Epigenetics In Transgenerational Responses To Environmental Impacts: Facts And Gaps

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Summary

There is increasing interest in non-genetic and non-cultural mechanisms transferring a memory of parental exposure to various environments and determining the reactivity of subsequent generations to their environment during their lifetimes. However, fundamental questions remain about the nature, roles and relative importance of epigenetic marks and processes, non-coding RNAs, or other mechanisms, and their persistence over generations. No model incorporating the various transmission systems, their nature, respective impact and mechanisms, whether direct or indirect, their cross-talk and windows of sensitivity as a function of the sex of the parent and offspring, has yet been built.

Revisiting the theories of J.B. Lamarck in the light of epigenetics

Our capacity to respond to the various challenges and hazards of life, and to stress and risks of disease, during childhood and adulthood, depends on the health and human capital with which we are born [1]. These observations underlie the concept of "developmental origins of health and disease" (DOHaD) [2]. The notion that non-genetic and non-cultural mechanisms are able to transmit the memory of exposure to diverse environmental conditions to subsequent generations, conditioning their reactions, has excited considerable interest and has brought the long-criticised proposals of J.B. Lamarck back into the limelight (box).

Box

The carving behind the base shows Jean-Baptiste Lamarck and his daughter, Aménaïde Cornélie. It bears the inscription: "*La postérité vous admirera, elle vous vengera, mon père*" (Posterity will admire you and avenge you, father).

Jean-Baptiste Pierre Antoine de Mont, Chevalier de Lamarck (1774-1829) was a French biologist/zoologist and anatomist who made a major contribution to the classification of life forms through his four laws:

First law: Life, through its own forces, tends to increase continually the volume of any body that it possesses and to extend the dimensions of its parts to a limit that it itself defines.

Second law: The production of a new organ in the body of an animal results from a new need that occurs and continues to be felt and a new movement that needs to be born and maintained.

Third law: The development of the organs and their force of action is constantly consistent with the use of these organs.

Fourth law: All that has been acquired, traced or changed in the organisation of individuals, during their lifetime, is conserved by the generation concerned and is transmitted to the new individuals produced by those that have experienced these changes.

Non-genetic transmission processes are often described as Lamarckian because they raise the possibility of inheriting characters acquired by previous generations. The key characteristics of Lamarckian mechanisms are: 1) an environmental factor directly causing "heritable" changes; 2) the changes induced target a limited set of cell components of functional relevance; 3) the changes provide a specific adaptation to the initial challenge. However, the proof-of-concept for a role of epigenetic processes in

Lamarckian evolution remains tenuous or fragmentary. The fourth law, which was formulated two centuries ago, may seem to go against the finding that the epigenetic marks carried by the gametes are extensively erased after fertilization, ensuring a state of totipotency that should not allow the passage of information about the experiences of parents or ancestors. However, Lamarck began from the notion that a change in environment provokes changes in the needs of the organisms living in that environment, in turn triggering changes in their behaviour. These changes in behaviour lead to greater or lesser use of the organ concerned, resulting in changes in the size of the organ (increases in size or disappearance) over time and generations.

The consequences of environmental factors such as diet, stress, chemical products or other psychoaffective, geographic, political or socioeconomic influences can simultaneously affect at least three generations — the mother and father (F0), their children (F1) and their grandchildren (F2) — through somatic and/or germline changes in the F1 generation (Figure 1) [1].

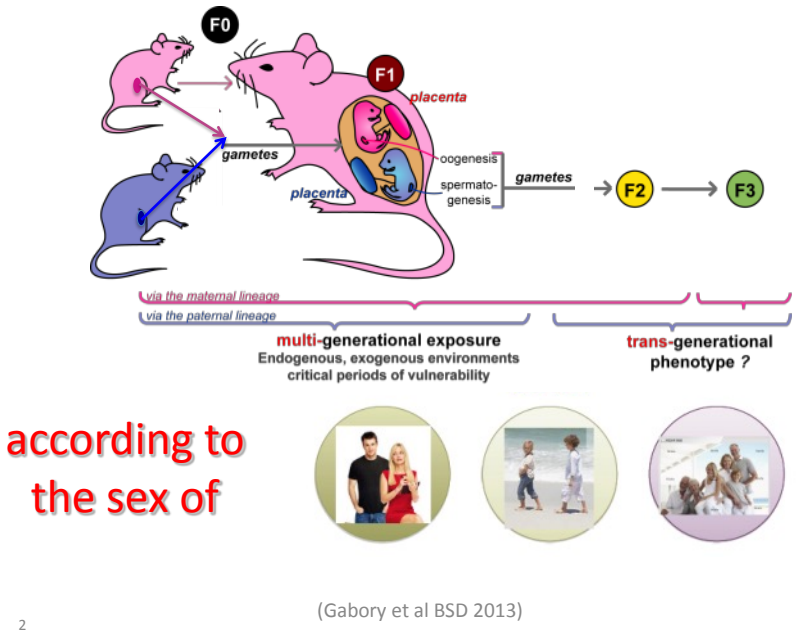

Figure 1. Sex-specific transmission of the memory of exposure to environmental factors to subsequent generations. *Environmental factors, including nutrition, psychosocial stress, toxins, endocrine disruptors, tobacco, alcohol, and microbiota, affect individual (F0) epigenetic landscapes and, therefore gene pathways and networks, in ways that differ between the sexes. For example, maternal and paternal exposures before the conception of their offspring can modify gamete quality and information about these exposures can be transmitted to the next (F1) generation. In addition, the consequences of maternal (F0) exposure during pregnancy (stress, metabolism, diet, hormonal changes, etc.) can be transmitted from the maternal to the foetal compartment via the placenta, in a sex-specific manner, with effects on F1 tissue development. The programming of somatic tissues can lead to changes in long-term health outcomes in the first generation. Moreover, primordial germ cells, which develop and undergo reprogramming during foetal development, can also be affected by the F0 maternal environment and may transmit genetic and epigenetic information to the F2 generation. These influences are transmitted differently by the maternal and paternal lineages. In particular, multigenerational exposure in the maternal lineage can be seen in the F0, F1 and F2 generations, with a transgenerational phenotype observed in the F3, whereas, in the paternal lineage, multigenerational exposure concerns the F0 and F1 generations, and a transgenerational phenotype is seen in the F2 and F3 generations. From [55].*

Our experiences *in utero* and during the first two years of life (the 1000-days concept) are a clear determinant of our health capital. However, the phases preceding conception, beginning with gametogenesis and distinguishing between effects on the primordial germline cells, the gametes, are also important and must be taken into account.

illustration of these differences. The risk of cardiovascular disease and diabetes in a man or a woman is dependent on the abundance or lack of food to which the grandparents, but only the paternal grandparents, were exposed before puberty, [13]. The information is transmitted by the paternal grandfather to his grandsons, but not to his granddaughters. Similar results have been reported for rodents, for undernutrition or the consumption of areca nuts [11, 20]. The transmission of behavioural characteristics from the father to his female descendants, but not to his male descendants, has also been observed in genetically identical mice displaying phenotypic heterogeneity in terms of behaviour [21].

Exposure to certain environments may affect the germline of the father or mother (or both), all their somatic tissues, and their reproductive systems, including the genital tract and environment. This results in a complex dialogue between these systems that may lead to concerted transfer to subsequent generations [10, 13, 14, 22](Figure 2)

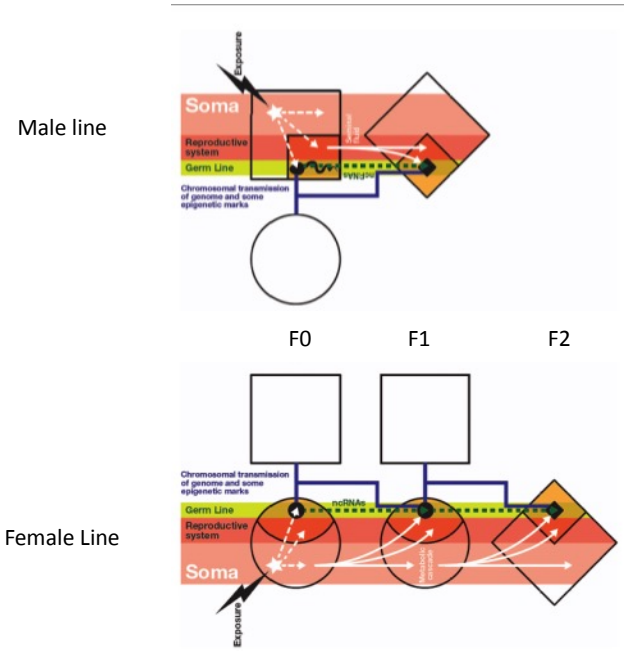

Figure 2. Schematic pedigree diagram showing the main routes for the biological transmission of the effects of exposure to the subsequent generations

Left, female line; right, male line. The exposure can potentially affect the germline, the reproductive system and the somatic tissues. The traditional pedigree lines (blue) show chromosomal transmission, with the possibility of exposure-induced epigenetic marks that escape erasure and affect the development of the offspring. The germline can potentially transmit exposure-induced non-coding RNAs (ncRNAs) that influence offspring development. Exposure-induced metabolic changes can set up a 'metabolic cascade', such that changes in the reproductive tract influence early embryonic programming of the offspring or change metabolic signals across the placenta. An additional maternal route of transmission is the influence of the mother's microbiome on that of her child. From [13].

The germline and gametes may display genetic (XX or XY), ontogenetic, morphological and functional differences between the sexes. The non-genetic differences result from epigenetic asymmetry, which may continue after fertilization [23, 24]. At conception, the gametes deliver the genetic heritage, DNA, which forms the genome of the embryo. They also transmit the different epigenomes and RNA molecules from both the father and mother, and mitochondria and a number of proteins from the mother only. Thus, in addition to the genetic heritage of the embryo, the parents also provide epigenetic, protein-based and metabolic information relating to exposure to environmental factors, experience, physiopathological state, age, social class, parental education, and birth rank and weight [11, 25].

Maternal transmission has traditionally been the most widely studied, but mostly as concerns inter- or multigenerational responses in terms of embryonic or foetal growth and development during gestation or lactation (Figure 1). Many maternal physiological conditions, not necessarily involving the germline, have been studied: metabolic conditions, nutrition, exposure to toxic substances or stress or free choice to mate with attractive males [4, 26-31]. Epigenetic transmission via the maternal line has been demonstrated in rodents [32-34], but it is generally difficult to distinguish what has been transmitted by the gamete from what has been transmitted through the materno-fetal unit during gestation. By contrast, studies of paternal transmission, although less common, have raised questions about the mechanisms by which spermatozoa transmit information: possibilities include via epigenomic marks, non-coding RNA or the seminal fluid [10, 11, 13, 25] (Figure 3).

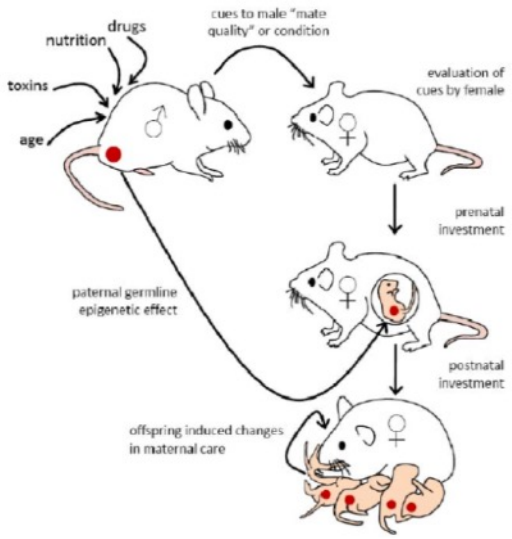

Figure 3 - Illustration of the non-genomic pathways through which paternal effects on offspring development may occur. *The experiences of males (drugs, nutrition, toxins, age, stress), particularly during early development, may lead to epigenetic alterations in the male germline (red circle), which are then transmitted to the offspring with consequences for phenotypic variation. Alternatively, or probably in combination with these direct paternal effects, the experiences of a male before mating may lead to changes in mate quality or preference, which may be assessed by the female at the time of mating. This assessment may lead to differences in maternal prenatal and/or postnatal investment in the growth and development of the offspring generated from this mating, with consequences for phenotypic variation in the offspring. Maternal investment may also vary with paternally mediated variations in offspring*

phenotype, during both the prenatal and postnatal periods. Differences in maternal investment as a function of paternal experiences or offspring traits may either enhance transmission of the memory of paternal exposure or compensate for deficits in functioning due to that exposure. From [11].

The various phases of reprogramming and the twists of mark erasure

Two principal phases of reprogramming, the erasure of parental marks, have been studied: the first occurs in the zygote, just after fertilization, and the others occur in the germline, when the primordial germ cells migrate towards the genital ridges before sexual differentiation (Figure 4a and 4c) [35].

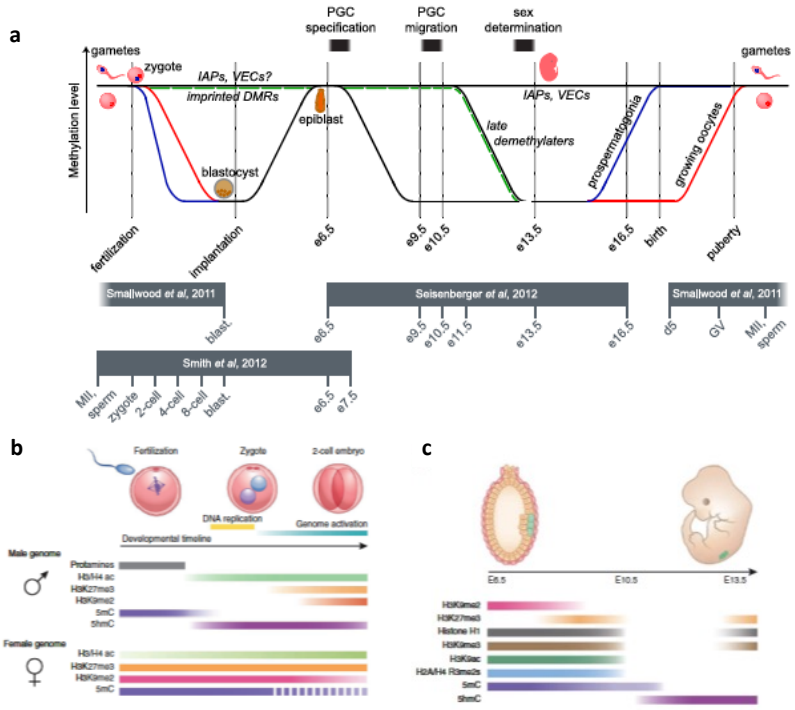

Figure 4. Epigenetic changes during in vivo reprogramming

(a) DNA methylation dynamics during developmental reprogramming. After fertilisation, the paternal genome (blue line) is rapidly demethylated by active mechanisms, whereas the maternal genome (red line) is passively demethylated. Differentially methylated regions (DMRs) associated with imprinted genes are protected from this erasure (dashed green line). De novo methylation occurs after implantation (black line), but primordial germ cells (PGCs) are not specified until the epiblast stage (shading at the top of the figure). This methylation must be reset in PGCs. The figure shows the methylation dynamics, from E6.5, of the cells forming the germline only. Most sequences are demethylated by E9.5 in PGCs. Some sequences are subject to late demethylation and are not reprogrammed until after PGC migration. These sequences include, but are not limited to, the imprinted DMRs. IAPs Intracisternal A particles are resistant to demethylation during both the post-fertilisation and PGC waves of reprogramming. Variably erased CG islands (VECs) can resist erasure during PGC reprogramming, but their methylation status during post-fertilisation reprogramming is unclear. Following sex determination, the germ cells undergo de novo methylation, but the dynamics are sex-specific. Methylation is completed in the prospermatogonia before birth, whereas methylation in the oocytes is established during postnatal growth. In adulthood, the gametes are appropriately methylated to form a new zygote and to restart the

cycle of methylation dynamics. We show below the developmental windows investigated in three key studies, with the specific time points analyzed indicated. blast., blastocyst. d5, day 5 oocytes. GV, germinal vesicle oocytes. MII, metaphase II oocytes. From [35].

(b). Epigenetic changes during in vivo reprogramming. Schematic diagram of the global DNA and histone modifications leading to transcriptional activation of the embryonic genome between the late zygote (paternal genome only) and the two-cell stage. Gamete genomes undergo different epigenetic programs after fertilisation, with the paternal genome mostly subject to epigenetic remodeling at the zygote stage and the maternal genome gradually losing repressive modifications during subsequent cleavages. (b) Global epigenetic changes during germline development from PGC specification (E6.5) to mitotic/meiotic arrest at E13.5. Two major reprogramming phases can be distinguished during PGC migration toward the genital ridges (E7.5–E10.5) and upon their arrival in the gonads (E10.5–E12.5). From [57]

(c). Global epigenetic changes during germline development from PGC specification (E6.5) to mitotic/meiotic arrest at E13.5. Two major reprogramming phases can be distinguished during PGC migration toward the genital ridges (E7.5–E10.5) and upon their arrival in the gonads (E10.5–E12.5). From [57]

The reprogramming of the parental genomes in the zygote was long considered to be almost complete. However, the histone marks and methylation patterns of certain DNA sequences may not be erased [36]. Two other phases may also be considered as reprogramming processes: the final compaction of the chromatin of the spermatozoa, linked to the replacement of a large proportion of the histones by protamines (Figure 4b) and the massive changes, particularly during the reorganization of the brain and its maturation during puberty. This last phase of reprogramming has not yet been studied in detail [37].

One of these phases, involving the erasure of specific epigenetic marks from the gametes, leads to the acquisition of a totipotent epigenome, allowing the cells of the embryo to differentiate into any type of cell (Figure 4b). Some sequences, such as those of genes subject to parental imprinting, escape this process. Following another phase of reprogramming linked to the germline, the remethylation of DNA occurring after sex determination facilitates the acquisition of a very specific expression programme, including imprinted genes, for gamete differentiation (Figure 4c). Given the epigenetic asymmetry of the gametes of the father and the mother, sensitive unerased marks may differ between chromosomes of paternal and maternal origin in the zygote. The mechanisms involved have yet to be determined, but these observations suggest that the possibilities for transmission may differ as a function of the transmitting parent [38] (Figure 5).

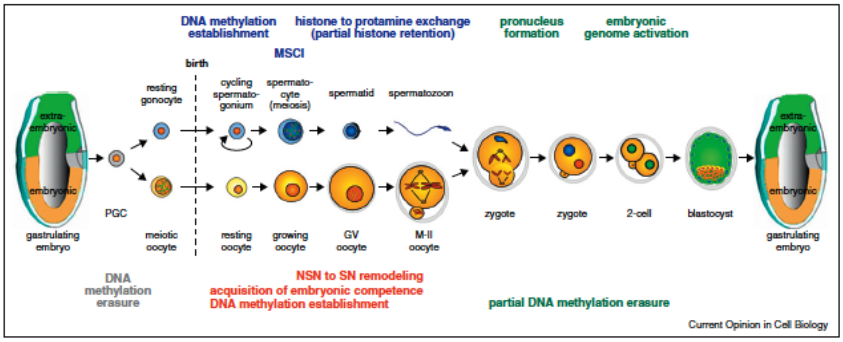

Figure 5. Life cycle of mammalian gametogenesis and embryogenesis

Primordial germ cells (PGCs) arise from proximal epiblast cells. They undergo extensive erasure of DNA methylation and chromatin changes during migration to and entry into the gonad. Directed by the somatic gonadal environment, germ cells are destined for a male or female fate. Male germ cells, initially called gonocytes, have arrested cell cycles and they begin to establish male-specific DNA methylation patterns. During the subsequent meiotic prophase, the X and Y chromosomes undergo meiotic sex chromosome inactivation (MSCI) characterised by major chromatin remodelling events. Following meiotic divisions, haploid spermatids undergo extensive nuclear and morphological changes, including an almost genome-wide replacement of histones with protamines. However, nucleosomes are retained on regulatory sequences, providing a potential means of epigenetic inheritance. Female germ cells enter meiotic prophase in the embryo and complete their meiotic divisions upon hormonal induction in the adult ovary and fertilisation by sperm. During the growing phase, oocytes establish DNA methylation at genes and imprinting control regions, undergo chromatin remodelling and acquire competence for the direction of embryogenesis. Upon fertilisation, the parental genomes form two pronuclei that are epigenetically different, reflecting the history of parental germline-specific chromatin remodelling events. The paternal and maternal genomes undergo active and passive erasure of DNA methylation. The asymmetry of the chromatin states of paternal and maternal chromosomes may potentially regulate the activation and repression of de novo gene expression in pre-implantation embryos, thereby directing embryogenesis. A latent epigenetic state, characterised by the presence of H3K4me3 and H3K27me3 bivalent marks in the promoters of genes involved in development, not expressed at these stages, is a fundamental property of the nucleus of mammalian germline cells, enabling differentiated gametes to initiate a totipotency programme immediately after fertilisation [58]. From [38].

The incomplete erasure of some parental epigenetic marks — DNA methylation and histone marks — and the polycomb and trithorax systems make possible the programming and transgenerational transmission of environmental impacts [36, 39]. These regions are thus ideal candidates for the transfer of environmental exposure information. Depending on the chromosome concerned, and particularly if the X and Y chromosomes display such differences, could these regions account for the differences in the effects on female and male offspring? The principal problem here is that the epigenetic mechanisms involved are dynamic and change rapidly with environmental variation. They are also based on multiple strata of partially redundant pathways, which may be synergic, inhibitory or activating, depending on the context [40, 41]. Thus, if the impact of the exposure of the future parents to environmental factors several years before conception affects precisely this type of sequence [4, 13, 14, 42], then these sequences may be responsible for the transgenerational responses observed in the descendants.

However, probably for technical reasons potentially linked to the composition of histone variants, the various studies performed did not identify the same types of sequence. The nucleosomes identified were located principally at genes critical for early or late development [43], and at regulatory sequences, but some were also found at repeated sequences containing few genes [44]. These sequences are potential candidates for epigenetic heredity.

Mysterious intermediaries passing on the message from generation to generation

At fertilisation, in both humans and mice, there are many more methylated sites in the spermatozoa than in the oocyte [45]. There is extensive, but site-specific demethylation in the male and female pronuclei after fertilization. This process involves both active and passive mechanisms, depending on the parental origin of the chromosome [45]. It is widely accepted that only imprinted genes escape this process of demethylation. However, one recent study showed that other genes are also resistant [46]. In this mouse model of undernutrition in the grandmother (F0), the spermatozoa of the father (F1) display a disturbance of the methylome in differentially methylated regions (DMRs), with effects on the metabolism of his descendants (F2) [46]. Interestingly, 43% of the DMRs hypomethylated in the F1 were also hypomethylated in the F2 generation and therefore had the potential to affect the development of this subsequent generation. Many of the genes affected are expressed in the germline, but some are also expressed in somatic tissues. However, although this differential methylation was lost from the F2 generation by the end of gestation, major differences persisted in the expression of genes involved in metabolism located close to these DMRs. It therefore seems unlikely that these changes in expression are directly controlled by DNA methylation [46]. A similar process has been reported for the repercussions in the second generation of the effects of diet-induced maternal obesity [47]. These examples show that epigenetic profiles deregulated early in development are capable of passing the torch to other entities, thereby inducing other, as yet unidentified changes that might affect chromatin architecture, networks of transcription factors, or the differentiation or structure of tissues. In the model of resistance to cocaine addiction, the same modification (histone acetylation) to the same gene (*Bdnf*) was observed in the spermatozoa of the father and in the prefrontal cortex of his resistant male progeny [48]. As histone acetylation is a mark associated with expression, this observation cannot be seen as proof that this is the mechanism responsible for information transfer. The two examples cited above only appear to be contradictory; they do not in any way exclude the possible involvement of an epigenetic process. The pertinent epigenetic marks involved have probably either not been studied or have not been studied at the appropriate stage. Given the dialogue known to occur between marks, we would expect more than one type of mark to be involved, together with other, non-epigenetic processes. Are these associations the cause or a consequence of the dynamics of these marks? The key question to be addressed here remains that of the true causal link between epigenetic marks and the observed phenotypes.

Non-coding RNAs

During fertilisation, the spermatozoid not only provides the paternal haploid genome, it also releases 24,000 non-coding RNAs (ncRNAs: siRNA, piRNA and miRNA…) into the oocyte. Sperm RNA has been shown to transmit acquired characters in rodents. In particular, the use of sperm from maltreated animals has been shown to reproduce metabolic or behavioural changes in the descendants similar to those observed in the father [5, 26, 32, 34, 49-51].

One recent report suggested that RNA isolated from sperm might provide the progeny with information about the history of precocious trauma (through maternal stress) in the life of the father, with the effects and responses persisting until the third generation [5]. However, once again, the absence of presumed causal epigenetic alteration suggests that the initial mark may be transposed to other marks or epigenetic complexes in a relay. The epigenetic modifications present in the sperm cells following exposure to maternal stress may thus be converted into other marks, which may or may not be epigenetic in nature, for subsequent transmission [30, 52].

The involvement of ncRNA in transgenerational effects and responses was recently demonstrated in an invertebrate species lacking DNA methylation, *C. elegans* [27]. Exposure to viral particles led to the appearance of ncRNAs derived from the virus, which inhibited the expression of the viral genome, by RNA interference mechanisms, over several generations, thereby conferring a transmissible "immunity" [53]. A lack of food during the larval stage also leads to the appearance of microRNAs (miRNAs) targeting transcripts for proteins involved in nutrition and leading to an increase in the longevity of the third generation. These miRNAs cope with all eventualities, as some also target genes that are normally switched off but may be induced in response to stress [54].

Perspectives

The influences of environmental factors on epigenetic processes have revolutionised our view of the transgenerational transmission of information, but several key questions remain unanswered: What is the true nature of the impact of environmental factors? What is the nature of the targets of these factors (marks and/or conformation)? What is the nature of the targets to which the information is transferred? Are the mechanisms involved direct or indirect? How does the stored information persist over generations? What are the windows of sensitivity or insensitivity to these factors? How do differences linked to the sex of the parents impose sexual dimorphism on the progeny and, even, on subsequent generations [4, 13, 26 , 29, 55]?

There is still no federative model for the role of epigenetics in inter- and transgenerational effects/responses [29]. Ideally, before concluding that a transgenerational effect is epigenetic in nature, given the two-directional relationships between genetics and epigenetics, sequencing should be carried out to check for *de novo* mutations; similarly, *in vitro* fertilisation and embryo transfer or cross-adoption should be carried out, to control for other possibilities, such as maternal investment induced by the father. Such experiments are possible in animal models, but much more difficult in humans. The genes and sequences escaping reprogramming and the mechanisms involved are beginning to be identified and are good candidates for involvement in transgenerational effects. Studies of the effects of the environment would make it possible to determine whether these sequences carry a memory of these effects or whether other sequences can obtain the same capacity to resist mark erasure. By contrast, the processes, epigenetic or otherwise, by which the information is propagated are unknown, as are those underlying the differences in transmission from the father and the mother. Above all, very few studies have focused on the effects of the environment on these processes, to determine how the memory of events can be transmitted and to reveal the nature of the successive intermediary supports. Most reprogramming studies

have been carried out in mice [35, 56]. The conservation of certain mechanisms between species opens up interesting possibilities.

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