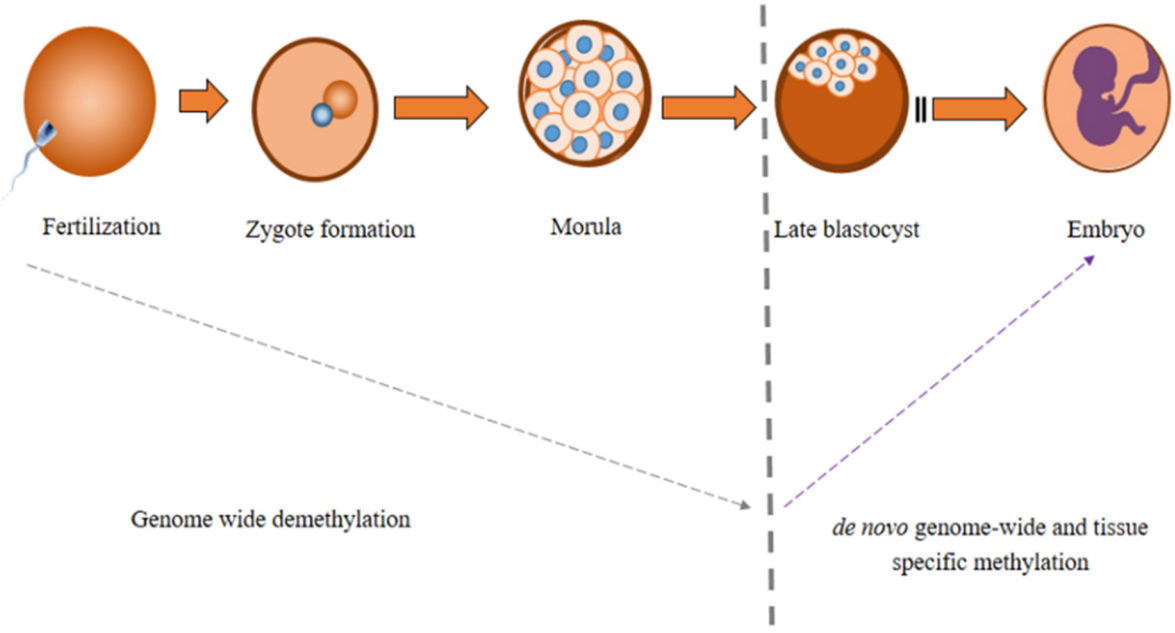

Fig. 2. DNA methylation changes during embryonic development. Most of the epigenetic DNA methylation marks are erased during early embryonic development. *De novo*, genome-wide DNA methylation marks are made soon after, during early embryogenesis after which tissue specific epigenetic marks are laid down
Adapted from Aguilera et al. (2010).

to environmental cues and therefore, changing environment can influence the epigenetic information both within developing individuals and across generations (Cavalieri and Spinelli, 2017; Bertoldo et al., 2015). Additionally, the transgenerational epigenetic effects can also originate either from direct changes in the ancestral germline or by the transfer of information from ancestral somatic cells to the ancestral germline (Devanapally et al., 2015; Huypens et al., 2016). Environmentally-derived epigenetic changes can be inherited mitotically through somatic cells. This is considered as a potential mechanism by which environmental effects on the epigenome can leave long-term effects on gene expression (Devanapally et al., 2015; Heard and Martienssen, 2014; Jirtle and Skinner, 2007). The ability of the parents for adaptation to the new environmental conditions determines the plasticity of the embryo towards that specific environmental variation. This information is passed on through germline transfer of the information (Devanapally et al., 2015).

5. Environmental cues, epigenetic modification and phenotypes

Apart from the epigenetic modifications that occur during the initial development and embryonic stages, the epigenetic modifications brought about by the environmental cues have also been reported to induce phenotypic development or variation within a number of organisms (e.g. *Artemia*, *Daphnia*, mouse). The resultant acquired phenotypic characteristics not only persist throughout life but also appear to be transmitted to subsequent generations (Aguilera et al., 2010; Norouzitallab et al., 2014, 2016). As described in the above section, during gametogenesis, the epigenome gets globally reprogrammed (Blunk et al., 2017; Kota and Feil, 2010; Norouzitallab et al., 2014; Rwigemera et al., 2017; Teixeira and Colot, 2010). The remodeling processes make gonadal cells particularly vulnerable to extrinsic factors, even in exposed adults (Yauk et al., 2008) and may explain why apparent transgenerational effects are observed. However, true epigenetic transgenerational inheritance implies that the maternal or paternal animal or plant already had the epigenetic change and transmitted the change to its offspring, whose cells were not exposed. In mammals, only epigenetic marks transmitted to the F3 generation are truly transgenerational, as the developing germ cells that give rise to the F2 generations are already present (and could thus have been exposed) during the embryonic development of the F1 generation (Drake and Liu, 2010; Feil and Fraga, 2011; Youngson and Whitelaw, 2008). Therefore, transgenerational inheritance of environmentally-induced epigenetic modification is considered authentic only if the acquired phenotypes are still present at F3 generation.

In animals, that include both vertebrates and invertebrates, many examples associate environmental influences to epigenetic changes. Epigenetic influences have been observed with environmental contaminants (e.g. inorganic contaminants, endocrine disruptors, chemicals used as pesticides or fungicides), nutritional factors, drugs, physiochemical and biochemical environmental variations, and even maternal/paternal behavior, such as culture, food, smoking, maternal care and depression (for details, see review Skinner, 2015; T. Wang et al., 2017, Y. Wang, 2017). The environmentally-induced epigenetic modifications affect the organism's phenotypes and that of subsequent generations by bringing about changes in gene expression. This phenomenon provides a useful mechanism for the progeny to adapt to the new environment. A growing body of evidence suggests that epigenetic inheritance could occur in most species (Table 1). Some examples of environmentally-induced epigenetic modifications and inheritance are described below.

5.1. Environmental contaminants and epigenetic inheritance

A variety of environmentally ubiquitous contaminants appear to have broad effects on the phenotypes of future generations even when the stressful environments no longer exist (Carvan et al., 2017; Kishimoto et al., 2017). A typical study showing this phenomenon involved the exposure of female rats to two different endocrine disruptors, vinclozolin and methoxychlor, at a critical time during gonadal sex determination (i.e. embryonic day (E) 8–15 in the rat). Results showed that exposure to toxicant resulted in adult testis phenotypes characterized by decreased spermatogenesis capacity and male infertility (20% decrease in sperm count and a 25–35% reduction in sperm motility) across four generations (M.D. Anway et al., 2005). Interestingly, these phenotypes were found to be associated with altered DNA methylation in a subset of genes in the male germline (Anway et al., 2005). However, the involvement of genetic factors e.g. mutations possibly caused by the chemical exposure cannot be fully excluded in this study. Additionally, the authors also did not identify the specific gene (s) responsible for this environmental toxicant-induced inheritance nor did they exclude the involvement of other epigenetic regulations, such as histone modification or sncRNAs. In another study, Asselman et al. (2017) showed that on exposure of water flea *Daphnia magna* to the toxic cyanobacterium *Microcystis aeruginosa*, a differential pattern of DNA methylation on exons was found between the exposed and unexposed animals. The observed patterns were enriched for serine/threonine amino acid codons and genes related to synthesis, transportation and degradation of protein. It was also observed that genes with differential methylation corresponded with genes that were susceptible to alternative splicing in response to *Microcystis* stress. In this study, the transgenerational effects of toxin exposure were not examined.

In another study, the epigenetic transgenerational effects in response to various environmental toxicants and their relevant mixtures, such as pesticide mixture (permethrin and insect repellant DEET), a plastic mixture (bisphenol A and phthalates), dioxin (TCDD) and a hydrocarbon mixture (jet fuel, JP8) was investigated in rats (Manikkam et al., 2012). The F0 gestating female rats were exposed to the toxicants during the period of embryonic gonadal sex determination. The animals from the subsequent F1–F3 generations were obtained in the absence of any contaminant. In those animals, the parental or ancestral exposure to plastics, dioxin and jet fuel promoted early-onset of female puberty, affected permatogenic cell apoptosis and decreased primordial follicle pool size transgenerationally. DNA methylome analysis of the F3 generation sperm (promoter epigenome) revealed that there were differentially methylated regions in DNA in the sperm of all exposure lineage males and was consistent within a specific exposure lineage, but different between the exposures. Furthermore, a number of other environmental chemicals, including fungicides, pesticides, or plastic compounds have also been shown to induce the epigenetic inheritance of abnormal reproductive or metabolic phenotypes in animals, including obesity, the polycystic ovary syndrome (PCOS), pregnancy defects, or germ cell apoptosis (Anway et al., 2005; Bhandari and Tillitt, 2015; Laing et al., 2017; Monk, 2015; Nilsson et al., 2012; Skinner et al., 2013).

Additionally, some studies reported the role of environmental pollutants, such as airborne particulate matters including black carbon (Tauheed et al., 2017) or arcenic (Zhenga et al., 2017) on chromatin remodeling through major histone tails modifications. In the study carried out by Tauheed et al. (2017), it was shown that in Bangladesh, where the water is heavily contaminated with arsenic, the mothers with higher levels of H3K27me3 in their plasma have lower chance for having the infant with myelomeningocele (bifida). In this study, the authors found that arsenic exposure, as estimated by arsenic concentration in toenails, was associated with lower total H3 concentrations in plasma in women with folate deficiency. The lower levels of H3 were associated with lower H3K27me3 and higher chances of having infants with bifida disease.

By carrying a study on truck drivers, Zheng et al. (2017) highlighted the epigenetic impacts of exposure to traffic air polutent. This study was perfomed on 60 truck drivers and 60 office workers of Beijing. The increased levels of exposure to air pollutants and more specifically black carbon were associated with lower H3K27me3 and H3K36me3 levels. Occupation-stratified analyses showed associations between black carbon and both H3K9ac and H3K36me3 that were stronger in office

workers than in truck drivers. From these evidences, it can be suggested that environmental contaminants are able to cause modifications within the epigenome of an organism and induce long-lasting phenotypic changes over generations. In most of the above studies, DNA methylation was used as an epigenetic marker to determine the involvement of epigenetics in the development of phenotypes. The involvement of more epigenetic marks, such as ncRNA, histones post translational modifications remained to be established.

5.2. Behavioral changes and epigenetic inheritance

The field of behavior epigenetics has brought about a paradigm shift in our understanding of the role of genetics in explaining human behavior. The parental adverse and traumatic experiences during the early period of life, including poor maternal care (Champagne, 2016; Conradt et al., 2016; Sauce et al., 2017; Weaver et al., 2004), unpredictable maternal separation (Franklin et al., 2010; Gapp et al., 2014), chronic variable stress (Deng et al., 2017; Dietz et al., 2011; Morgan and Bale, 2011; Rodgers et al., 2015, 2013; Sagarkar et al., 2017) resulted in behavioral and emotional disorders in individuals later in life or in their offspring across successive generations. Temporary mental stress caused by maternal separation during the early developmental period modified the epigenetic status of the promotor of the glucocorticoid receptor (Gr) in the rat infant hippocampus. This led to changes in gene expression caused by an altered epigenome in the pups and it resulted in persisted abnormal gene expression and behavior throughout life (Weaver, 2007). Furthermore, Franklin et al. (2010) also provided evidence that unpredictable maternal separation could model the transgenerational inheritance of complex behavioral alterations in mice. Subjecting mice to maternal separation at early stage induced depressive behaviors and altered the animals' response to aversive environments. Interestingly, some of the behavioral phenotypes were transmitted to F1 male offspring and also to the subsequent generation (F2 female and F3 male offsprings). The exact mechanisms behind this complex expression mode remain obscure. However, the maternal separation caused a marked alteration in the level of DNA methylation at CpG islands of the methylated CpG binding protein 2 (Mecp2), cannabinoid receptor 2 (Cnr2), and corticotropin release factor receptor 2 (Crfr2) genes in adult sperm of stressed males that experienced separation. Similar changes in DNA methylation were also found in the brain and sperm of the offspring (Franklin et al., 2010). These results suggest that early traumatic stress amends behavior and modifies the epigenetic status across generations, providing behavioral and molecular correlates to complex traits induced by the early environment (T. Wang et al., 2017, Y. Wang, 2017).

Another example of parental care effects on the offspring phenotype was observed in licking-grooming behavior of maternal rats towards their pups (Weaver et al., 2004). The F1 pups that experienced increased grooming and licking and arch-back nursing from the mother at the beginning of their lives and while growing, exhibited decreased fearfulness and more modest hypothalamic–pituitary–adrenal (HPA)-axis responses to stress than those who did not experience this care (Weaver et al., 2004). Alterations in both DNA methylation and histone modification at the nuclear receptor subfamily 3 group C, member 1 (*Nr3c1*) locus in the hippocampus of the F1 pups receiving higher maternal care were observed during the first week of postnatal life and were associated with changes in *Nr3c1*-encoded glucocorticoid receptor expression (Weaver et al., 2004). These findings suggest that increased parental care positively influences appropriate behavioral responses and causes adaptive behaviors in F1 offspring. In a similar study, Champagne et al. (2006), reported that the promoter region of the alpha subunit of the estrogen receptor was hypermethylated in the hippocampus of low-licking grooming pups, and these changes resulted in suppressed expression of these receptors. In the study of Weaver et al. (2004), however, the generation-to-generation acquisition of the nurturing behavior does not occur through the gametes but represents a learned trait, likely through epigenetic regulation in genes such as estrogen receptor α1b in the medial preoptic area of the brain (Champagne et al., 2006). Also in the mice model, maternal's grooming and licking behaviors towards pups induced epigenetic changes that modified the animals stress response in the adulthood (Champagne et al., 2006; Meaney and Szyf, 2005; Weaver et al., 2004). This maternal care caused increased expression of the hippocampal glucocorticoid receptor (GR) through histone acetylation and DNA demethylation which later altered the hypothalamic-pituitary-adrenal axis and the stress response of the pups (Weaver, 2007). In a further study in non-inbred mice, it was shown that chronic and unpredictable stress in early life of mice altered behavioral response not only in the stressed animals when becoming adult but also in their successive, unstressed generations (up to generation F3) (Franklin et al., 2010). Also, a link has been established between the childhood environmental variation and chances for mental diseases such as depression (Gouin et al., 2017; Lockwood et al., 2015; Smearman et al., 2016; Uddin et al., 2017). It was found that glucocorticoid receptor and brain-derived neurotrophic factor (BDNF) gene promoters were hypermethylated in suicide victims who were exposed to childhood trauma (Keller et al., 2010; McGowan et al., 2009). In another study it was found that gene and environment interaction has been responsible for the transgenerational likelihood of developing migraine via epigenetic modifications such as DNA methylation (Tietjen, 2016). All these findings suggest that evolution has equipped organisms with mechanisms to react specifically and efficiently to certain critical experiences, such as maternal separation and reduced maternal care, and to transmit this information effectively to their offspring without the need for the typically slow process of natural selection (Szyf, 2015b).

5.3. Environmental stress and epigenetic inheritance

A number of studies have shown transgenerational effects of stress in organisms. One of the best examples was our previous work showing the effects of environmental stress on the emergence and inheritance of phenotypic traits across three subsequent non-stressed generations (Norouzitallab et al., 2014). In this study, parthenogenetic *Artemia*, which are having apomictic breeding behavior, were used as model organism. Apomixis implies that a parthenogenetic *Artemia* population clone has no other mechanism for genotypic change but mutation, which may induce genetic differentiation (Abatzopoulos et al., 2003). On exposure to an abiotic stressor i.e. non-lethal heat stress, the parental population of parthenogenetic *Artemia* exhibited increased resistance towards a subsequent pathogenic *Vibrio campbellii* infection and this acquired phenotypic trait was transmitted to three successive generations, of which none was exposed to the parental stressor. Interestingly, this transgenerational inheritance of increased disease resistance was associated with alterations in the levels of epigenetic marks, such as global DNA methylation and total histones H3 and H4 acetylation levels (Norouzitallab et al., 2014).

Considering that environmental stress can cause genetic (DNA sequence) mutational events, such as environmentally facilitated single-nucleotide polymorphisms, the involvement of genetic factors in the development of observed phenotypes was not excluded in this study. However, from the available information, it may be suggested that a non-genetic process is involved in the emergence/inheritance of the observed phenotypic traits or regulation and persistence of epigenetic modifications. Other examples of the inheritance of the environmentally responsive phenotypes over multiple generations in (genetically identical) animal or plant models have also been described. For instance, using a genetically identical *Arabidopsis thaliana* Heynh line plant model, Whittle et al. (2009) demonstrated that plants exposed to a mild heat (30 °C) treatment in the parental and F1 generations exhibited markedly improved fitness (5-fold increase in seed production per individual) in a later generation (F3). The heat-specific fitness improvements among F3 plants were preserved even after one generation (F2) of reproduction under normal temperature circumstances, which

led to the conclusion of an environmentally induced epigenetic and heritable adaptive phenomenon.

Another relevant example of transgenerational inheritance of acquired traits in response to environmental stress was reported by Seong et al. (2011) on the model organism *Drosophila*. The authors demonstrated that heat shock-induced changes in heterochromatin are transmitted to successive generations. Specifically, a transcription factor, *drosophila* activation transcription factor 2 (dATF-2), the homolog of which functions in the nucleation and spread of heterochromatin in fission yeast (Jia et al., 2004), was shown to be involved in the heat shock-induced epigenetic inheritance (Seong et al., 2011). Using position-effect variegation-mediated alterations in *white* gene silencing as a read-out of heterochromatin formation, Seong et al. (2011) showed that upon heat shock or osmotic stress, dATF-2 was phosphorylated by stress-activated protein kinases such as p38, which in turn led to the release of phosphorylated dATF-2 from the heterochromatin region. The stress-induced heterochromatin disruption was found to be transmitted through the germline. The phenotypes examined (eye color and wing notches) eventually faded and disappeared in successive generations unless the stress was applied again. Furthermore, stress-induced heterochromatin formation occurs when unstressed insects harboring the *white* gene are mated with stressed insects, suggesting that these acquired traits are inherited in a non-Mendelian manner. This result resembles the extensively studied phenomenon of paramutation in plants, in which a paramutagenic allele causes another allele in the same nucleus to become silenced (Chandler, 2010). Although the stress-induced, dATF-2-dependent epigenetic change described in this study has high penetrance, the phenomenon has not received much attention to date, in part owing to a lack of morphological, physiological, or behavioral phenotypes in successive generations in response to the new epigenetic states. Nevertheless, the findings from this work suggest that environmental cues could possibly induce changes in chromatin state, thereby altering the expression of a subset of genes and creating specific phenotypes, which then pass on to subsequent generations. These findings were further supported by the transgenerational experiments carried out in aphids (also known as plant lice), in which the presence of predators, crowding or other environmental stresses brought a shift in the population from animals with no wings to winged animals. This adaptive switch took place at early stages of development, through unknown epigenetic mechanisms (Feil and Fraga, 2011). Further investigation of the gene for juvenile hormone (JH) binding protein revealed one CpG site was significantly hypermethylated in winged animals compared to the wingless asexual females (Walsh et al., 2010). Similarly, in *Daphnia* (water flea) species, external stressors, such as water-borne chemicals or predators instigated dramatic morphological changes. In this case, *Daphnia* arms itself with long pointy helmets, tail spikes and neck teeth, on exposure to the predators during development and these acquired phenotypes persisted over several generations in the population (Agrawal et al., 1999; Harris et al., 2012). These modifications changed the size of the animals two times bigger than the original one which makes it impossible for certain predators to consume them as a prey (Lloyd et al., 2012). Helmet growth and neck teeth development in *Daphnia* can be induced epigenetically by the animals exposure to kairomones (i.e. an aquatic chemicals released by predators) at their early life stages (Harris et al., 2012).

5.4. Nutrition and epigenetic inheritance

The nutritional status of an organism, particularly during the early stages of development, plays a critical role in regulating the epigenome, and eventually in modulating the growth and health of an organism both within and across generations. Numerous studies have shown strong associations between phenotypic traits (e.g. health, development, sex ratio etc.) and nutritional status of an individual in the pre- or periconception period. A classical example for the role of nutrition on transgenerational epigenetic inheritance is the Dutch Hunger Winter (1944–1945). It was reported that the male individuals whose mothers were exposed to famine during the last trimester of pregnancy were less obese, whereas exposure in the first half of pregnancy resulted in higher obesity rates (Heijmans et al., 2008). The authors showed that individuals who experienced famine at the prenatal stage during the Dutch Hunger Winter exhibited decreased DNA methylation on their imprinted (phenomenon in which a gene's epigenetic state is determined by its parental origin) IGF2 gene, six decades after the incidence, compared to the non-exposed ones from the same sex siblings. Interestingly, examination of the F2 generation showed higher weights and body mass index (BMI) in adult offspring of prenatally exposed F1 fathers compared to the offspring of unexposed ones (Veenendaal et al., 2013). However, this effect was sex-specific and the offspring of prenatally exposed mothers did not exhibit these phenotypes. In a more recent study, Tobi et al. (2018) provided new insights into the transgenerational epigenetic effects of Dutch hunger. The authors evaluated whether DNA methylation (whole blood) mediated the association between prenatal famine exposure and metabolic health in 422 individuals exposed to famine in utero compared to the 463 (sibling) controls. The authors also found that the DNA methylation on key genes, such as PIM3 (a gene involved in energy metabolism and affects individuals BMI), TXNIP (influencing β cell function) and ABCG1 (affecting lipid metabolism) together mediated 80% of the association between famine exposure and serum triglycerides. DNA methylation was associated with gene expression in an external data set and correlated with DNA methylation levels in fat depots in additional postmortem data (Tobi et al., 2018).

Another relevant example for the role of nutrition in development of phenotypes was reported by Huck et al. (1987) in female golden hamsters (*Mesocricetus auratus*). In this animal, early food deprivation has shown to cause sex ratios shifts of their first descendants with lower numbers of males popping up in the population as compared with the normal fed controls. Apart from sex ratio, there were no (typically) greater weight male pups in the food restricted population relative to their females at birth compared to the control group. However, in later developmental stages, the weight of the restricted animals, both male and females was significantly lower than that of the controls. Interestingly, these modifications persisted for 2 generations.

In the honey bees (*Apis mellifora*) for instance, female bees can be sterile workers or fertile queens. Both the females are developed from genetically identical larvae but only the ones fed with royal jelly develop into queens. The underlying mechanisms behind such transformation are unclear yet. However, *de novo* methyltransferase DNMT3 was suggested to cause differential DNA methylation and the differential expression of many genes between queen and worker larvae (Lyko et al., 2010). Spannhoff et al. (2011) showed that royal jelly contains a fatty acid, (E)-10-hydroxy-2-decenoic acid (10 HDA) that inhibits the histone deacetylation. This fatty acid accounts for up to 5% of royal jelly and has the ability to reactivate the expression of epigenetically silenced genes in mammalian cells (Spannhoff et al., 2011). In another study in the *Drosophila* model of paternal-diet-induced intergenerational metabolic reprogramming, it was revealed that an acute sugar dietary intervention in fathers elicited obesity in the F1 progeny via the male germline. Using identical or comparable position-effect variegation lines, the authors further revealed that this intergenerational reprogramming in response to dietary manipulation modified the chromatin state and transcription in offspring in a manner sensitive to the functions of Polycomb, enhancer of zeste [E(z), a histone H3K27 methyltransferase], SetDB1 (a H3K9 histone methyltransferase), Su(var)3-9 (a H3K9 histone methyltransferase), and heterochromatin protein 1 (HP1). Numerous genes vital to both cytosolic and mitochondrial metabolism appeared to be embedded into H3K9me3- and polycomb-controlled regions. Chromatin-dependent transcriptional depression in the sperm of high-sugar-fed males was also observed, suggesting that chromatin-dependent signatures of metabolic reprogramming are forecast in the paternal germline (Öst et al., 2014).

Also there are studies demonstrating the roles of micro nutrients in the development and transgenerational inheritance of phenotypes in Gambian women (Dominguez-salas et al., 2014). In another example of nutritional effects on multigenerational epigenetic inheritance of acquired traits, Benyshek et al. (2006) demonstrated on a rat model (non-inbred lines) that impaired glucose metabolism in F1 rats exposed to a nutritional stress during gestation period persisted through maternal transmission to the F3 generation. However, this study did not provided evidence for the identification of epigenetic mechanisms underlying these phenotypes and requires further investigation. Considering that feeding/nutrition is a rather common phenomenon for animals over evolutionary timescales, knowing the underlying mechanisms thus carries profound implications for our understanding of phenotypic diversity and evolution.

5.5. Environmental biotic cues and epigenetic inheritance

Host-pathogen interactions are amongst the highly plastic, dynamic and competitive system interactions (Gómez-Díaz et al., 2012). In an environment, apart from abiotic variants, living organisms are surrounded by different species of micro-organisms including pathogenic bacteria and viruses, and they have a significant evolutionary impact on the host fitness and life history. Upon a pathogen attack, healthy cells of the host impose selective constrains to restrict or eliminate the threats. Therefore, many pathogens evolved developing an extreme level of phenotypic plasticity in order to cope with the pressures imposed by the host (Fernández-Morera et al., 2010; Moore, 2002). In the same way, the host phenotype is drastically modified (positive/negative) by the presence of a pathogen. In some cases these acquired phenotypes can be even inherited by subsequent generations (Norouzitallab et al., 2015, 2016; Poulin and Thomas, 2008). A good example of such adaptation was reported by Adamo (1998) in crickets (*Acheta domesticus*) exposed to pathogenic bacteria (*Serratia marcescens*) or to parasitic larvae of the parasitoid fly (*Ormia ochracea*). The authors showed that the females which were injected with either pathogenic bacteria or the cell wall from the same bacteria exhibited high productivity in terms of numbers of laid eggs. This phenotype was not observed in the animals challenged with the parasite. Similar phenotype was observed in an invertebrate model *Artemia* challenged at early life stages with pathogenic bacteria *Vibrio campbellii* (Norouzitallab et al., 2016). Additionally, it was also observed that the F1–F3 progenies whose ancestors were exposed at early stages to *V. campbellii* exhibited a significantly resistant phenotype compared to the respective progeny of control *Artemia* that did not experience *V. campbellii* exposure at their early stage (Norouzitallab et al., 2015, 2016). Interestingly, the increased resistance phenotype was associated with elevated levels of heat shock protein *hsp70* and high mobility group box 1 protein *hmgb1* signaling molecules and alteration in the expression of key innate immunity-related genes. Additionally, there was a stochastic pattern in the acetylation and methylation levels of H4 and H3K4me3 histones, respectively, in the progenies whose ancestors were challenged. Overall results from this study suggested that epigenetic reprogramming of (selected) innate immune effectors in response to exposure to biotic stress at early stage is likely to play key role in the mechanisms leading to increased resistance phenotype. The swift modifications accruing during the host-pathogen interactions and co-evolution leave no doubt about interference of epigenetic modifications in this entire process (Gómez-Díaz et al., 2012). It is because the induction of splice variants results in additional phenotypes the host can use in its arms race against pathogens (Decaestecker et al., 2013).

6. Conclusions

In the light of the state of the art outlined above, it appears that genomic information does not fully account for all the phenotypic variations in organisms, and that the phenotype of an organism may result from the interplay between the genome and the epigenome, which itself depends on the environmental conditions the organism experiences during its development and adult life. Environmentally-induced epigenetic variations therefore appears to play critical roles in defining individual variations and phenotypic outcomes not only within generation but also across successive generations (Norouzitallab et al., 2014, 2015, 2016; Stadlbauer, 2017; Veilleux et al., 2015). It has taken a long time to fully accept the notion that 'phenotypic complexity is not just a simple matter of Mendelian genetics' but possibly that of the interaction between genetics and epigenetics (Deans and Maggert, 2015). Future research should focus on expediting fundamental research on how epigenetic events interact with genotype, possibly to influence the induction of phenotypic traits under different conditions, and use this fundamental information for applications in human and animal health care, farmed food production, and in understanding biological adaption and evolution.

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Conflict of interest

The authors declare that there exist no conflicts of interest which may bias this research.

Ethical approval

This article does not need any ethical approval.

Informed consent

Not applicable.

Author contributions

The first and second authors have contributed equally as first authors for the writing of the manuscript and making the figures. The last two authors have contributed equally as senior authors. They edited the manuscript. All authors read and approved the final manuscript.

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