CHAPTER

24

Transgenerational Epigenetics

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OUTLINE

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 stable and heritable variations in gene expression [1]. Environmentally induced changes in DNA methylation, posttranslational histone modifications, and expression of non-coding 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 (i.e., DNA methyltransferase, DNMT1, DNMT3) which promote maintenance and de novo DNA methylation [2]. The process of DNA methylation is dependent on the presence of methyl donors (provided by nutrients such as folic acid, methionine, and choline [3,4]) and the transcriptional repression associated with DNA methylation is sustained through methyl-binding proteins such as methyl CpG binding protein 2 (MeCP2, [5]). Oxidation of methylated cytosines through the activity of Ten-eleven translocation (Tet) proteins can lead to DNA hydroxymethylation which may be a critical step in the process of active demethylation of DNA [6]. Histone proteins, which form the core of the nucleosome, also significantly alter gene expression through interactions with DNA [7]. Histones can undergo multiple post-translational modifications, including methylation (di- and tri-), acetylation, and ubiquitination, which can alter the accessibility of DNA and chromatin density [7]. The prediction of transcriptional activation vs suppression in response to histone modifications is dependent on the type and location of modification [8]. 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 [9,10]. Non-coding RNAs (RNA molecules that do not encode for a protein, for example, microRNAs, piRNAs

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[piwi-interacting RNAs], lncRNAs [long non-coding RNAs]), play a critical role in gene regulation through inhibition of translation and interplay with DNA methylation and chromatin [11,12]. Importantly, there is crosstalk between these epigenetic mechanisms that contributes to dynamic yet potentially stable levels of transcriptional activity [13,14].

Experiences across the lifespan can induce modifications to the epigenome [15]. 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 [16]. Within mammals, the experience of offspring during the earliest periods of development are largely shaped by interactions with parents, with the broader characteristics of the social and physical environment influencing developing organisms via parent-offspring interactions [17]. Maternal effects on offspring development occurring prenatally or postnatally are well established [18,19]. In addition to paternal effects occurring among biparental species, there is evidence for paternal pre-conception influences among species where there is no postnatal contact between fathers and offspring [20]. These parental effects are associated with epigenetic variation and in some cases can be observed to influence descendants across multiple generations [20]. In this review, we will discuss evidence of maternal and paternal epigenetic influence on offspring development (intergenerational effects), with particular focus on studies indicating an association between parental experiences/environmental exposures and epigenetic alterations in offspring (Fig. 24.1). 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. These epigenetic effects may be a mechanism of adaptive plasticity that confers the ability of an organism to be prepared for the challenges of current and future environments [21].

EPIGENETIC CONSEQUENCES OF PRENATAL MATERNAL EXPOSURES

A defining feature of mammalian development is the in utero gestation of offspring. During this gestational period, the growth and development of offspring is dependent on maternal physiology and sensitive to a wide range of maternal environmental exposures. In this section, we will highlight studies that focus on maternal nutrition, toxicological exposures, and stress during pregnancy and the epigenetic and phenotypic effects in offspring.

The quality of the maternal nutritional environment during pregnancy can have a significant impact on the

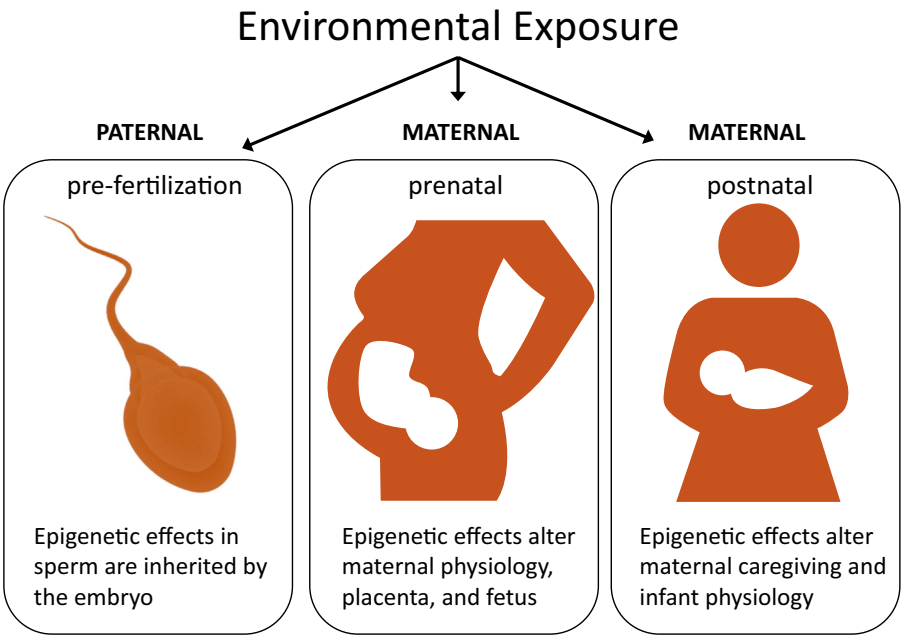

FIGURE 24.1 A summary figure of the parental targets of environmental exposure at different stages in reproduction/development and the nature of the epigenetic effects in each stage that shape offspring outcomes.

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 [22,23]. 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 [24]. 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 be implicated in growth, metabolic, and neurodevelopmental outcomes [25]. Genome-wide analyses of DNA methylation in adults who were exposed gestationally to famine indicate that variation in DNA methylation within several genomic regions is a mediator between famine exposure and specific metabolic outcomes, including increased body mass index (BMI), lipid metabolism and triglyceride levels [26].

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 [27–29]. Moreover, these transcriptional and epigenetic effects could be largely reversed when gestational protein restriction is accompanied by folic acid supplementation [27,28]. 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 [27,30] and brain tissue [31] 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 [32]. 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 [33]. 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 [27,30] or supplementation (i.e., high fat diet [34]) directly within developing fetal tissues or within the placenta [35,36] 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 [34] and expression of microRNAs [37] 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 hippocampus of offspring [38]. Exposure of pregnant mice to inhaled diesel exhaust particles results in decreased DNA methylation within *PPARγ* in offspring adipose tissue [39] and increased DNA methylation within *BDNF IV* in offspring hippocampus [40]. 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 [41]. In rats, prenatal exposure to the antiandrogenic fungicide vinclozolin results in increased rates of prostate disease, kidney disease, testis abnormalities, and tumor development [42]. 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 [43,44]. 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 [45], increased hippocampal DNA methylation within *BDNF IV* [46] and the promoter region of the gene encoding estrogen receptor alpha (*ESR1*) within the cortex of juvenile offspring [47] and altered hepatic levels of histone acetylation, di-methylation and trimethylation of the carnitine palmitoyltransferase I gene (*CPT1*) in male offspring [48]. Obesity-related phenotypes are also observed in association with prenatal BPA exposure and there is evidence that BPA-induced alterations in DNA methylation within growth-promoting genes, such as insulin-like growth factor II receptor (*IGF2R*) and mesoderm-specific transcript (*MEST*) are a mediator of these effects [49,50]. Though prevention or

reduction of exposure to toxins during prenatal development may be an optimal strategy for shifting developmental outcomes, there is evidence that exposure-associated phenotypic and epigenetic effects can be altered by dietary interventions during pregnancy [51]. For example, 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 [52]. In humans, the effects of prenatal smoking on DNA methylation in newborns is reduced in association with high folate intake [53]. Other prenatal dietary supplements, such as vitamin C and B may also be able to counteract the epigenetic effects of toxin exposure and highlight the complexity of the prenatal "exposome" [51].

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. These maternal experiences may also exacerbate the effects of prenatal toxins on developmental outcomes [54]. Among infants born to mothers with elevated ratings of depression during pregnancy, there is significant differential DNA methylation within the genome [55], elevated *NR3C1* promoter DNA methylation levels [56], and decreased DNA methylation within the oxytocin receptor gene (*OXTR*) [57]. 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 exposure to maternal depression, with some overlap with epigenetic markers detected in blood [55]. While ameliorating maternal depression during pregnancy using pharmacological approaches may be necessary to reduce developmental risk in offspring, concerns regarding the developmental consequences of prenatal exposure to antidepressants have emerged [58] and there is evidence for epigenetic effects in offspring associated with use of antidepressants during pregnancy [59].

In rodents, chronic gestational stress is associated with decreased hypothalamic DNA methylation of the corticotrophin-releasing-factor (*CRF*) gene promoter [60], increased hypothalamic DNA methylation of the *NR3C1* promoter region [60], increased *DNMT1* expression in the cortex and hippocampus [61], decreased hippocampal histone acetylation [62], and modified expression of microRNAs [63]. Prenatal stress can exacerbate the epigenetic effects of other prenatal exposures, such as exposure to lead [64], and it is 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 [36,47,60,64]. These sex-specific effects extend to the placenta, where epigenetic variation has been found to be induced by stress in studies of humans [65,66] and rodents [60,67,68] 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 [69]. Reduced levels of postnatal maternal licking/grooming (LG) behavior in rats, 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* [70], glutamate decarboxylase 1 (*GAD1*) [71], and *GRM1* (encoding metabotropic glutamate receptor 1) [72] gene promoters in adult male offspring. In female rat 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 [73,74]. Cross-fostering manipulations have been used to illustrate the link between the postnatal experience of high vs. low levels of LG and these epigenetic outcomes [70]. In addition, pharmacological manipulations of histone acetylation and DNA methylation can be used to reverse the epigenetic and neurobehavioral consequences of variation in postnatal maternal LG [70,73,75]. Epigenetic effects within the brain have also been observed in rodents as a consequence of postnatal exposure to maternal separation [76], abusive caregiving [77], and communal rearing [78]. 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 [79,80]. Exposure to high versus low levels of postnatal maternal touch is associated with differential DNA methylation across the genome [81] and there is also an association between breastfeeding and offspring DNA methylation [82]. 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 [83].

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 [20]. In rodents, premating exposure of males to alcohol is associated with reduced offspring birth weight, increased mortality, and numerous cognitive and behavioral abnormalities [84–86]. Likewise, offspring of cocaine-exposed males perform poorly on tests of spatial attention/working memory and have a reduced cerebral volume [87,88]. In rats, premating paternal exposure to delta-9-tetrohydrocannabinol (THC) is associated with impaired attention in offspring [89]. 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 [90] and premating chronic paternal caloric restriction results in reduced serum leptin and altered behavior in offspring [91]. Studies across a diverse range of species [92–96], including humans [97], 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 [98]. Laboratory studies of paternal age effects in isogenic rodents also indicate that offspring of "old" fathers have reduced longevity, increased social deficits, and perform more poorly on learning and memory tasks [99–101]. 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 germ cells with consequences for postfertilization embryonic development [102].

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 non-coding RNAs) may propagate the effects of paternal experiences on development [102–104]. 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 [105,106]. In particular, alcohol exposure has been shown to decrease *DNMT* mRNA levels in the sperm cells of adult male rats [107], 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 [88], and cocaine self-administration by males is associated with increased H3 acetylation within the *BDNF* promoter [108]. 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 [106]. In the case of paternal age, overall reductions in DNA methylation are observed in the sperm of "old" (12–14 months) compared to "young" (3 months) male mice [109] 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 [110]. 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. Postnatal maternal separation in male mice is associated with increased expression of several microRNAs, downregulation of piRNAs and increased DNA methylation within the regulatory region of *MECP2* [111,112]. Chronic stress exposure in adulthood is also associated with increased expression of several microRNAs in sperm [96] 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 [113]. Thus, environmental exposures may lead to altered epigenetic marks in male gametes with both broad and gene-specific consequences [103]. 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 [111,114].

TRANSGENERATIONAL EFFECTS OF PARENTAL INFLUENCE

The stability of epigenetic modifications within an individual's own lifespan and evidence suggestive of 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 non-genomic inheritance can be maintained over multiple generations, such that in addition to the developmental effects of parental experiences on F1 generation offspring (intergenerational effects), 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 vs experience-dependent/non-germline-mediated (Fig. 24.2). Within germline-mediated transgenerational effects, environmental exposures are thought to induce epigenetic alterations within the developing gametes that persist in the germline of descendants in the absence of continued exposure with consequences for F1, F2, and F3 generations. In contrast, experience-dependent/non-germline mediated epigenetic transmission requires that an experience or environmental exposure be present in each generation to re-establish 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 [115,116].

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 [117]. Interestingly, these effects are sex-specific, with paternal grandfather nutrition predicting grandson mortality and paternal grandmother nutrition predicting granddaughter 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* [118]. 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 [119]. This diet-induced effect can also be observed in the F3 generation, but only when that generation is derived from the F1 exposed patriline [120]. In human cohort studies, paternal pre-conception consumption of betel nuts

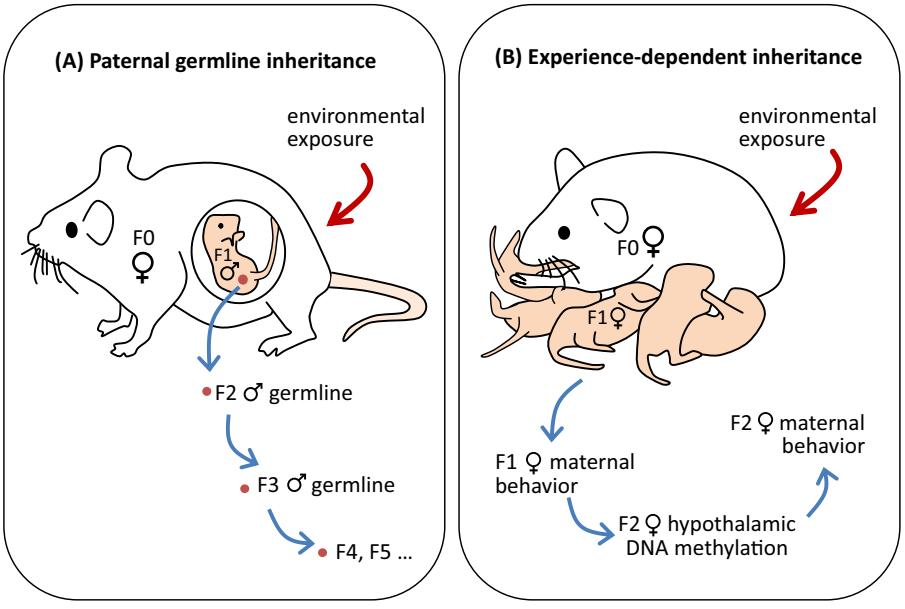

FIGURE 24.2 Illustration of the distinction between a paternal germline epigenetic inheritance (A) and an experience-dependent inheritance of an epigenetic effect (B). In an example of a paternal germline inheritance, an environmental exposure occurring during prenatal development results in an epigenetic 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 is exposed to different maternal care in infancy.

(which contain nitrosamines) leads to dose-dependent increases in offspring risk of metabolic syndrome [121] and in transgenerational studies of mice, 2–6 days of pre-conception betel nut consumption by F0 generation males is associated with increased glucose intolerance amongst F1, F2, and F3 generation offspring [122]. 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 non-exposed females [123]. 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 [43]. Prenatal 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 [124]. Interestingly, mate-choice studies suggest that females presented with F3 vinclozolin-exposed or non-exposed males show a significant partner preference for non-exposed males, indicating an additional measure of decreased reproductive success as a consequence of treatment with endocrine disruptors [125]. The persistence of these disruptions beyond the F2 generation (with the F3 generation being the first "non-exposed" 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 [115]. 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 [126]. 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 [112]. 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 [111,112]. 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 paternal germline inheritance [95]. 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 [113]. 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.

Though the stability and inheritance of epigenetic characteristics of the genome during the process of mitosis is well-established and supported by specific enzymes, such as DNMT1, the mechanisms accounting for the persistence of epigenetic effects during gametogenesis, fertilization, and postfertilization genomic reorganization are yet to be fully understood. The phenomenon of genomic imprinting establishes a pathway for the erasure and re-establishment of epigenetic marks within the genome and, in particular, within the germline [127]. However, it is unclear whether a similar process can be utilized following de novo epigenetic changes. Environmental exposures can impact the retention of histones, expression of non-coding RNAs and DNA methylation in sperm and these epigenetic changes can be observed in subsequent generations [103]. A critical question to address is the degree to which the induced epigenetic modification is directly inherited or influences the general molecular processes of epigenomic organization that occur during the pre- and postfertilization period resulting in a recapitulation of environmentally induced effects in non-exposed generations.

EXPERIENCE-DEPENDENT EPIGENETIC 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 [128] as are levels of parental bonding [129]. In rhesus and pigtail macaques, rates of postnatal maternal rejection and infant abuse are transmitted across matrilines and cross-fostering studies conducted between abusive and non-abusive macaques females indicates that the transmission of abusive behavior from mother to daughter is dependent on the experience of abuse during the postnatal period [130,131]. This matrilineal transmission is also evident in laboratory rodents. Natural variations in postnatal maternal LG observed in the F0 generation are associated with similar levels of LG in F1 and F2 generation females [132]. As such, under stable environmental conditions, offspring (F1) and grand-offspring (F2) of low-LG females display low levels of LG; whereas, offspring (F1) and grand-offspring (F2) of high-LG females display high levels of LG [132]. Similar to the multigenerational effects of abuse in macaques, cross-fostering 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 [133]. Communal postnatal 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 [134]. A similar behavioral transmission can occur when the F0 maternal behavior is altered through a genetic mutation that is not inherited by offspring [135]. 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 [136] or manipulation of the juvenile environment [132]. These environmental exposures impact maternal behavior (particularly LG) leading to a disruption of the inheritance of the predicted maternal phenotype. Since postnatal maternal LG can impact a broad range of behavioral and neurobiological outcomes, the transmission of LG maternal phenotypes can act as a vector for the transmission of F0 environmental exposures on the development of subsequent generations [137].

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 accounts for the reduced level of postpartum maternal behavior observed in these females [138]. Female offspring reared by a low-LG dam have increased DNA methylation, decreased H3K4me3, and increased H3K9me3 at the *ESR1* gene promoter [73,74]. 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 [73]. 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 offspring 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 multigenerational 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 postnatal abusive maternal care (dragging, burying, etc.) [77]. 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 transmission. 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, and involve epigenetic modification of genes within the brain regions that regulate these phenotypic outcomes.

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 non-directed, 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 [139], 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 use and which promotes storage of glucose—with adverse health consequences associated with a mismatch between the quality of the prenatal and postnatal nutritional environment [140]. Similar adaptive consequences may be relevant to the development of heightened stress 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 [141]. 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 [70,132,136]. Though this environmentally induced phenotype is associated with impaired cognitive performance under standard testing conditions [142], synaptic plasticity is enhanced in offspring of low-LG mothers when corticosterone levels are elevated [143]. 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 may play a critical role in shaping these phenotypic adaptations. The match between parental and offspring environmental conditions may also be an important predictor of whether transgenerational effects occur [21], further highlighting the adaptive role played by within and across generation plasticity that has been described

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 [144]. 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 [145]. Importantly, though there is growing support for multigenerational and transgenerational epigenetic consequences of environmental exposures, our understanding of the molecular, cellular, and behavioral pathways through which these outcomes are achieved is still evolving. These processes occur within the context of genetic variation and other inheritance systems and there are likely interactions between inheritance systems that make the prediction of individual-level outcomes challenging. 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 [108,146,147]. Thus, broadening our concept of inheritance to include both genetic and epigenetic mechanisms and the interplay between these pathways [148] 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.

SUMMARY

In this chapter, we explore the epigenetic and developmental effects of maternal and paternal environmental exposures in offspring and emerging evidence for the role of epigenetics in transmitting environmental effects across generations. Evidence for the multigenerational and transgenerational impact of the environment is described and the chapter explores the unique routes through which mothers and fathers mediate this generational transmission. We differentiate between germline and experience-dependent routes of epigenetic inheritance and discuss the role of these mechanisms of inheritance in adaptation and plasticity.

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