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Transgenerational Epigenetics

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INTRODUCTION

The regulation of gene expression through epigenetic modifications provides a dynamic route through which environmental experiences can lead to persistent changes in cellular phenotype. This plasticity plays an important role in mediating cellular differentiation and the potential stability of these modifications can lead to persistent and heritable variations in gene expression. Environmentally-induced changes in DNA methylation, posttranslational histone modifications, and expression of small noncoding RNAs have been observed following a broad range of environmental exposures. The process of DNA methylation whereby cytosine is converted to 5-methylcytosine is mediated by methyltransferases which either promote maintenance (i.e., DNA methyltransferase 1, DNMT1) or de novo DNA methylation (i.e. DNA methyltransferase 3, DNMT3) [1]. The process of methylation is dependent on the presence of methyl donors (provided by nutrients such as folic acid, methionine, and choline [2,3]) and the transcriptional repression associated with DNA methylation is sustained through methyl-binding proteins such as methyl CpG binding protein 2 (MeCP2, [4]). Histone proteins, which form the core of the nucleosome, also significantly alter gene expression through interactions with DNA [5]. Histones can undergo multiple posttranslational modifications, including methylation (di- and tri-), acetylation, and ubiquitination, which can alter the accessibility of DNA and chromatin density. The prediction of transcriptional activation versus suppression in response to histone modifications is dependent on the type and location of modification [6]. For example, tri-methylation (me3) of histone 3 (H3) at the lysine 4 (K4) position within the histone tail is associated with transcriptional activation whereas H3K27me3 is associated with both increased and decreased transcriptional activity [7,8]. Small noncoding RNAs (RNA molecules approximately 20–30 base pairs in length that do not encode for a protein, for example, microRNAs, piRNAs), play a critical role in gene regulation through inhibition of translation and interplay with DNA methylation and chromatin [9]. Importantly, there is cross-talk between these epigenetic mechanisms that contributes to dynamic yet potentially stable levels of transcriptional activity [10,11].

It has become increasingly evident that experiences across the lifespan can induce modifications to the epigenome. Moreover, these epigenetic effects can have

implications for neurobiology, physiology, and behavior of an organism leading to divergent developmental outcomes. Thus, the molecular mechanisms that regulate gene expression can contribute to the "epigenesis" of phenotype as described by Waddington in the 1940s, in which the term "epigenetics" has its roots [12]. Within the study of mammalian development, the quality of interactions between parents and offspring is a particularly salient aspect of the early environment which impacts gene expression and behavior [13,14]. Though maternal effects have been well established in the literature, there is increasing evidence for paternal regulation of offspring development which may provide important insights into the role of epigenetic mechanisms in developmental programming. In this review, we will discuss evidence of maternal and paternal epigenetic influence on offspring development, with particular focus on studies indicating an association between parental experiences/environmental exposures and epigenetic alterations in offspring. An emerging theme within these studies is the multigenerational and transgenerational implications of these environmentally-induced effects. Though both multigenerational and transgenerational effects typically involve altered phenotypes that can be observed across several generations (i.e., grand-offspring generations or later), these effects can be distinguished based on the persistence and transmission of the phenotype in the absence of direct exposure (a phenomenon considered transgenerational). Here we will explore the pathways through which parental influences may persist across multiple generations leading to the stable inheritance of an epigenetically-mediated phenotype.

EPIGENETIC CONSEQUENCES OF PRENATAL MATERNAL EXPOSURES

The quality of the maternal nutritional environment during pregnancy can have a significant impact on the growth and development of the fetus, with long-term consequences for brain development and metabolism. Epidemiological studies of cohorts exposed prenatally to conditions of famine, suggest a heightened risk of metabolic disease, schizophrenia and other neurodevelopmental abnormalities with the specific consequences dependent on the timing of exposure to maternal undernutrition [15,16]. Analysis of blood samples from siblings gestated during periods with or without maternal famine indicates an impact of early gestational exposure on genome-wide DNA methylation patterns, particularly within gene regulatory regions [17]. Though multiple biological pathways exhibit an epigenetic impact of prenatal famine, the decreased DNA methylation of the insulin-like growth factor II (*IGF2*) gene as a consequence of maternal periconceptual exposure to famine may account for growth, metabolic, and neurodevelopmental outcomes [18]. Laboratory studies in rodents have identified specific nutritional deficits, such as prenatal protein restriction or folic acid/choline deficiency, as having similar epigenetic consequences. Offspring of female rats placed on a protein deficient diet throughout gestation were found to have altered hepatic gene expression and DNA methylation profiles, including elevated glucocorticoid receptor (encoded by the *NR3C1* gene) and peroxisomal proliferator-activated receptor alpha (*PPARα*) gene expression associated with decreased DNA methylation of these genes [19–21]. Moreover, these transcriptional and epigenetic effects could be largely reversed when gestational protein restriction is accompanied by folic acid supplementation [19,20]. Dietary effects on levels of DNMT1 may account for these observed modifications in global and gene-specific methylation, as *DNMT1* expression is altered in hepatic [19,22] and brain tissue [23] as a function of protein/choline restriction. The impact of dietary supplementation with methyl-donors during fetal development is also demonstrated by the consequences for phenotype among mice with the A^{vy} allele of the Agouti gene. The expression of the A^{vy} allele is epigenetically regulated through levels of DNA methylation, with decreased methylation associated with yellow coat color and obesity among A^{vy} mice [24]. Though the maternal Agouti phenotype is typically inherited by offspring, gestational exposure to methyl donors through dietary supplementation of the mother can effectively silence the expression of the A^{vy} allele, inducing a pseudo wild-type phenotype [25]. Thus the maternal nutritional environment can have a sustained impact on development through alterations in gene expression that are maintained through DNA methylation. These effects may manifest in response to both nutrient restriction [19,22] or supplementation (i.e., high fat diet [26]) directly within developing fetal tissues or within the placenta [27,28] with consequences for the fetal environment. Beyond DNA methylation, the epigenetic effects of prenatal dietary manipulation are increasingly evident on measures of histone acetylation and tri-methylation [26] and expression of microRNAs [29] in offspring tissues.

The rapid period of cellular proliferation and differentiation that occurs during fetal development provides a critical temporal window during which maternal gestational exposure to toxins may lead to long-term disruptions in offspring and there is increasing evidence for the epigenetic basis of these effects. In utero methyl mercury exposure in mice leads to DNA hypermethylation, increased histone trimethylation and decreased histone acetylation within the IV promoter of the brain derived neurotrophic factor (*BDNF*) gene in the hippo-

campus of offspring [30]. Exposure of pregnant mice to inhaled diesel exhaust particles results in decreased DNA methylation within *PPARγ* in offspring adipose tissue [31] and increased DNA methylation within *BDNF IV* in offspring hippocampus [32]. In humans, comparable levels of exposure to inhaled pollutants is associated with reduced global DNA methylation in white blood cells derived from cord blood samples [33]. In rats, prenatal exposure to the antiandrogenic fungicide vinclozolin results in increased rates of prostate disease, kidney disease, testis abnormalities, and tumor development [34]. This prenatal exposure to an endocrine disrupting chemical is associated with altered DNA methylation patterns in sperm, altered expression of microRNAs in primordial germ cells and impairments in reproduction in male offspring [35,36]. In utero exposure to the endocrine disruptor bisphenol-A (BPA) has been demonstrated to induce genome-wide changes in promoter DNA methylation in the fetal mouse brain [37], increased hippocampal DNA methylation within *BDNF IV* [38] and the promoter region of the gene encoding estrogen receptor alpha (*ESR1*) within the cortex of juvenile offspring [39] and altered hepatic levels of histone acetylation, di-methylation and trimethylation of the carnitine palmitoyltransferase I gene (*CPT1*) in male offspring [40]. BPA-induced hypomethylation of the A^{vy} allele in mice leads to metabolic abnormality and obesity in adulthood and similar to the case of prenatal protein restriction, BPA-induced effects can be reversed through folate supplementation in the mother's diet [41], suggesting that abnormalities in DNA methylation can be ameliorated through exposure to increased levels of methyl-donors.

Evidence for the epigenetic influence of prenatal maternal mood and psychosocial stress has emerged from human cohort studies and animal models—providing further support for the role of epigenetic mechanisms in mediating developmental outcomes. Among infants born to mothers with elevated ratings of depression, there is significant differential DNA methylation within the genome [42], elevated *NR3C1* promoter DNA methylation levels [43], and decreased DNA methylation within the oxytocin receptor gene (*OXTR*) [44]. Though most epigenetic studies in human subjects have been dependent on the use of blood or buccal samples, epigenetic variation in human postmortem hippocampal tissue have also been observed in relationship to maternal depression, with some overlap with epigenetic markers detected in blood [42].

In rodents, chronic gestational stress is associated with decreased hypothalamic DNA methylation of the corticotrophin-releasing-factor (*CRF*) gene promoter [45], increased hypothalamic DNA methylation of the *NR3C1* promoter region [45], increased *DNMT1* expression in the cortex and hippocampus

[46], decreased hippocampal histone acetylation [47], and modified expression of microRNAs [48]. Prenatal stress can exacerbate the epigenetic effects of other prenatal exposures [49] and it is also evident that the effects of stress and other exposures occurring during fetal development are sex-specific, with males and females exhibiting differential epigenetic responses to prenatal adversity [28,39,45,49]. These sex-specific effects extend to the placenta, where epigenetic variation has been found to be induced by stress in studies of humans [50,51] and rodents [45,52,53] and may serve as a critical mediator of prenatal effects on offspring development.

POSTNATAL MATERNAL REGULATION OF THE EPIGENOME

Though dynamic epigenetic modifications were once thought to be limited to the very early stages of development, evidence for continued epigenetic influence of parents beyond the prenatal period has challenged this view. Studies of the effects of natural variations in postnatal care in rodents have established the mediating role of epigenetic factors in shaping individual differences in brain and behavior [54]. Reduced levels of postnatal maternal licking/grooming (LG) behavior, in particular, has been found to alter hippocampal gene expression, histone acetylation and DNA methylation globally, with specific increases in DNA methylation and decreases in H3K9 acetylation within the *NR3C1* [55], glutamate decarboxylase 1 (*GAD1*) [56], and *GRM1* (encoding metabotropic glutamate receptor 1) [57] gene promoters in adult male offspring. In female offspring, the experience of low levels of LG during postnatal development leads to increased DNA methylation and decreased H3K4me3 within the hypothalamus at the *ESR1* promoter region [58,59]. Epigenetic effects within the brain have also been observed in rodents as a consequence of postnatal exposure to maternal separation [60], abusive caregiving [61], and communal rearing [62]. In humans, analyses of postmortem hippocampal tissue reveal similar epigenetic signatures in response to childhood maltreatment that have been observed in rodent studies of variation in parental care, with a significant parallel in the finding of increased hippocampal *NR3C1* DNA methylation in response to a history of abusive caregiving [63,64]. Though the pathways through which these postnatal effects are achieved have yet to be elucidated, it is likely that activation of transcription factors in response to variation in the quality of postnatal mother-infant interactions leads to a cascade of cellular/molecular changes with consequences for epigenetic profiles [65].

PATERNAL INFLUENCE ON OFFSPRING DEVELOPMENT

Mammalian development is characterized by intense prenatal and postnatal mother–infant interactions and thus studies of parental influence have primarily focused on maternal rather than paternal effects. However, even among species in which biparental care is not typical, significant paternal modulation of offspring development has been observed. In rodents, premating exposure of males to alcohol is associated with reduced offspring birth weight, increased mortality, and numerous cognitive and behavioral abnormalities [66–68]. Likewise, offspring of cocaine-exposed males perform poorly on tests of spatial attention/working memory and have a reduced cerebral volume [69,70]. Moreover, variation in the dietary environment of fathers appears to be transmissible to offspring. For instance, reduced serum glucose and altered levels of corticosterone and IGF1 are found among offspring of male mice that undergo a 24-h complete fast two weeks before mating [71] and premating chronic paternal caloric restriction results in reduced serum leptin and altered behavior in offspring [72]. Studies across a diverse range of species [73–77], including humans [78], indicate that paternal exposure to stress at a broad range of developmental time points can induce sex-specific alterations in the behavior and neurobiology of offspring. Finally, epidemiological studies in humans have demonstrated increased risk of autism and schizophrenia that emerge as a function of increased paternal age [79]. Laboratory studies of paternal age effects in genetically-identical rodents also indicate that offspring of "old" fathers have reduced longevity, increased social deficits and perform more poorly on learning and memory tasks [80–82]. The transmission of these paternal effects to offspring in the absence of any postnatal contact with fathers suggests that these exposures may lead to alterations in the male germline with consequences for embryonic development [83].

Investigation of the role of epigenetic mechanisms in mediating paternal effects suggests that environmentally-induced epigenetic changes within sperm cells (including DNA methylation, histone modifications and expression of microRNAs) may propagate the effects of paternal experiences on development [77,83,84]. In males, chronic exposure to alcohol or cocaine can induce chromatin remodeling and changes in DNA methylation within numerous genes in both the brain and periphery [85,86]. In particular, alcohol exposure has been shown to decrease *DNMT* mRNA levels in the sperm cells of adult male rats [87], chronic cocaine exposure in adult male mice has been shown to decrease *DNMT1* while increasing *DNMT3* mRNA expression in the germ cell-rich cells of the seminiferous tubules of the testes [70] and cocaine self-administration by males is associated with

increased H3 acetylation within the *BDNF* promoter [88]. These epigenetic alterations may impact genomic imprinting—the parent-of-origin epigenetic effects on gene expression—as analysis of sperm DNA methylation levels in human males that are heavy drinkers indicates reduced DNA methylation in the normally hypermethylated *H19* and *IG* regulatory regions [86]. In the case of paternal age, overall reductions in DNA methylation are observed in the sperm of "old" (12–14-month) compared to "young" (3-month) male mice [89] and hypermethylation of ribosomal DNA has been found in the sperm and liver cells of "old" (21–28 months) compared to "young/adult" (6 months) male rats [90]. Though there are many genetic and morphological abnormalities in sperm associated with aging, these epigenetic modifications may contribute to the aberrant developmental outcomes associated with increasing paternal age. Male stress exposure occurring during postnatal development and in adulthood can also impact epigenetic outcomes in sperm. Early life maternal separation is associated with increased expression of several microRNAs, downregulation of piRNAs and increased DNA methylation within the regulatory region of *MECP2* [91,92]. Chronic stress exposure in adulthood is also associated with increased expression of several microRNAs in sperm [77] and fear conditioning to a specific odorant molecule (acetophenone) results in reduced DNA methylation in sperm within the gene encoding the odorant receptor responsive to that molecule [93]. Thus, environmental exposures may lead to altered epigenetic marks in male gametes with both broad and gene specific consequences. It has also been determined that direct manipulation of these environmentally-sensitive epigenetic marks in sperm can recapitulate the predicted phenotypic consequences in offspring, providing strong support for the role of paternal epigenetic transmission [91,94].

TRANSGENERATIONAL EFFECTS OF PARENTAL INFLUENCE

The stability of epigenetic modifications within an individual's own development and evidence supporting a transmission of parental epigenetic changes to offspring provide a new perspective on the stable inheritance of traits. Moreover, there is increasing evidence that this nongenomic inheritance can be maintained over multiple generations, such that in addition to the developmental effects of parental experiences on offspring, there may be observed influences of parental (F0) experiences on grand-offspring (F2) and possibly great-grand-offspring (F3). In general, there may be two distinct routes through which these types of epigenetic inheritance patterns can occur: germline-mediated versus experience-dependent/nongermline-mediated (Fig. 24.1). Within
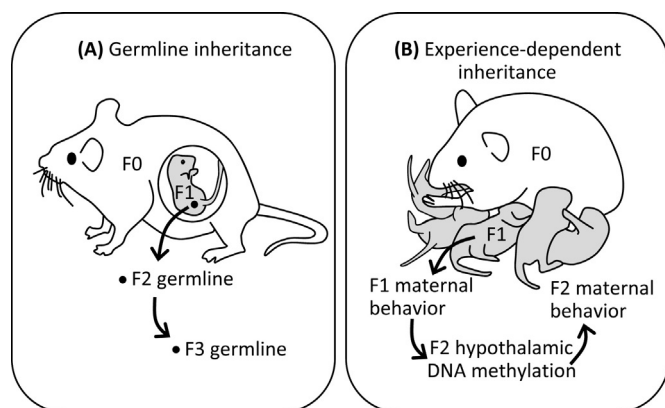
FIGURE 24.1 Illustration of the distinction between a paternal germline epigenetic inheritance (A) and an experience-dependent inheritance of an epigenetic effect (B). In an example of a paternal germline inheritance, an environmental exposure occurring during prenatal development results in an epigenetic alteration within the male F1 germline that is transmitted to F2 and F3 generation male offspring. In contrast, experience-dependent inheritance, such as the transmission of maternal behavior across generations, requires that each generation of females is exposed to differential maternal care in infancy.

germline-mediated transgenerational effects, grandparental environmental exposures are thought to induce epigenetic alterations within the developing gametes that persist in the absence of continued exposure with consequences for F1, F2, and F3 generations. In contrast, experience-dependent/nongermline mediated epigenetic transmission requires that a particular experience or environmental exposure be repeated in each generation to reestablish the epigenetic modifications which permit the trait to persist in subsequent generations. This process results in a multigenerational continuity of a phenotype. The distinction between these two routes can be difficult to establish experimentally, particularly in the case of prenatal exposures in which F1 offspring and the F1 offspring's germline, which will give rise to the F2 generation, are exposed to the inducing environmental factor. Though both of these processes can lead to the stable inheritance of phenotype, there is certainly divergence in the routes through which this is achieved.

GERMLINE-MEDIATED TRANSGENERATIONAL INHERITANCE

There is growing evidence for the transgenerational impact of nutrition, toxins and stress exposure that provides support for an inheritance pattern that is likely germline-mediated. Analysis of archival records from Sweden in which crop success (used as a proxy for food intake) and longevity can be determined in multiple generations, suggests that in humans, a high level of nutrition during the slow growth period that precedes puberty is associated with diabetes and cardiovascular

disease mortality of grand-offspring [95]. Interestingly, these effects are sex-specific, with paternal grandfather nutrition predicting grandson mortality and paternal grandmother nutrition predicting grand-daughter longevity. Laboratory studies in rodents have confirmed the transgenerational impact of nutrition and indicate that prenatal protein restriction can exert effects on growth and metabolism of offspring and grand-offspring through changes in DNA methylation status of *NR3C1* [96]. When F0 female mice are exposed to caloric restriction during late gestation, F2 grand-offspring are found to have impaired glucose tolerance and this effect is maintained even when the F1 generation is provided with ad libitum food throughout their lifetime. Among descendants of female mice (F0) placed on a high-fat diet throughout pregnancy, offspring (F1) and grand-offspring (F2) exhibit increased body length [97]. This diet-induced effect can also be observed in the F3 generation, but only when that generation is derived from the F1 exposed patriline [98]. In human cohort studies, paternal consumption of betel nuts (which contain nitrosamines) leads to dose-dependent increases in offspring risk of metabolic syndrome [99] and in transgenerational studies of mice, 2–6 days of betel nut consumption by F0 generation males is associated with increased glucose intolerance amongst F1, F2, and F3 generation offspring [100]. Similar metabolic effects are observed when males are exposed in utero to dexamethasone, with increased glucose intolerance observed among the offspring of these males when mated with nonexposed females [101]. However, in the case of prenatal dexamethasone exposure, these metabolic phenotypes do not persist beyond the F2 generation indicating that there is either compensation for the germline effects or that the effect is mediated by experience-dependent transmission.

The consequences of in utero exposure to endocrine-disrupting compounds has also been explored within a transgenerational model and provides evidence for the pervasive effects on epigenetic profiles of these early life exposures. In utero exposure to vinclozolin in rats has been demonstrated to disrupt DNA methylation in sperm and increase rates of infertility and risk of prostrate and kidney disease in F1, F2, and F3 offspring with the transmission though the patriline [35]. Vinclozolin-induced alterations in gene expression within the hippocampus and amygdala have also been observed for up to three generations postexposure with sex-specific effects on anxiety-like behavior [102]. Interestingly, mate-choice studies suggest that females presented with F3 vinclozolin-exposed or nonexposed males show a significant partner preference for nonexposed males, indicating an additional measure of decreased reproductive success as a consequence of treatment with endocrine disruptors [103]. The persistence of these disruptions beyond the F2 generation (with the F3 generation being the

first "nonexposed" generation) suggests that the effects of these exposures have become incorporated into the germline and there is incomplete erasure of the associated epigenetic marks during the process of gametogenesis, fertilization, and embryogenesis [104]. Similar effects have been observed following F0 gestational exposure to a mixture of BPA and other endocrine disrupting compounds, with reproductive and sperm epigenome consequences observed in the F3 generation [105]. Understanding the mechanisms through which these toxin exposures lead to alterations in the epigenome will have significant implications for our understanding of environmental health issues.

The profound effects of stress exposure on development can be transmitted to offspring and grand-offspring and there is increasing evidence for the role of stress-induced epigenetic variation in the paternal germline in mediating the inheritance of these effects. Increased anxiety-like and depressive-like behavioral indices are observed in the female offspring (F2) of maternally separated males (F1) and though these behavioral effects are not observed in F2 male offspring, the grand-offspring (F3) generated from F2 exposed males exhibit these behavioral traits [92]. Moreover, the increased DNA methylation observed within the *MECP2* gene in the sperm of exposed males are recapitulated in the cortex of F2 male offspring and microRNAs differentially expressed in the sperm of exposed F1 males are similarly observed in the F2 hippocampus [91,92]. Chronic social stress in juvenile male mice results in behavioral deficits (social deficits and anxiety) that persist to the F3 generation—though only when this generation is derived from the exposed patriline—further supporting a germline inheritance [76]. Finally, the impact of fear conditioning of F0 generation males to acetophenone results in olfactory sensitivity to this specific odorant in subsequent F1 and F2 generations [93]. Altered DNA methylation of the olfactory receptor responsive to acetophenone is observed in the sperm of both F0 and F1 males suggesting a germline basis to the transmission of memory of fear-related stimuli.

EXPERIENCE-DEPENDENT TRANSGENERATIONAL INHERITANCE

Across species, there is evidence for the transmission of individual differences in maternal behavior from mother to offspring and grand-offspring. In humans, mother–infant attachment classifications (secure, anxious/resistant, avoidant, disorganized) are similar across generations of female offspring [47] as are levels of parental bonding [106]. In rhesus and pigtail macaques, rates of maternal rejection and infant abuse are

transmitted across matrilines and crossfostering studies conducted between abusive and nonabusive macaques females indicates that the transmission of abusive behavior from mother to daughter is dependent on the experience of abuse during the postnatal period [107,108]. This matrilineal transmission is also evident in laboratory rodents. Natural variations in maternal LG observed in the F0 generation are associated with similar levels of LG in F1 and F2 generation females [109]. As such, under stable environmental conditions, offspring and grand-offspring of low-LG females display low levels of LG whereas offspring and grand-offspring of high-LG females display high levels of LG [109]. Similar to the transgenerational effects of abuse in macaques, crossfostering studies have demonstrated that the transmission of maternal LG from mother to female offspring is dependent on the level of maternal LG received in infancy [110]. Communal rearing in mice results in increased postpartum maternal behavior in F0 females, in F1 females, and in F2 females that have not been communally reared but are the offspring of communally reared females [111]. A similar behavioral transmission can occur when the F0 maternal behavior is altered through a genetic mutation that is not inherited by offspring [112]. The experience-dependent nature of the transmission of maternal behavior is further highlighted in studies where environmental conditions of mothers are altered through chronic exposure to stress [113] or manipulation of the juvenile environment [109]. These environmental exposures impact maternal behavior (particularly LG) leading to a disruption of the inheritance of the predicted maternal phenotype.

Epigenetic mechanisms may be critical in mediating the transmission of maternal behavior across generations and for the recapitulation of behavioral and neurobiological phenotypes that emerge as a consequence of this multigenerational transmission. Female offspring of low-LG mothers exhibit a reduced sensitivity to estrogen and have reduced levels of hypothalamic *ESR1* expression within the medial preoptic area (MPOA) of the hypothalamus which likely account for the reduced level of postpartum maternal behavior observed in these females [114]. Female offspring reared by a low-LG dam have increased DNA methylation, decreased H3K4me3 and increased H3K9me3 at the *ESR1* gene promoter [58,59]. This epigenetic variation results in reduced binding of signal transducer and activator of transcription (Stat)5 to the *ESR1* promoter with consequences for the transcriptional activity of this gene [58]. Thus, epigenetic modifications to a gene that regulates several aspects of reproduction, including postpartum maternal behavior, results in differential levels of expression of *ESR1* in adulthood, which alters estrogen sensitivity and consequently leads to variations in the

level of maternal care that these females (F1) provide to their own offspring (F2). The transmission from mother to daughter of variations in maternal LG within this transgenerational framework is mediated by the stability of brain region-specific epigenetic modifications that occur in infancy and influence behavior in adulthood. Similar experience-dependent effects of the postnatal environment in rats have been induced through exposure to abuse. Increase in DNA methylation in the *BDNF* IV promoter and consequent decrease in *BDNF* mRNA in the prefrontal cortex has been found in association with exposure to periods of abusive maternal care (dragging, burying etc.) [61]. Moreover, these effects on *BDNF* IV promoter DNA methylation are perpetuated to the F1 offspring of abused females suggesting a role for epigenetic mechanisms in this transgenerational effect. Overall, these studies highlight the stable inheritance of traits that can be achieved through a behavioral transmission of epigenetic modifications. Moreover, the consequences of this transmission extend to all systems that are impacted by variation in maternal behavior, including social behavior, stress responsivity, and cognition.

EPIGENETICS, PLASTICITY, AND EVOLVING CONCEPTS OF INHERITANCE

Though the study of mechanisms of inheritance and the origins of divergent developmental trajectories has traditionally been the domain of the field of genetics, there is increasing evidence for the role of epigenetic modifications in maintaining environmentally-induced variations in phenotype both within and across generations. The dynamic nature of these epigenetic effects provides a mechanism through which a single genotype can give rise to multiple phenotypic outcomes conferring a heightened level of developmental plasticity to an organism. In contrast to environmentally-induced genetic alterations/mutations, which are thought to be nondirected, there may be adaptive consequences associated with experience-dependent epigenetic modifications. For example, nutritional "programming" of fetal metabolism has been explored as an adaptive consequence of early life experience [115] and there is clearly a role for epigenetic mechanisms in mediating the effects of variations in prenatal food intake. When the prenatal period is characterized by undernutrition, a "thrifty phenotype" may result which allows an individual to be conservative with regard to energy output and which promotes storage of glucose—with adverse health consequences associated with a mismatch between the quality of the prenatal and postnatal nutritional environment [116], Similar adaptive consequences may be relevant to the development of heightened HPA reactivity. Though

elevated stress responses are typically considered to be a negative outcome and associated with increased susceptibility to physical and psychiatric disease, within an evolutionary perspective, the ability to respond rapidly to threat would be particularly advantageous under conditions of high predation/low resource availability [117]. Laboratory studies of maternal care in rodents suggest that chronic stress and social impoverishment can lead to reduced LG with consequences for the increased stress response of offspring via differential hippocampal *NR3C1* DNA methylation [55,109,113]. Though this environmentally-induced phenotype is associated with impaired cognitive performance under standard testing conditions [118], synaptic plasticity is enhanced in offspring of low-LG mothers when corticosterone levels are elevated [119]. Thus, the consequences of early life experience can be considered as adaptive or maladaptive dependent on the consistency or "match" between early and later environmental conditions, and epigenetic mechanisms play a critical role in shaping these phenotypic adaptations.

The concept that experience-induced characteristics can be transmitted across generations is reminiscent of Lamarckian theories of use/disuse and the inheritance of acquired characteristics [120]. Though the role of heritable epigenetic modifications in evolutionary processes certainly remains a topic of debate, both germline and experience-dependent epigenetic transmission may be important processes to be considered within an extended evolutionary synthesis and a more dynamic and interactive view of development [121]. Importantly, athough there is growing support for transgenerational epigenetic consequences of environmental exposures, our understanding of the molecular, cellular, and behavioral pathways through which these outcomes are achieved is still evolving. Moreover, these epigenetic effects have often been explored from the perspective of pathology, yet the potential for multigenerational improvements in health and behavioral outcomes or resistance to subsequent environmental exposures are being increasingly observed [88,122,123]. Thus, broadening our concept of inheritance to include both genetic and epigenetic mechanisms and the interplay between these pathways [124] may provide insights into effective therapeutic approaches and lead to a greater appreciation of the benefits that can be achieved through intervention in parental and grandparental generations.

Acknowledgments

References

[1] Feng J, Fan G. The role of DNA methylation in the central nervous system and neuropsychiatric disorders. Int Rev Neurobiol 2009;89:67–84.

[2] Anderson OS, Sant KE, Dolinoy DC. Nutrition and epigenetics: an interplay of dietary methyl donors, one-carbon metabolism and DNA methylation. J Nutr Biochem 2012;23(8):853–9.

[3] Pauwels S, Ghosh M, Duca RC, Bekaert B, Freson K, Huybrechts I, et al. Dietary and supplemental maternal methyl-group donor intake and cord blood DNA methylation. Epigenetics 2017;12(1):1–10.

[4] Fan G, Hutnick L. Methyl-CpG binding proteins in the nervous system. Cell Res 2005;15(4):255–61.

[5] Cheung P, Allis CD, Sassone-Corsi P. Signaling to chromatin through histone modifications. Cell 2000;103(2):263–71.

[6] Jenuwein T, Allis CD. Translating the histone code. Science 2001;293(5532):1074–80.

[7] Vakoc CR, Sachdeva MM, Wang H, Blobel GA. Profile of histone lysine methylation across transcribed mammalian chromatin. Mol Cell Biol 2006;26(24):9185–95.

[8] Young MD, Willson TA, Wakefield MJ, Trounson E, Hilton DJ, Blewitt ME, et al. ChIP-seq analysis reveals distinct H3K27me3 profiles that correlate with transcriptional activity. Nucleic Acids Res 2011;39(17):7415–27.

[9] Sato F, Tsuchiya S, Meltzer SJ, Shimizu K. MicroRNAs and epigenetics. FEBS J 2011;278(10):1598–609.

[10] Molina-Serrano D, Schiza V, Kirmizis A. Cross-talk among epigenetic modifications: lessons from histone arginine methylation. Biochem Soc Trans 2013;41(3):751–9.

[11] Denis H, Ndlovu MN, Fuks F. Regulation of mammalian DNA methyltransferases: a route to new mechanisms. EMBO Rep 2011;12(7):647–56.

[12] Jablonka E, Lamb MJ. The changing concept of epigenetics. Ann NY Acad Sci 2002;981:82–96.

[13] Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu Rev Neurosci 2001;24:1161–92.

[14] Braun K, Champagne FA. Paternal influences on offspring development: behavioural and epigenetic pathways. J Neuroendocrinol 2014;26(10):697–706.

[15] Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. Arch Gen Psychiatry 1992;49(12):983–8.

[16] Hulshoff Pol HE, Hoek HW, Susser E, Brown AS, Dingemans A, Schnack HG, et al. Prenatal exposure to famine and brain morphology in schizophrenia. Am J Psychiatry 2000;157(7):1170–2.

[17] Tobi EW, Goeman JJ, Monajemi R, Gu H, Putter H, Zhang Y, et al. DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nat Commun 2014;5:5592.

[18] Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci USA 2008;105(44):17046–9.

[19] Altobelli G, Bogdarina IG, Stupka E, Clark AJL, Langley-Evans S. Genome-wide methylation and gene expression changes in newborn rats following maternal protein restriction and reversal by folic acid. PloS One 2013;8(12):e82989.

[20] Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. J Nutr 2005;135(6):1382–6.

[21] Lillycrop KA, Phillips ES, Torrens C, Hanson MA, Jackson AA, Burdge GC. Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in the hepatic PPAR alpha promoter of the offspring. Br J Nutr 2008;100(2):278–82.

[22] Lillycrop KA, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br J Nutr 2007;97(6):1064–73.

[23] Kovacheva VP, Mellott TJ, Davison JM, Wagner N, Lopez-Coviella I, Schnitzler AC, et al. Gestational choline deficiency causes global and Igf2 gene DNA hypermethylation by up-regulation of Dnmt1 expression. J Biol Chem 2007;282(43):31777–88.

[24] Morgan HD, Sutherland HG, Martin DI, Whitelaw E. Epigenetic inheritance at the agouti locus in the mouse. Nat Genet 1999;23(3):314–8.

[25] Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol 2003;23(15):5293–300.

[26] Suter MA, Ma J, Vuguin PM, Hartil K, Fiallo A, Harris RA, et al. In utero exposure to a maternal high-fat diet alters the epigenetic histone code in a murine model. Am J Obstet Gynecol 2014;210(5):463.e1–463.e11.

[27] Reamon-Buettner SM, Buschmann J, Lewin G. Identifying placental epigenetic alterations in an intrauterine growth restriction (IUGR) rat model induced by gestational protein deficiency. Reprod Toxicol 2014;45:117–24.

[28] Gabory A, Ferry L, Fajardy I, Jouneau L, Gothié J-D, Vigé A, et al. Maternal diets trigger sex-specific divergent trajectories of gene expression and epigenetic systems in mouse placenta. PloS One 2012;7(11):e47986.

[29] Casas-Agustench P, Fernandes FS, Tavares do Carmo MG, Visioli F, Herrera E, Dávalos A. Consumption of distinct dietary lipids during early pregnancy differentially modulates the expression of microRNAs in mothers and offspring. PloS One 2015;10(2):e0117858.

[30] Onishchenko N, Karpova N, Sabri F, Castrén E, Ceccatelli S. Long-lasting depression-like behavior and epigenetic changes of BDNF gene expression induced by perinatal exposure to methylmercury. J Neurochem 2008;106(3):1378–87.

[31] Yan Z, Zhang H, Maher C, Arteaga-Solis E, Champagne FA, Wu L, et al. Prenatal polycyclic aromatic hydrocarbon, adiposity, peroxisome proliferator-activated receptor (PPAR) γ methylation in offspring, grand-offspring mice. PloS One 2014;9(10):e110706.

[32] Miller RL, Yan Z, Maher C, Zhang H, Gudsnuk K, McDonald J, et al. Impact of prenatal polycyclic aromatic hydrocarbon exposure on behavior, cortical gene expression and DNA methylation of the Bdnf gene. Neuroepigenetics 2016;5:11–8.

[33] Herbstman JB, Tang D, Zhu D, Qu L, Sjödin A, Li Z, et al. Prenatal exposure to polycyclic aromatic hydrocarbons, benzo[a]pyrene-DNA adducts, and genomic DNA methylation in cord blood. Environ Health Perspect 2012;120(5):733–8.

[34] Anway MD, Leathers C, Skinner MK. Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology 2006;147(12):5515–23.

[35] Anway MD. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 2005;308(5727):1466–9.

[36] Brieño-Enríquez MA, García-López J, Cárdenas DB, Guibert S, Cleroux E, Děd L, et al. Exposure to endocrine disruptor induces transgenerational epigenetic deregulation of microRNAs in primordial germ cells. PloS One 2015;10(4):e0124296.

[37] Yaoi T, Itoh K, Nakamura K, Ogi H, Fujiwara Y, Fushiki S. Genome-wide analysis of epigenomic alterations in fetal mouse forebrain after exposure to low doses of bisphenol A. Biochem Biophys Res Commun 2008;376(3):563–7.

[38] Kundakovic M, Gudsnuk K, Herbstman JB, Tang D, Perera FP, Champagne FA. DNA methylation of BDNF as a biomarker of early-life adversity. Proc Natl Acad Sci USA 2015;112(22):6807–13.

[39] Kundakovic M, Gudsnuk K, Franks B, Madrid J, Miller RL, Perera FP, et al. Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. Proc Natl Acad Sci USA 2013;110(24):9956–61.

[40] Strakovsky RS, Wang H, Engeseth NJ, Flaws JA, Helferich WG, Pan Y-X, et al. Developmental bisphenol A (BPA) exposure leads to sex-specific modification of hepatic gene expression and epigenome at birth that may exacerbate high-fat diet-induced hepatic steatosis. Toxicol Appl Pharmacol 2015;284(2):101–12.

[41] Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci USA 2007;104(32):13056–61.

[42] Nemoda Z, Massart R, Suderman M, Hallett M, Li T, Coote M, et al. Maternal depression is associated with DNA methylation changes in cord blood T lymphocytes and adult hippocampi. Transl Psychiatry 2015;5:e545.

[43] Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 2008;3(2):97–106.

[44] Unternaehrer E, Bolten M, Nast I, Staehli S, Meyer AH, Dempster E, et al. Maternal adversities during pregnancy and cord blood oxytocin receptor (OXTR) DNA methylation. Soc Cogn Affect Neurosci 2016;11(9):1460–70.

[45] Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. J Neurosci 2008;28(36):9055–65.

[46] Dong E, Dzitoyeva SG, Matrisciano F, Tueting P, Grayson DR, Guidotti A. Brain-derived neurotrophic factor epigenetic modifications associated with schizophrenia-like phenotype induced by prenatal stress in mice. Biol Psychiatry 2015;77(6):589–96.

[47] Benoit JD, Rakic P, Frick KM. Prenatal stress induces spatial memory deficits and epigenetic changes in the hippocampus indicative of heterochromatin formation and reduced gene expression. Behav Brain Res 2015;281:1–8.

[48] Monteleone MC, Adrover E, Pallarés ME, Antonelli MC, Frasch AC, Brocco MA. Prenatal stress changes the glycoprotein GPM6A gene expression and induces epigenetic changes in rat offspring brain. Epigenetics 2014;9(1):152–60.

[49] Schneider JS, Anderson DW, Kidd SK, Sobolewski M, Cory-Slechta DA. Sex-dependent effects of lead and prenatal stress on post-translational histone modifications in frontal cortex and hippocampus in the early postnatal brain. Neurotoxicology 2016;54:65–71.

[50] Appleton AA, Armstrong DA, Lesseur C, Lee J, Padbury JF, Lester BM, et al. Patterning in placental 11-B hydroxysteroid dehydrogenase methylation according to prenatal socioeconomic adversity. PloS One 2013;8(9):e74691.

[51] Monk C, Feng T, Lee S, Krupska I, Champagne FA, Tycko B. Distress during pregnancy: epigenetic regulation of placenta glucocorticoid-related genes and fetal neurobehavior. Am J Psychiatry 2016;173(7):705–13.

[52] Jensen Peña C, Monk C, Champagne FA. Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. PloS One 2012;7(6):e39791.

[53] Howerton CL, Morgan CP, Fischer DB, Bale TL. O-GlcNAc transferase (OGT) as a placental biomarker of maternal stress and reprogramming of CNS gene transcription in development. Proc Natl Acad Sci USA 2013;110(13):5169–74.

[54] Curley JP, Champagne FA. Influence of maternal care on the developing brain: mechanisms, temporal dynamics and sensitive periods. Front Neuroendocrinol 2016;40:52–66.

[55] Weaver ICG, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nat Neurosci 2004;7(8):847–54.

[56] Zhang T-Y, Hellstrom IC, Bagot RC, Wen X, Diorio J, Meaney MJ. Maternal care and DNA methylation of a glutamic acid decarboxylase 1 promoter in rat hippocampus. J Neurosci 2010;30(39):13130–7.

[57] Bagot RC, Zhang T-Y, Wen X, Nguyen TTT, Nguyen H-B, Diorio J, et al. Variations in postnatal maternal care and the epigenetic regulation of metabotropic glutamate receptor 1 expression and hippocampal function in the rat. Proc Natl Acad Sci USA 2012;109(Suppl 2):17200–7.

[58] Champagne FA, Weaver ICG, Diorio J, Dymov S, Szyf M, Meaney MJ. Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. Endocrinology 2006;147(6):2909–15.

[59] Peña CJ, Neugut YD, Champagne FA. Developmental timing of the effects of maternal care on gene expression and epigenetic regulation of hormone receptor levels in female rats. Endocrinology 2013;154(11):4340–51.

[60] Suri D, Veenit V, Sarkar A, Thiagarajan D, Kumar A, Nestler EJ, et al. Early stress evokes age-dependent biphasic changes in hippocampal neurogenesis, BDNF expression, and cognition. Biol Psychiatry 2013;73(7):658–66.

[61] Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatry 2009;65(9):760–9.

[62] Branchi I, Karpova NN, D'Andrea I, Castrén E, Alleva E. Epigenetic modifications induced by early enrichment are associated with changes in timing of induction of BDNF expression. Neurosci Lett 2011;495(3):168–72.

[63] Suderman M, McGowan PO, Sasaki A, Huang TCT, Hallett MT, Meaney MJ, et al. Conserved epigenetic sensitivity to early life experience in the rat and human hippocampus. Proc Natl Acad Sci USA 2012;109(Suppl 2):17266–72.

[64] McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009;12(3):342–8.

[65] Hellstrom IC, Dhir SK, Diorio JC, Meaney MJ. Maternal licking regulates hippocampal glucocorticoid receptor transcription through a thyroid hormone-serotonin-NGFI-A signalling cascade. Philos Trans R Soc Lond B Biol Sci 2012;367(1601):2495–510.

[66] Abel E. Paternal contribution to fetal alcohol syndrome. Addict Biol 2004;9(2):127–33.

[67] Ledig M, Misslin R, Vogel E, Holownia A, Copin JC, Tholey G. Paternal alcohol exposure: developmental and behavioral effects on the offspring of rats. Neuropharmacology 1998;37(1):57–66.

[68] Meek LR, Myren K, Sturm J, Burau D. Acute paternal alcohol use affects offspring development and adult behavior. Physiol Behav 2007;91(1):154–60.

[69] Abel EL, Moore C, Waselewsky D, Zajac C, Russell LD. Effects of cocaine hydrochloride on reproductive function and sexual behavior of male rats and on the behavior of their offspring. J Androl 1989;10(1):17–27.

[70] He F, Lidow IA, Lidow MS. Consequences of paternal cocaine exposure in mice. Neurotoxicol Teratol 2006;28(2):198–209.

[71] Anderson LM, Riffle L, Wilson R, Travlos GS, Lubomirski MS, Alvord WG. Preconceptional fasting of fathers alters serum glucose in offspring of mice. Nutrition 2006;22(3):327–31.

[72] Govic A, Penman J, Tammer AH, Paolini AG. Paternal calorie restriction prior to conception alters anxiety-like behavior of the adult rat progeny. Psychoneuroendocrinology 2016;64:1–11.

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[73] Dietz DM, Laplant Q, Watts EL, Hodes GE, Russo SJ, Feng J, et al. Paternal transmission of stress-induced pathologies. Biol Psychiatry 2011;70(5):408–14.

[74] Hoyer C, Richter H, Brandwein C, Riva MA, Gass P. Preconceptional paternal exposure to a single traumatic event affects postnatal growth of female but not male offspring. Neuroreport 2013;24(15):856–60.

[75] Kinnally EL, Capitanio JP. Paternal early experiences influence infant development through non-social mechanisms in Rhesus Macaques. Front Zool 2015;12(Suppl 1):S14.

[76] Saavedra-Rodríguez L, Feig LA. Chronic social instability induces anxiety and defective social interactions across generations. Biol Psychiatry 2013;73(1):44–53.

[77] Rodgers AB, Morgan CP, Bronson SL, Revello S, Bale TL. Paternal stress exposure alters sperm microRNA content and reprograms offspring HPA stress axis regulation. J Neurosci 2013;33(21):9003–12.

[78] Yehuda R, Daskalakis NP, Lehrner A, Desarnaud F, Bader HN, Makotkine I, et al. Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. Am J Psychiatry 2014;171(8):872–80.

[79] McGrath JJ, Petersen L, Agerbo E, Mors O, Mortensen PB, Pedersen CB. A comprehensive assessment of parental age and psychiatric disorders. JAMA Psychiatry 2014;71(3):301–9.

[80] Janecka M, Manduca A, Servadio M, Trezza V, Smith R, Mill J, et al. Effects of advanced paternal age on trajectories of social behavior in offspring. Genes Brain Behav 2015;14(6):443–53.

[81] García-Palomares S, Pertusa JF, Miñarro J, García-Pérez MA, Hermenegildo C, Rausell F, et al. Long-term effects of delayed fatherhood in mice on postnatal development and behavioral traits of offspring. Biol Reprod 2009;80(2):337–42.

[82] García-Palomares S, Navarro S, Pertusa JF, Hermenegildo C, García-Pérez MA, Rausell F, et al. Delayed fatherhood in mice decreases reproductive fitness and longevity of offspring. Biol Reprod 2009;80(2):343–9.

[83] Jenkins TG, Carrell DT. The sperm epigenome and potential implications for the developing embryo. Reproduction 2012;143(6):727–34.

[84] Carrell DT, Hammoud SS. The human sperm epigenome and its potential role in embryonic development. Mol Hum Reprod 2010;16(1):37–47.

[85] Novikova SI, He F, Bai J, Cutrufello NJ, Lidow MS, Undieh AS. Maternal cocaine administration in mice alters DNA methylation and gene expression in hippocampal neurons of neonatal and prepubertal offspring. PloS One 2008;3(4):e1919.

[86] Ouko LA, Shantikumar K, Knezovich J, Haycock P, Schnugh DJ, Ramsay M. Effect of alcohol consumption on CpG methylation in the differentially methylated regions of H19 and IG-DMR in male gametes: implications for fetal alcohol spectrum disorders. Alcohol Clin Exp Res 2006;33(9):1615–27.

[87] Bielawski DM, Zaher FM, Svinarich DM, Abel EL. Paternal alcohol exposure affects sperm cytosine methyltransferase messenger RNA levels. Alcohol Clin Exp Res 2002;26(3):347–51.

[88] Vassoler FM, White SL, Schmidt HD, Sadri-Vakili G, Pierce RC. Epigenetic inheritance of a cocaine-resistance phenotype. Nat Neurosci 2013;16(1):42–7.

[89] Milekic MH, Xin Y, O'Donnell A, Kumar KK, Bradley-Moore M, Malaspina D, et al. Age-related sperm DNA methylation changes are transmitted to offspring and associated with abnormal behavior and dysregulated gene expression. Mol Psychiatry 2015;20(8):995–1001.

[90] Oakes CC, Smiraglia DJ, Plass C, Trasler JM, Robaire B. Aging results in hypermethylation of ribosomal DNA in sperm and liver of male rats. Proc Natl Acad Sci USA 2003;100(4):1775–80.

[91] Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, et al. Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat Neurosci 2014;17(5):667–9.

[92] Franklin TB, Russig H, Weiss IC, Gräff J, Linder N, Michalon A, et al. Epigenetic transmission of the impact of early stress across generations. Biol Psychiatry 2010;68(5):408–15.

[93] Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. Nat Neurosci 2014;17(1):89–96.

[94] Rodgers AB, Morgan CP, Leu NA, Bale TL. Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress. Proc Natl Acad Sci USA 2015;112(44):13699–704.

[95] Pembrey ME, Bygren LO, Kaati G, Edvinsson S, Northstone K, Sjöström M, et al. Sex-specific, male-line transgenerational responses in humans. Eur J Hum Genet 2006;14(2):159–66.

[96] Zambrano E, Martínez-Samayoa PM, Bautista CJ, Deás M, Guillén L, Rodríguez-González GL, et al. Sex differences in transgenerational alterations of growth and metabolism in progeny (F2) of female offspring (F1) of rats fed a low protein diet during pregnancy and lactation. J Physiol 2005;566(Pt 1):225–36.

[97] Dunn GA, Bale TL. Maternal high-fat diet promotes body length increases and insulin insensitivity in second-generation mice. Endocrinology 2009;150(11):4999–5009.

[98] Dunn GA, Bale TL. Maternal high-fat diet effects on third-generation female body size via the paternal lineage. Endocrinology 2011;152(6):2228–36.

[99] Chen TH-H, Chiu Y-H, Boucher BJ. Transgenerational effects of betel-quid chewing on the development of the metabolic syndrome in the Keelung Community-based Integrated Screening Program. Am J Clin Nutr 2006;83(3):688–92.

[100] Boucher BJ, Ewen SW, Stowers JM. Betel nut (Areca catechu) consumption and the induction of glucose intolerance in adult CD1 mice and in their F1 and F2 offspring. Diabetologia 1994;37(1):49–55.

[101] Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol 2005;288(1):R34–8.

[102] Skinner MK, Anway MD, Savenkova MI, Gore AC, Crews D. Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior. PloS One 2008;3(11):e3745.

[103] Crews D, Gore AC, Hsu TS, Dangleben NL, Spinetta M, Schallert T, et al. Transgenerational epigenetic imprints on mate preference. Proc Natl Acad Sci USA 2007;104(14):5942–6.

[104] Skinner MK. What is an epigenetic transgenerational phenotype? F3 or F2. Reprod Toxicol 2008;25(1):2–6.

[105] Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PloS One 2013;8(1):e55387.

[106] Miller L, Kramer R, Warner V, Wickramaratne P, Weissman M. Intergenerational transmission of parental bonding among women. J Am Acad Child Adolesc Psychiatry 1997;36(8):1134–9.

[107] Maestripieri D. Early experience affects the intergenerational transmission of infant abuse in rhesus monkeys. Proc Natl Acad Sci USA 2005;102(27):9726–9.

[108] Maestripieri D, Wallen K, Carroll KA. Infant abuse runs in families of group-living pigtail macaques. Child Abuse Negl 1997;21(5):465–71.

[109] Champagne FA, Meaney MJ. Transgenerational effects of social environment on variations in maternal care and behavioral response to novelty. Behav Neurosci 2007;121(6):1353–63.

[110] Francis D, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science 1999;286(5442):1155–8.

[111] Curley JP, Davidson S, Bateson P, Champagne FA. Social enrichment during postnatal development induces transgenerational effects on emotional and reproductive behavior in mice. Front Behav Neurosci 2009;3:25.

[112] Curley JP, Champagne FA, Bateson P, Keverne EB. Transgenerational effects of impaired maternal care on behaviour of offspring and grandoffspring. Anim Behav 2008;75(4):1551–61.

[113] Champagne FA, Meaney MJ. Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. Biol Psychiatry 2006;59(12):1227–35.

[114] Champagne FA, Weaver ICG, Diorio J, Sharma S, Meaney MJ. Natural variations in maternal care are associated with estrogen receptor alpha expression and estrogen sensitivity in the medial preoptic area. Endocrinology 2003;144(11):4720–4.

[115] McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev 2005;85(2):571–633.

[116] Wells JCK. The thrifty phenotype: an adaptation in growth or metabolism? Am J Hum Biol 2011;23(1):65–75.

[117] Cameron NM, Champagne FA, Parent C, Fish EW, Ozaki-Kuroda K, Meaney MJ. The programming of individual differences in defensive responses and reproductive strategies in the rat through variations in maternal care. Neurosci Biobehav Rev 2005;29(4–5):843–65.

[118] Liu D, Diorio J, Day JC, Francis DD, Meaney MJ. Maternal care, hippocampal synaptogenesis and cognitive development in rats. Nat Neurosci 2000;3(8):799–806.

[119] Champagne DL, Bagot RC, van Hasselt F, Ramakers G, Meaney MJ, de Kloet ER, et al. Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. J Neurosci 2008;28(23):6037–45.

[120] Lamarck J-B. Philosophie Zoologique.

[121] Laland KN, Uller T, Feldman MW, Sterelny K, Müller GB, Moczek A, et al. The extended evolutionary synthesis: its structure, assumptions and predictions. Proc Biol Sci 2015;282(1813):20151019.

[122] Zeybel M, Hardy T, Wong YK, Mathers JC, Fox CR, Gackowska A, et al. Multigenerational epigenetic adaptation of the hepatic wound-healing response. Nat Med 2012;18(9):1369–77.

[123] Arai JA, Li S, Hartley DM, Feig LA. Transgenerational rescue of a genetic defect in long-term potentiation and memory formation by juvenile enrichment. J Neurosci 2009;29(5):1496–502.

[124] Danchin É, Charmantier A, Champagne FA, Mesoudi A, Pujol B, Blanchet S. Beyond DNA: integrating inclusive inheritance into an extended theory of evolution. Nat Rev Genet 2011;12(7):475–86.