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Review

Epigenetic inheritance and evolution: A paternal perspective on dietary influences

Adelheid Soubry

Epidemiology Research Group, Department of Public Health and Primary Care, Faculty of Medicine, KU Leuven, Kapucijnenvoer 35, Blok D, Box 7001, 3000 Leuven, Belgium

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ABSTRACT

The earliest indications for paternally induced transgenerational effects from the environment to future generations were based on a small number of long-term epidemiological studies and some empirical observations. Only recently have experimental animal models and a few analyses on human data explored the transgenerational nature of phenotypic changes observed in offspring. Changes include multiple metabolic disorders, cancer and other chronic diseases. These phenotypes cannot always be explained by Mendelian inheritance, DNA mutations or genetic damage. Hence, a new compelling theory on epigenetic inheritance is gaining interest, providing new concepts that extend Darwin's evolutionary theory. Epigenetic alterations or "epimutations" are being considered to explain transgenerational inheritance of parentally acquired traits. The responsible mechanisms for these epimutations include DNA methylation, histone modification, and RNA-mediated effects. This review explores the literature on a number of time-dependent environmentally induced epigenetic alterations, specifically those from dietary exposures. We suggest a role for the male germ line as one of nature's tools to capture messages from our continuously changing environment and to transfer this information to subsequent generations. Further, we open the discussion that the paternally inherited epigenetic information may contribute to evolutionary adaptation.

Contents

1. Epigenetic inheritance of environmental exposures through the father: the role of sperm

The idea of heritability of ancestral environmental exposures and their influences on phenotypic characteristics and risk of diseases in the offspring has fascinated many scientists for decades

Abbreviations: ALT, alanine aminotransferase; BMI, Body Mass Index; DMRs, differentially methylated regions; DNMT, DNA methyltransferase; HDAC, histone deacetylase; PGC, primordial germ cells; ROS, reactive oxygen species; SC, spermatocytes; SG, spermatogonia; SZ, spermatozoa.

E-mail address: adelheid.soubry@hotmail.com.

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(Nelson and Nadeau, 2010; Pembrey, 2010; Soubry et al., 2014). While some observational studies in the 1930s and 70s have led to the suggestion of a paternal role in this transgenerational process (Fabia and Thuy, 1974; Price, 1939), the focus of most research studies in the last decade was on influences from periconceptional or *in vitro* exposures through the mother. Numerous animal and epidemiological data on mothers and their offspring have provided evidence that besides genetic damage also epigenetic features may be affected by environmental changes, leading to heritable phenotypic alterations that persist through multiple generations. The biological mechanism underlying this transgenerational inheritance has been proposed to involve the epigenome. Only in the last few years have some researchers started to invest in a search for potential paternal contributions in epigenetic inheritance of environmental exposures. Some of the controversial literature and theories on paternally inherited phenotypic changes from occupational harmful exposures include paint, industrial solvents, agriculture, war, and ionizing radiation but also effects from paternal diet or life-style and environmental pollution have been reported (Soubry et al., 2014). The physiological consequences in children or even grandchildren have often been attributed to DNA damage or mutations in paternal germ cells but to date this has not always been proven. Increasing evidence supports the idea that at least some epigenetic marks acquired during spermatogenesis may be sustained through embryonic development. Fig. 1 links the effects of several environmental exposures with potential molecular changes during male gametogenesis, causing persistent epigenetic alterations and phenotypic consequences in the next generation(s). The sperm epigenetic machinery includes DNA methylation, histone modifications, and transcription of non-coding RNAs (such as microRNAs) (Jenkins and Carrell, 2011). During gametogenesis, from primordial germ cells (PGCs) to spermatozoa (SZ) (Fig. 1), epigenetic marks are created in a sex-specific way (Marques et al., 2011; Niemitz and Feinberg, 2004). Imprinted genes are perfect candidate genes to capture and keep the environmental messages, since they escape the large-scale DNA methylation erasure after fertilization. However, other yet unidentified genes or gene promoters cannot be excluded from this selective protection. Modification and retention of histones and/or retention of other proteins or enzymes at specific DNA sequences are possible mechanisms to regulate the inheritance of environmentally induced epigenetic changes (Jenkins and Carrell, 2012; Jirtle and Skinner, 2007; Miller et al., 2010). In the fetus (not presented in the figure), after embryonic reprogramming, primordial germ cells lose their epigenetic marks as they migrate to the genital ridge. Complete epigenetic erasure is suspected, including erasure of imprint regulatory regions. Hence, theoretically, a new epigenetic pattern is created in the second generation and DNA methylation is guaranteed in a sex-specific manner (Murphy and Jirtle, 2003). However, some studies indicate that "permanent" epigenetic alterations induced by the environment are possible; germ cells may harbor this ancestral environmental information as epigenetic alterations, and subsequently transfer this to the next generations (Manikkam et al., 2013; Tracey et al., 2013). It should be noted that the terminology used to describe transmission of parental exposures varies. Terms like transgenerational, multigenerational and intergenerational are used interchangeably (Burton and Metcalfe, 2014; Skinner, 2008). The term "transgenerational effect" has generally been used if the effect is (still) present in the generation that was not exposed directly. If it was the germ line that was exposed, the effect can only become "transgenerational" if a permanent reprogramming occurred. This can only be verified if phenotypic consequences are analyzed in the next (non-exposed) generation (Skinner et al., 2014); which is not always feasible in studies on humans. Although we do not exclude any effects through the mother and the female germ line, studies on paternal exposures make it possible to

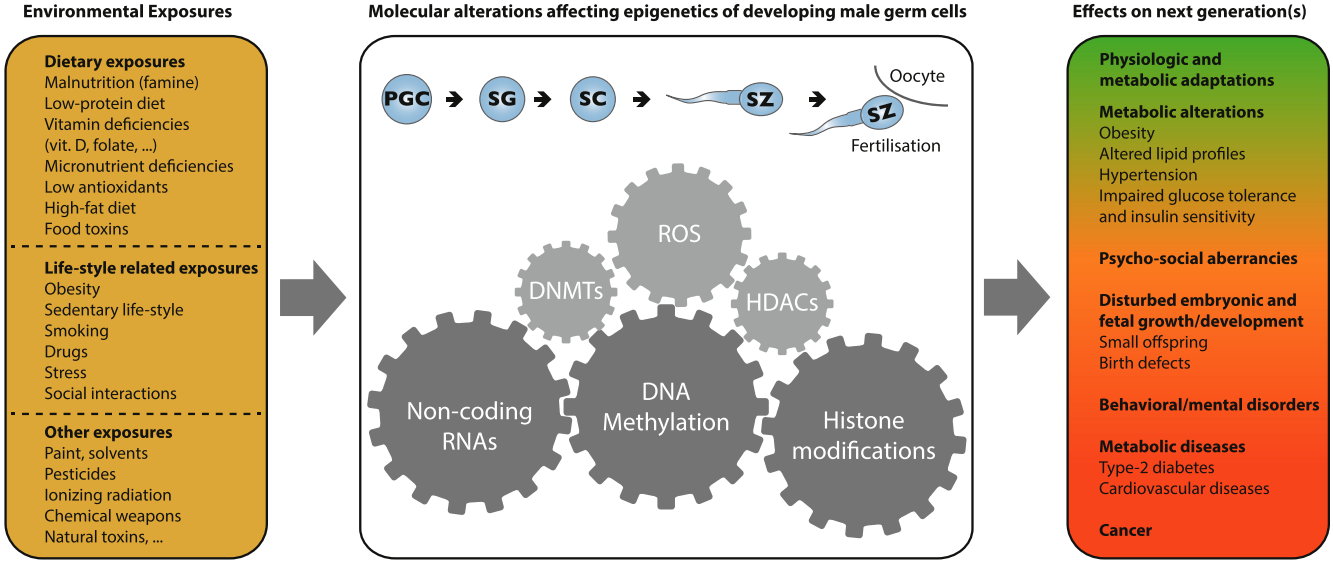

Fig. 1. The sperm epigenome: a messenger of ancestral exposures. Schematic overview of environmentally acquired epigenetic changes and disorders in the offspring through the paternal germ line. Examples of studies on transgenerational inheritance include exposures to malnutrition (such as famine (Heijmans et al., 2008) or overnutrition (Pembrey et al., 2006)), low-protein diet (Carone et al., 2010), vitamin or micronutrient deficiencies (Mejos et al., 2013), high fat diet (Ng et al., 2010; Wei et al., 2014), plastic-derived toxins (Manikkam et al., 2013), obesity (Soubry et al., 2013b), smoking (Northstone et al., 2014), stress (Gapp et al., 2014; Rodgers et al., 2013), paint and solvents (Reid et al., 2011; Wilkins and Sinks, 1984), pesticides (Skinner et al., 2013), ionizing radiation (Gardner et al., 1990; Koturbash et al., 2006), and war (Ngo et al., 2010). Although the molecular components are largely known, it is unclear how they are interlinked and how or when the environment interferes in these processes. Male germ cells develop from primordial germ cells (PGCs) to spermatogonia (SG) before puberty. They further differentiate to spermatocytes (SC) and finally spermatozoa (SZ) during each reproductive cycle. Candidate epigenetic components important in sperm development include DNA methylation, histone modifications, and non-coding RNAs (e.g. microRNAs). Enzymes, such as DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), often form a link between these components; they are important to fine-tune intermolecular effects. Unbalanced reactive oxygen species (ROS) generation may also to trigger this fine-tuning. Environmental messages are able to alter the epigenetic machinery in male germ cells. If the effects persist, these alterations may be either beneficial (green), they may disturb homeostasis or metabolism (orange), or they may be harmful (red) to the next generations.

easily separate preconceptional from *in utero* exposures. Obviously, sperm cells are easier to access than oocytes. Furthermore, because spermatogenic stem cells develop *in utero*, stay mitotically quiescent until the peri-pubertal period and are subsequently able to undergo perpetual renewal and/or differentiation throughout the reproductive lifespan, they are excellent tools to capture time-related messages, as well as chronic messages, from the environment. Earlier we described a number of critical developmental time points at which the male germ line may be susceptible to epigenetic alterations through several environmentally induced exposures (Soubry et al., 2014). In the current review we focus on reports concerning dietary influences, the timing of the exposure, and the molecular, epigenetic, and phenotypic effects in the offspring, in sperm cells and in the embryo.

2. Time-related exposures to paternal dietary conditions and the epigenetic effects

2.1. Effects in the offspring

Historical data from the isolated municipality of Överkalix in Sweden have revealed effects of early influences from grandparents to grandchildren. Longevity of grandsons was determined by the paternal grandfather's diet during pre-puberty (Pembrey et al., 2006). These data suggest that information acquired from the environment in early life, when paternal sperm cells are developing from PGCs to spermatogonia, can be stored and transmitted to the next generations. In the long-term cohort of the Framingham Heart Study, an association was observed between early-onset paternal obesity and elevated serum alanine aminotransferase (ALT) levels in the offspring. High levels of ALT predict metabolic complications. Interestingly, late-onset paternal and maternal obesity were not associated with elevated ALT levels in the offspring (Loomba et al., 2008). The study did not clarify whether the fathers had already been obese during childhood. Periconceptional nutrient deprivation, especially during famine, has been associated with increased risk of obesity (Ravelli et al., 1976), hypertension (Roseboom et al., 1999), elevated lipid profiles (Lumey et al., 2009), cardiovascular diseases (Painter et al., 2006b) and cancer (Painter et al., 2006a) in the offspring. Exposures to these adverse nutritional conditions have been related to aberrant methylation at the *IGF2* imprint regulatory region in the offspring more than forty years later (Heijmans et al., 2008). Similarly, a study in Gambian children showed that DNA methylation at several metastable epialleles can be altered by seasonal nutritional circumstances at the time of conception (Waterland et al., 2010). These studies did not discuss a potential effect of paternal diet. Instead, the authors interpreted their findings as a result of maternal influences and left the question open if the effect was caused by pre- or postconceptional exposures. Hence, it is unclear if these dietary conditions caused an indirect epigenetic effect (through the parental germ cells) or a direct epigenetic effect (on the early embryo).

The first human evidence for a paternally induced epigenetic effect in the offspring through nutritional conditions or life-style originates from the Newborn Epigenetics Study (NEST). We have recently explored this birth cohort for potential associations between epigenetic changes in the offspring and paternal periconceptional body mass index. We found significant differences in DNA methylation at differentially methylated regions (DMRs) of several imprinted genes if the father was obese (Soubry et al., 2013a, 2013b). DNA methylation marks are known to establish during gametogenesis and deregulation of methylation at DMRs is related to chronic diseases or metabolic disorders in the offspring (Jirtle and Skinner, 2007; Murphy and Jirtle, 2003). Although the NEST data suggested a transgenerational influence of paternal diet (or lack of exercise) on the progeny through sperm, metabolic effects or other implications for children of these obese fathers have not been studied yet.

In a mice model, a transgenerational effect on metabolic- and growth-related parameters in the offspring was first shown if fathers suffered from preconceptional food deprivation (Anderson et al., 2006). Although a role for epigenetic reprogramming as a potential underlying mechanism was suggested, epigenetic tests were only included in later experimental studies. In 2010, Carone et al. reported that male mice consuming a low-protein diet from weaning (3 weeks of age) until sexual maturity produced offspring with increased methylation at a putative enhancer for a key lipid regulator, PPARalpha, in the liver. In the same year, Ng et al. published their results on male mice that were overfed through a high-fat diet from 4 weeks of age. These mice not only became heavier or had impaired glucose tolerance and insulin sensitivity, but their female offspring also developed impaired glucose–insulin homeostasis. Furthermore, expression levels of several genes important in glucose–insulin homeostasis or other regulatory pathways were altered and the *interleukin 13 receptor alpha 2* (*Il13ra2*) gene was hypomethylated (Ng et al., 2010). Further analyses revealed changes in the transcriptomes of retroperitoneal adipose and pancreatic islet tissues in female offspring (Ng et al., 2014). Most recently, Wei et al. confirmed an effect on the offspring's metabolic status in a pre-diabetic mouse model with male mice on a high-fat diet from 3 weeks of age. Offspring of pre-diabetic fathers exhibited impaired glucose tolerance and insulin insensitivity. Gene expression profiling showed altered expression of genes involved in glucose metabolism and differential DNA methylation patterns were observed in the pancreatic islets of offspring from pre-diabetic fathers (Wei et al., 2014). Interestingly, similar observations have been reported on other dietary compounds or deficiencies. Mejos et al. showed that a folate-deficient diet in male rats resulted in a decrease in global DNA methylation in liver of the offspring (Mejos et al., 2013).

2.2. Effects in sperm

In mice, Lambrot et al. provided evidence that very early exposure to folate-deficiency may cause altered sperm DNA methylation. The effect was seen if a low-folate diet was administered to females through pregnancy and lactation (Lambrot et al., 2013). Hence, males were already exposed during *in utero* development, when epigenetic patterning in germ cells begins to form. A similar observation has been reported recently when pregnant mice suffered undernourishment; their male offspring showed an altered sperm methylome (Radford et al., 2014). In Carone et al.'s mouse model, where males were fed a low-protein diet, sperm samples showed different chromatin packaging and RNA content, as compared to sperm from control males (Carone et al., 2010). Others have confirmed a diet-induced impact on male germ cells. Wei et al. linked a high-fat diet to altered methylation patterns in sperm cells (Wei et al., 2014). Lane's research group showed that male mice on a high-fat diet from 5 weeks of age onwards had a significant reduction in global DNA methylation and modulated sperm microRNA content. In some cases the effects were still measured in the second generation (Fullston et al., 2013). Interestingly, microRNAs are able to regulate DNA methylation (Sinkkonen et al., 2008). For instance, an increase in miR-29 has been associated with a decrease in methylation of repeat elements in the male germline. Members of this family of microRNAs have been predicted to downregulate DNA methyltransferase-3a (DNMT3a), an enzyme necessary for establishing genomic methylation (Filkowski et al., 2010; Takada et al., 2009). Although not reported via dietary exposures, Gapp et al. demonstrated a causal link between sperm

RNAs and metabolic and behavioral alterations in the offspring. Microinjecting purified RNAs from sperm from mice exposed to traumatic stress into wild-type fertilized oocytes resulted in offspring with the same outcomes as if their parents were exposed. This supports the hypothesis that environmentally induced changes in sperm microRNAs can serve as a vector modifying other epigenetic marks, such as DNA methylation and/or histone modifications, for further transmission (Gapp et al., 2014). Lane further reported an obesity-related increase in histone acetylation in spermatids (Palmer et al., 2011). Acetylated histones represent an epigenetic component of the chromatin. Acetylation during late spermatogenesis transforms the chromatin in a more relaxed structure and facilitates removal of histones, so they can be replaced by protamines. If this process is disturbed and acetylation occurs too early in sperm development the rate of DNA damage increases, which contributes to poor sperm characteristics. Indeed, male mice receiving a high-fat diet from week 6 to week 15 showed an increase in sperm DNA damage and a decrease in percentage of motile spermatozoa (Bakos et al., 2011b). Diet-induced impaired spermatogenesis can also be attributed to unbalanced reactive oxygen species (ROS) generation. High levels of ROS were measured in sperm of mice fed with a high-fat diet (Bakos et al., 2011b). ROS are normal by-products of metabolism. However, it is known that when ROS production exceeds the cell's ability to metabolize or detoxify them, a state of oxidative stress emerges. This contributes to DNA damage and ineffective DNA repair mechanisms.

In humans, obesity has been related to a decrease in sperm quality while some fail to detect this association (Sermondade et al., 2013). An abnormally high content of unesterified, unsaturated fatty acids in defective sperm has also been linked with ROS production (Koppers et al., 2010). A negative correlation was found between ROS production and global DNA methylation in human sperm. Supplementation with antioxidants significantly improved sperm DNA methylation (Tunc and Tremellen, 2009). The mechanism of how changes in ROS can modulate DNA methylation in sperm is still unknown. However, Lim et al. suggested from an *in vitro* experiment in cancer cells that a ROS-induced site-specific DNA hypermethylation occurs through altered activity of histone deacetylase 1 (HDAC1) and DNMT 1 (Lim et al., 2008). The here-described mechanistic components of the epigenetic machinery in sperm are depicted in Fig. 1.

2.3. Effects in the embryo and pregnancy outcomes

Pre-diabetic male mice on a high-fat diet not only showed altered methylation patterns in their sperm cells compared to controls, a partial inheritance of DNA methylation was also detected in E3.5 blastocysts at genes not reported as being imprinted (Wei et al., 2014). The latter, amongst others (Lambrot et al., 2013; Ng et al., 2010, 2014), suggests that the theory on complete reprogramming of non-imprinted genes after fertilization may have some exceptions. Some acquired changes may withstand reprogramming and explain the transgenerational character of inherited environmental messages. Binder et al. provided evidence for a diet-induced change in blastocysts' carbohydrate metabolism, with significantly increased glycolysis if the fathers were obese (Binder et al., 2012b). Other observations in these diet-induced obese male mice were impaired sperm quality, delayed cell cycle progression during preimplantation, reduced implantation rate, affected placental size, and smaller offspring (Binder et al., 2012a, 2012b). Interestingly, improving metabolic health through diet and/or exercise 9 weeks before conception restored embryo and fetal growth (McPherson et al., 2013).

If observations from mice can be translated to humans, it might have important implications regarding public health recommendations. Studies on diet or exercise intervention in obese future fathers may help us understand if there are any effects in humans. To our knowledge, few studies have focused on male obesity in relation to embryonic development and/or quality in humans and those that have done so report conflicting results. While Merhi et al. failed to detect an association between male obesity and early embryo development (Merhi et al., 2013), others showed that BMI negatively influences blastocyst development and live birth after IVF treatment (Bakos et al., 2011a; Petersen et al., 2013). Growth of the fetus has been associated with paternal BMI in a sex-specific manner (Chen et al., 2012). A potential effect of paternal obesity has been ratified by others (Anifandis et al., 2013; Bellver, 2013).

The obese population generally eats an energy-dense and nutrient-poor diet, hence their vitamin status can be considered to be inadequate (Aasheim et al., 2008; Drewnowski, 2009). It has been reported that folate deficiency of male mice is associated with increased birth defects in the offspring (Lambrot et al., 2013). Supplementation of folic acid (the synthetic form of folate) to future mothers to reduce the risk of congenital defects has been a major focus of public health agencies for many years, but the potential effects of paternal folate deficiencies have not attracted any attention yet. Little is known about the consequences of low or high dietary folate concentrations on sperm and its DNA methylation patterns. Hence, currently future fathers do not receive any public health recommendations.

3. Epigenetic inheritance of paternal dietary conditions and potential effects on evolution

As described above, multiple studies indicated that dietary conditions can induce epigenetic changes through the male germ line. These changes can be transferred to the embryo, inducing phenotypic or metabolic perturbations in the offspring. In some cases the phenotypic alterations sustain for several generations. Although the biological mechanisms remain to be elucidated, a growing number of reports support the hypothesis that the acquired inherited epigenetic signatures may be nature's way to steer development and to adapt relatively quickly to environmental variations or changes. The epigenetic output and accompanying changes in gene expression patterns and phenotypes, evolving from ancestral (chronic) exposures, are most likely supposed to benefit evolution (Colaneri et al., 2013; House, 2014; Hunter, 2008; Jablonka, 2013; Mazzio and Soliman, 2014; Mendizabal et al., 2014; Rebollo et al., 2010; Richards, 2006; Varriale, 2014). However, a side effect of this yet unrevealed mechanism may be that if an individual is exposed to a contradictory environmental insult or trait, such as famine, malnutrition, a new chemical, pollutant or pathogen during a particular developmental stage in life, the risk of developing diseases or metabolic disorders in the next generation(s) increases. A compelling question is whether and how environmentally induced epigenetic changes are able to persist or eventually accumulate over longer evolutionary time periods; ultimately contributing to the formation of new species. Some links have been reported between environmental inheritance and evolution; in some cases epigenetic mechanisms have been suggested. Supporting evidence originates from observations in plant populations. Epigenetic variation in plants may be subject to natural selection, resulting in novel phenotypes of ecological isolated micro-populations or populations exposed to certain environmental conditions (Hirsch et al., 2012; Schmitz et al., 2013). One of the underlying causes may include polymorphisms or insertions of repetitive sequences (such as transposable elements or TEs) influencing the surrounding epigenome (Martin et al., 2009; Schmitz et al., 2013), or epigenetically driven mobilization of TEs (Rebollo

et al., 2010). Transgenerational (epigenetic) inheritance of environmental factors has also been suggested to contribute in environmental adaptation of other species, such as birds (Skinner et al., 2014), insects (Bonduriansky and Head, 2007), mammals, fishes and reptiles (Pfennig and Servedio, 2013; Varriale, 2014). Genomic imprinting, an epigenetic mechanism that is crucial in development and sensitive to periconceptional nutritional conditions from mother and father (Soubry et al., 2013a), has been implicated in the evolution of human health (Das et al., 2009), but also in accelerating mammalian speciation (Hunter, 2007). Crossing two rodent species (Peromyscus) resulted in loss of imprinting and skewing of X-chromosome inactivation in hybrids. These results from Vrana et al. demonstrated how imprinting might have enforced separation between two closely related species, suggesting a role for epigenetic gene regulation in the establishment and maintenance of reproductive isolation barriers in mammals (Vrana et al., 2000). Although the following is speculative, it is possible that nutritional differences in the environment alter the epigenome (given its malleable characteristics) in such way that this change contributes to speciation and evolution (Hunter, 2007; Mazzio and Soliman, 2014). Epigenetics and genetics may jointly promote evolution. It has been suggested that epigenetic shifts influence and accelerate genetic variation such that both drive transformation or development of the organism (Pfennig and Servedio, 2013; Shea et al., 2011; Skinner et al., 2014). A more controversial theory suggests that epigenetic changes can influence evolutionary novelty independent of changes in DNA sequences (Badyaev and Uller, 2009; Pfennig and Servedio, 2013). One possible explanation has been suggested via entrenched parental effects (Badyaev and Uller, 2009). Parent-related epigenetic inheritance may accelerate the likelihood that populations diverge in a way that contributes to reproductive isolation such that speciation may occur (Pfennig and Servedio, 2013). Bonduriansky et al. showed in flies (*T. angusticollis*) that if males were administered a specific diet they produced larger offspring, influencing fecundity of female offspring and mating success of male offspring (Bonduriansky and Head, 2007). Paternal dietary effects were also found in offspring of other flies species, such as in *D. melanogaster* (Valtonen et al., 2012). Based on these findings, Bonduriansky and Day investigated a model allowing to question the role of non-genetic paternal effects in the evolution of female preferences (Bonduriansky and Day, 2013). Their research supports evidence that epigenetic inheritance has the potential to generate and maintain heritable variation in fitness, as an alternative to genetic variation in fitness (Bonduriansky and Day, 2013; Bonduriansky and Head, 2007). Herewith, a new and exciting scientific area has been entered that undoubtedly will continue the debate that started more than a century ago on the “origin of species”.

4. Conclusive remarks and future directions

The idea that paternally acquired exposures can be captured and transmitted to the next generation has been considered a possibility for many years. Historically obtained human data suggested a potential link between paternal environmental exposures and phenotypic outcomes in the offspring, but they generally lacked the exploration for molecular mechanisms behind their observations; mainly due to the inevitable limitations of (longitudinal) epidemiological studies. Hence, animal experiments were mostly indispensable to provide proof. Over the last 5 years, an increasing number of animal model studies has indicated that early-onset exposures to dietary conditions, but also to harmful environmental pollutants (Soubry et al., 2014), affect male gametogenesis, change gene programming, and thereby disturb homeostasis, metabolic balances and/or increase risk of disease in the offspring. Other exposures affecting sperm and offspring's epigenome and/or health status, not discussed in this review, include social and behavioral interactions, stress, and other psychological adversities (Gapp et al., 2014; Rodgers et al., 2013; Szyf, 2013a, 2013b). Literature suggests that timing of the exposure is crucial. During some stages in life the epigenome may be more susceptible to permanent changes. The fact that the epigenome is malleable, that epigenetic variation exists and that environmentally induced epigenetic alterations can be inherited through multiple generations are good reasons to think that the epigenome plays a role in long-term evolutionary trends. If it is true that the epigenetic machinery is involved in evolution, unraveling the epigenetic mechanisms and the potential epimutations from environmental events in developing germ cells and the early embryo is of great interest. In order to gain a better understanding of the molecular mechanisms of transgenerational inheritance of early environmental exposures recommendations to improve study designs have been suggested recently (Lecomte et al., 2013). We further recommend that it would be worthwhile if researchers explored their environmental factor of interest by timing of the exposure, for instance through a comparison of exposures at different stages of female and male germ cell development in animal models. This would provide insights into which time windows of life are most decisive in creating persistent epigenetic alterations. Furthermore, more research is needed to understand the mechanisms of how the acquired environmental message withstands developmental processes, and persists through multiple generations. Future research on organisms that reproduce rapidly may further clarify this transgenerational process.

Since epigenetics has been considered as the underlying mechanism of transgenerational effects, the original concept of the gene as the sole tool for inheritance of ancestral characteristics is changing. Primordial germ cells possess the capacity to give rise to a new individual through successive epigenetic events, while enduring a link with ancestral experiences. The plasticity of the epigenome during development of these germ cells is most likely strongly involved in the “fine-tuning” or adaptation to our environment. We suggest that depending on timing of the exposure, for instance to changing nutritional circumstances, this environmental message may be successfully transferred to the next generation(s). Although the mechanisms have not yet been elucidated, we do not exclude a potential role for the sperm epigenome as one of the drivers of evolution. Future research is necessary to confirm this hypothesis.

Conflict of interest

The author declares no conflict of interest.

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