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Review

Epigenetic inheritance in mammals: Evidence for the impact of adverse environmental effects

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ABSTRACT

The epigenome is the overall epigenetic state of a cell and represents the ensemble of chromatin modifications. It is an essential mechanism for the regulation of the genome that depends on modifications of DNA and histones but does not involve any change of the DNA sequence. It was previously assumed that in order for appropriate cellular development and differentiation to occur in mammals, the epigenome was fully erased and reestablished between generations. However, several examples of incomplete erasure at specific genes have been reported, and this is suggested to be associated with the epigenetic inheritance of gene profiles. Although the existence of such a mode of inheritance has been controversial, there is increasing evidence that it does occur in rodents and humans. In this review, we discuss the evidence that adverse environmental factors can affect not only the individuals directly exposed to these factors but also their offspring. Because the epigenome is sensitive to environmental influence and, in some cases, can, in part, be transmitted across generations, it provides a potential mechanism for the transgenerational transmission of the impact of environmental factors. Environmental factors examined include exposure to toxicants, diet, and postnatal care, and DNA methylation is the main mechanism discussed in this review.

Contents

It is commonly accepted that heritable information is transmitted to offspring through sequences of DNA and that any change of the DNA sequence during transmission is random and, except for mutagens, is not influenced by environmental factors. However, recent work in the field of epigenetics has proposed that inheritance of DNA sequences is not the only mechanism underlying the transgenerational transmission of physical, behavioral, and emotional traits in mammals. Furthermore, it is now known that the epigenome can be modulated by a variety of environmental factors, including chemicals, nutrition, and early environment, as well as by aging (Anway et al., 2005, 2006; Roth et al., 2009; Waterland et al., 2006; Weaver et al., 2004, 2005; Wilson and Jones, 1983). The epigenome therefore provides an important interface between genes and the environment and may be viewed as a potential mechanism for a rapid form of environmentally driven transgenerational adaptation.

Conrad Waddington coined the term "epigenetics" in the 1940s to describe gene–environment interactions that ultimately lead to a particular phenotype (Waddington, 1942). He originally used this term in a developmental context to depict the permanent changes in gene activation and deactivation required for cellular differentiation.

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While the mechanisms for these changes were unknown at the time, they are now considered to be most likely the result of altered DNA methylation and/or post-translational chemical modifications of the chromatin (Holliday and Pugh, 1975; Riggs, 1975; Scarano, 1971). The current use of the term has thus shifted to emphasize mitotically or meiotically heritable changes in gene expression not due to any alteration in the nucleotide sequence but rather to modifications of the DNA molecule itself and of the chromatin. These modifications of the DNA include biochemical alterations of specific base pairs, in particular methylation of CpGs (cytosines immediately followed by a guanine), or of core or variant histone proteins, as well as DNA looping or chromatin structure (Mager and Bartolomei, 2005).

In mammals, the most common epigenetic modification of the DNA strand involves the enzymatic transfer of a methyl group to the fifth position of cytosine residues in CpG dinucleotides (Richards, 2006). DNA methylation has many well-known roles in the mammalian organism. During development, it is necessary to establish tissue-specific patterns of gene expression (Scarano, 1971). It is also crucial for X-chromosome inactivation, in which one X-chromosome is silenced in females, and for parental imprinting, in which one parental allele is inactivated (Delaval and Feil, 2004; Riggs, 1975). The pattern of DNA methylation in CpG islands located within or near promoter regions is known to affect the transcription rate of the gene by altering local chromatin structure and thereby modifying the access of transcription factors to DNA (Richards, 2006; Wang et al., 2004). DNA methylation patterns are established and maintained by DNA methyltransferases (DNMTs), methyl CpG-binding proteins, and, as recently demonstrated, small RNA molecules (Chahrour et al., 2008; Cheng, 1995a,b; Fan and Hutnick, 2005; Matzke and Birchler, 2005; Ooi et al., 2009; Wassenegger, 2005; Zemach and Grafi, 2007).

Transgenerational transmission of epigenetic information

RNA-mediated paramutation in the mouse

A well-characterized example of transmission of epigenetic information across generations is paramutation. Paramutation is a phenomenon by which the silencing of one allele is meiotically inherited by interaction *in trans* with the homologous allele (Ashe and Whitelaw, 2007). Most examples of paramutation reported to date are in plants (Ashe and Whitelaw, 2007; Bond and Finnegan, 2007; Chandler, 2007), but paramutation has also now been demonstrated in the mouse, firstly at the *Kit* locus that codes for a tyrosine kinase receptor (Rassoulzadegan et al., 2006; Wagner et al., 2008). Mice heterozygous for *Kit* mutations have reduced *Kit* mRNA expression and an altered pigment pattern (white spots). Remarkably, some of the offspring from heterozygous *Kit* mice have a similar altered pigmentation, despite carrying two wild-type alleles (Rassoulzadegan et al., 2006). Abnormal RNA in the sperm of *Kit* mutant mice was suggested to be responsible for this phenomenon because microinjection of sperm RNA from *Kit* mutant mice or injection of miRNAs targeting *Kit* mRNA reproduces this effect (Rassoulzadegan et al., 2006). These results suggested that functional information not encoded in the DNA sequence itself, but likely to be carried by RNA, can be transmitted through the germ line. This idea was corroborated by a recent study demonstrating that injection of a miRNA targeting cyclin-dependent kinase 9 (Cdk9), a regulator of cardiac growth, in fertilized mouse eggs induces cardiac hypertrophy in adult animals (Wagner et al., 2008). This correlated with the presence of trace amounts of the miRNA in sperm cells. Importantly, the cardiac hypertrophy was inherited across at least three generations and mimicked human hypertrophic cardiomyopathy, a disease that is often familial (Wagner et al., 2008). The injection of a *miR-124* microRNA into fertilized eggs resulting in a giant phenotype in the progeny of transgenic males was also recently reported as a model of RNA-mediated heritable epigenetic modifications (Grandjean et al., 2009).

Epigenetic inheritance at endogenous alleles Agouti viable yellow (A^{vy}) and axin-fused ($Axin^{Fu}$)

The *agouti viable yellow* (A^{vy}) and *axin-fused* ($Axin^{Fu}$) alleles are metastable epialleles, characterized by an inter- or intra-individual variability in expression state. Here, variations in expression are not the result of any genotypic alteration but result from modifications in the level of DNA methylation of an intra-cisternal A particle (IAP) long terminal repeat. This IAP is a retrotransposon located upstream of the coding sequence in the case of A^{vy} and within intron 6 in the case of $Axin^{Fu}$ (Morgan et al., 1999; Rakyan et al., 2003). These variations in DNA methylation and gene expression induce a diversity in phenotypes that occurs despite the genetic identity (isogenic A^{vy} or $Axin^{Fu}$mice). The ectopic expression of the A^{vy} protein results in yellow fur, obesity, and diabetes and increases tumor susceptibility, while the ectopic expression of $Axin^{Fu}$ induces a kinked tail (Duhl et al., 1994; Reed, 1937). These naturally occurring variable phenotypes resulting from differential methylation can be transmitted to the subsequent generation, paternally for A^{vy} and both maternally and paternally for $Axin^{Fu}$ (Blewitt et al., 2006; Morgan et al., 1999; Rakyan et al., 2003).

Furthermore, the level of methylation of A^{vy} and $Axin^{Fu}$ and gene expression can also be modulated by environmental factors, in particular maternal diet. Administration of a methyl-rich diet to pregnant female mice increases the level of DNA methylation at the A^{vy} and $Axin^{Fu}$ genes in the offspring and induces the associated variability in phenotype (Waterland et al., 2006; Waterland and Jirtle, 2003). This is most likely mediated by *in utero* effects occurring as a result of the methyl supplement. Somewhat unexpectedly, diet-induced changes in A^{vy} methylation are not transmitted maternally to the next generation (Waterland et al., 2007). Thus, while the differential methylation of IAPs in A^{vy} and $Axin^{Fu}$ genes can induce variable phenotypes across generations in isogenic mice, data from A^{vy} mice suggest that the impact of maternal diet on these phenotypes may be reset between generations.

The A^{vy} case provides an additional example of transgenerational mechanisms that are independent of epigenetic variation at the A^{vy} gene (Waterland et al., 2008). A^{vy} mice have a tendency to become obese when adult, even when fed regular diet *ad libitum* (Duhl et al., 1994; Waterland et al., 2008). Interestingly, the interindividual variation in maternal obesity demonstrates a transgenerational amplification of body weight across generations, which is independent of methylation at A^{vy} (Waterland et al., 2008). Furthermore, diet-induced hypermethylation blocks the transgenerational effect of maternal adiposity on the body weight of their offspring (Waterland et al., 2008). Thus, while diet-induced hypermethylation at A^{vy} is not transmitted, methyl supplementation may interact with epigenetic mechanisms at other genomic loci, in particular those involved in body weight regulation (Waterland et al., 2008).

DNA methylation and familial cancer

Aberrant genome-wide changes in DNA methylation have been consistently observed in cancer cells. Although a global hypomethylation is often detected in tumors, localized increases in DNA methylation in the promoter-associated CpG islands of genes also occur (Fleming et al., 2008; Wilson et al., 2007). The cause of such concomitant hypomethylation and hypermethylation is not known but could result from local alterations in DNMTs, which are expressed at higher levels in tumor cells (Fleming et al., 2008; Jones and Baylin, 2002). Global hypomethylation is linked to carcinogenesis because it can induce aberrant gene expression, chromosomal instability, reactivation of retrotransposons, and/or loss of imprinting (Fleming

et al., 2008; Wilson et al., 2007). In contrast, hypermethylation in CpG islands may lead to a deactivation of tumor suppressor genes that should normally be active (Ahuja and Issa, 2000; Fraga et al., 2007). These mechanisms provide a potential treatment strategy in preventive and therapeutic medicine. Indeed, hypomethylating agents like decitabine and 5-azacytidine are currently used for the treatment of cancer (Kurkjian et al., 2008).

Hypermethylation at the promoter of two tumor suppressor mismatch repair genes, *MLH1* and *MSH2*, has been associated with hereditary non-polyposis colorectal cancer (Chan et al., 2006; Herman et al., 1998; Hitchins et al., 2007). Hypermethylation of both *MLH1* and *MSH2* was also observed in the germline, albeit in a low proportion of cells (Chan et al., 2006; Suter et al., 2004). Intriguingly, the *MLH1* epimutation appears to be more easily transmitted through the maternal line, raising the possibility that epigenetic errors are more likely to occur during oogenesis than spermatogenesis (Fleming et al., 2008). The heritable germline epimutation described here suggests transgenerational epigenetic inheritance. However, because the subjects are not genetically identical, it is possible that DNA variants are present within the family and may predispose the individuals to an atypical epigenetic state at each generation (Chong et al., 2007). Indeed, it was recently demonstrated that a deletion in the last exons of a gene located directly upstream of *MSH2* correlates with epigenetic inactivation of the *MSH2* allele. This suggests that, at least in the case of *MSH2*, DNA variants and not epigenetic inheritance may lead to epigenetic alterations present in each generation (Ligtenberg et al., 2009).

Transgenerational transmission of environmental effects

Epigenetic inheritance and environmental toxicants

There is accumulating evidence that chemical toxicants have detrimental effects not only on individuals directly exposed to the toxicant but also on their offspring. One of the most dramatic examples is with diethylstilbestrol, a synthetic nonsteroidal estrogen prescribed in the 1970s to prevent miscarriage in women with prior history. While the drug helped pregnancies to go to term, it induced severe developmental abnormalities and increased the risk for breast cancer and a rare form of adenocarcinoma in girls whose mothers were exposed to the drug during the first trimester of pregnancy (Palmer et al., 2006). Furthermore, the risk of cancer appeared to be transmitted to the following generation. A clinical study reported that a 15-year-old girl whose maternal grandmother was exposed to diethylstilbestrol during pregnancy was diagnosed with a very rare case of small cell carcinoma in the ovary (Blatt et al., 2003). Many more of maternal granddaughters than expected also developed ovarian cancer (Titus-Ernstoff et al., 2008). Although these findings are among the first and need to be confirmed by further transgenerational studies, they suggest that the detrimental effect of a drug can be transmitted across generations. Such transgenerational effect of diethylstilbestrol was also observed in mice. Similar to humans, perinatal exposure to the drug induced abnormalities in uterine development and uterine cancer in first and second generations. These abnormalities were suggested to result from aberrant DNA methylation in a gene that controls uterine development (homeobox gene HOXA10) and in uterine cancer genes (Bromer et al., 2009; Li et al., 2003; Newbold et al., 2006; Walker and Haven, 1997).

Transgenerational transmission of the detrimental effects of endocrine disruptors present in our environment was demonstrated in rats, through both females and males. Rats exposed to the endocrine disruptor vinclozolin, a fungicide commonly used for agricultural fruit crops, or the pesticide methoxychlor, during the period of gonadal sex determination (embryonic stage E8–E15, F1), have reduced epididymal sperm counts and sperm motility and increased spermatogenic cell apoptosis (Cupp et al., 2003; Uzumcu et al., 2004). These drug-induced traits are transmitted to the male offspring through the male germline down to three generations from exposure to the toxicant (F2–F4) and are associated with aberrant DNA methylation in sperm (Anway et al., 2005). Exposure to vinclozolin from E8 to E14 was also found to induce pregnancy abnormalities, including uterine hemorrhage and/or anemia, down to two generations in females (Nilsson et al., 2008). Further to affecting fertility, vinclozolin also increases the incidence rate of tumor formation in aging males exposed to vinclozolin prenatally (F1) and their offspring (F2–F4) (Anway et al., 2006). Thus, it is now apparent that exposure to chemical toxicants during critical periods of development impacts fertility and tumor development across multiple generations via transmission through both females and males. These effects persist across the lifespan and are still present in aged animals. The mechanism of transmission itself is suggested to be the result of aberrant DNA methylation in the germline.

Epigenetic inheritance and diet

It is now becoming clear that poor nutrition or reduced food availability can have detrimental effects across several generations. A marked example of such effects is in women subjected to severe food restriction during the last trimester of pregnancy, due to a Nazi embargo on food supplies in Western Holland during World War II. Babies born from these women were reported to have lower birth weight, and this was also observed in the subsequent generation despite no further dietary restriction during conception or rearing. These observations suggest a transgenerational effect of diet on birth weight (Susser and Stein, 1994). A recent study further reported that paternal grandmother's and grandfather's food supply is linked to the risk of mortality in granddaughters and grandsons, respectively. This was observed when food supply was insufficient during the slow growth period in mid-childhood in both grandparents, or during early prenatal and postnatal life of the grandmother (Pembrey et al., 2006).

A similar phenomenon was observed in experimental animals, in particular in rats malnourished before or during gestation (Cowley and Griesel, 1966; Zamenhof et al., 1971). Like for the Dutch famine, female rats fed a low-protein diet prior to and during gestation delivered pups with lower body and brain weight, an effect that correlated with reduced level of DNA and protein in the brain. This reduction was not observed when food restriction occurred after delivery. However the effect was inherited by the offspring of the malnourished pups that also had abnormally low brain and body weight (Zamenhof et al., 1971). Second-generation offspring had comparable low birth weight, had slower maturation rate, and displayed poor cognitive performance in the Hebb-Williams maze (Cowley and Griesel, 1966). Since these studies in rodents were carried out prior to molecular advances in epigenetics, the mechanisms underlying the transmission of the effects of a poor diet remain unknown but would be interesting to investigate.

Due to the increase in obesity in Western countries, the transgenerational effect of a maternal high-fat diet on subsequent generations has also been studied. Maternal high-fat diet exposure increases body length and reduces insulin sensitivity two generations downstream from the initial exposure (Dunn and Bale, 2009). These abnormalities can be transmitted both maternally and paternally, and the effect is further amplified when female and male offspring of maternal high-fat diet exposure are bred (Dunn and Bale, 2009).

Overall, these findings in human and rodent suggest that epigenetic and environmental factors are involved in the transmission of the effect of insufficient or excessive diet, but these factors remain unknown. They are likely to be multiple, but a recent study showed alterations in DNA methylation of the gonadotrophin hormone secretagogue receptor (GHSR) promoter in the brain of offspring of mice exposed to a high-fat diet (Dunn and Bale, 2009). More research

is however required to determine the extent of the contribution of epigenetic mechanisms.

Epigenetic inheritance and poor early environment

The influence of the quality of the environment early in life has been under intense research. It is now largely recognized that early abuse or trauma strongly affects individuals throughout their adult life. Long-term studies revealed that infant attachment predicts the ability of a child to form appropriate peer relationships and his/her sociability, risk-taking behaviors, school success, or dropout rate. Success in school is indeed an important parameter that can be predicted with 77% accuracy, based solely on the quality of early care (Harper, 2005; Sroufe, 2002). Furthermore, maltreatment and childhood trauma are known to increase the risk of depression and anxiety disorders in adult individuals (Iversen et al., 2007). While there is a high level of transmission of anxiety disorders and a strong link between parent and child anxiety disorders, this cannot be explained by parenting alone, but instead can be predicted by constitutional factors, like temperament (Dierker et al., 1999; Manassis et al., 1995; Merikangas et al., 1998; Shamir-Essakow et al., 2005; Weissman et al., 1984).

The persistence of disorders that may have arisen from maltreatment in childhood drove researchers to investigate whether DNA methylation plays a role. In rat, the amount of maternal care provided during early development has been shown to influence the pattern of DNA methylation in the pup's brain when adult. Based on naturally occurring individual fluctuations in maternal care provided by female rats, Michael Meaney and colleagues explored the mechanisms that may underlie such fluctuations. Female rats were selected based on their nurturing ability and placed in two treatment groups, high arch-back nursing and licking/grooming (ABN-LG), and low ABN-LG. Studies of pups reared by high ABN-LG dams showed that these pups, when adult, have higher glucocorticoid receptor (GR) expression in the hippocampus, stronger and glucocorticoid feedback sensitivity than pups from low ABN-LG dams (Weaver et al., 2004). These effects were associated with lower DNA methylation in the promoter region of GR and an associated increase in binding of the nerve growth factor-inducible protein-A transcription factor to the promoter region of GR (Weaver et al., 2004). They further showed that all effects of high ABN-LG rearing could be reversed in the adult offspring by intracerebroventricular infusion of L-methionine, which acts as a methyl group donor (Weaver et al., 2005). This demonstrates that changes in the epigenome established by the environment during early development may be reversed by environmental stimuli even in adults, emphasizing the plasticity of DNA methylation in the adult brain.

Findings from rodent experiments were recently corroborated by a study in humans that implicated the early environment in the establishment of methylation patterns. This study provided evidence that childhood abuse is also associated with abnormal methylation in the adult human brain (McGowan et al., 2008). Methylation in the neuron-specific glucocorticoid receptor promoter in the brain of suicide victims who experienced childhood abuse was significantly higher than in suicide victims who were not abused, or in controls. The increase in methylation was associated with decreased glucocorticoid receptor expression (McGowan et al., 2008).

Further to altering methylation, a poor postnatal environment was also recently demonstrated to result in transgenerational transmission of methylation anomalies in the rat brain. Pups receiving daily abusive maternal care including stepping, dropping, dragging, and active avoidance, from non-biological dams during postnatal days (PNDs) 1 to 7 have reduced BDNF expression and increased methylation of the BDNF gene in the prefrontal cortex when adult (Roth et al., 2009). The offspring of females exposed to maltreatment during early life also showed increased BDNF methylation in the prefrontal cortex (Roth et al., 2009). The findings are particularly interesting because, in humans, increased methylation of the BDNF gene in the frontal cortex is associated with major psychoses such as schizophrenia and bipolar disorder (Mill et al., 2008). Thus, this study in rat suggests that maltreatment during early development may not only predispose individuals to major psychoses but also their offspring via transmission of abnormal methylation patterns across generations. Importantly, maltreatment during early development induced poor maternal care in the female offspring when they themselves had pups (Roth et al., 2009). Thus, the alterations in BDNF methylation in the brain of the offspring from abused dams may result from either transmission of methylation via the gametes or changes in methylation elicited by the transmission of poor maternal care across generations. Interestingly, cross-fostering did not fully reverse alterations in methylation levels, suggesting that postnatal experience is not the only factor contributing to this transmission (Roth et al., 2009).

Conclusions

A growing number of reports describe transmission of complex behavioral traits and adult-onset disease states across multiple generations that are non-genomic. The extent to which transgenerational epigenetic inheritance occurs, as well as the persistence and plasticity of this mechanism, still need to be determined. A point sometimes overlooked in transgenerational epigenetic research is the need for transmission two generations downstream from the original manipulation (reviewed in Skinner, 2008). While transmission to the offspring of perturbed animals may suggest epigenetic rather than environmental factors, it does not completely rule out environmental influence, because the cells that ultimately generate the offspring are present at the time of treatment. Thus, transmission to a subsequent third generation is important to demonstrate that the phenotype is indeed transgenerational, germline-dependent, and is not a direct effect of the treatment itself (Skinner, 2008). Several studies have taken this point into consideration and provided evidence for transgenerational transmission across several generations. Furthermore, growing interest in the field also provided new experimental evidence that alteration in DNA methylation in germ cells may underlie epigenetic inheritance. Because a wide range of environmental factors are known to be associated with changes in DNA methylation in both humans and rodents, it is now clear that epigenetic inheritance may be occurring on a much broader scale than previously thought. Finally, further to DNA methylation, other epigenetic mechanisms such as RNA interference, histone posttranslational modifications, and DNA repair may also contribute to epigenetic inheritance (Godmann et al., 2009).

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