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Epigenetic legacy of parental experiences: Dynamic and interactive pathways to inheritance

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Abstract

The quality of the environment experienced by an individual across his or her lifespan can result in a unique developmental trajectory with consequences for adult phenotype and reproductive success. However, it is also evident that these experiences can impact the development of offspring with continued effect on subsequent generations. Epigenetic mechanisms have been proposed as a mediator of both these within- and across-generation effects, and there is increasing evidence to support the role of environmentally induced changes in DNA methylation, posttranslational histone modifications, and noncoding RNAs in predicting these outcomes. Advances in our understanding of these molecular modifications contribute to increasingly nuanced perspectives on plasticity and transmission of phenotypes across generations. A challenge that emerges from this research is in how we integrate these "new" perspectives with traditional views of development, reproduction, and inheritance. This paper will highlight evidence suggestive of an epigenetic impact of the environment on mothers, fathers, and their offspring, and illustrate the importance of considering the dynamic nature of reproduction and development and inclusive views of inheritance within the evolving field of behavioral and environmental epigenetics.

The complex nature of gene regulation provides critical insights into the process through which a highly stable genome can generate broad biological diversity (see Figure 1). In the past decade, there has been a significant shift in focus from a deterministic genetic view of development to a dynamic and interactive view in which epigenetic processes have featured prominently as an explanation for diverse developmental trajectories. This shift in perspective has been aided by increasing understanding of the role of epigenetics in gene regulation that includes both the stable silencing of genes and the activation of transcription. Epigenetic mechanisms, including DNA methylation (Jones & Taylor, 1980; Razin, 1998), posttranslational histone modifications (Jenuwein & Allis, 2001), and noncoding RNA molecules (Sato, Tsuchiya, Meltzer, & Shumizu, 2011), offer a biological explanation for the complex relationship between genotype (i.e., DNA sequence) and phenotype (i.e., the characteristics of an organism). These epigenetic mechanisms also contribute to environmentally induced biological changes and are increasingly viewed as the biological substrate on which the environment acts to exert both short- and long-term biological change.

Although the term *epigenetic* has its roots within developmental biology (Jablonka & Lamb, 2002; Waddington, 1942), *genetic* implies that these mechanisms account for the inheritance of characteristics across generations. Challenging the DNA-centric views of both phenotypic variation and inheritance is increasing evidence for environmentally induced epigenetic variation within an organism, including the germline, which may lead to the transmission of environmentally induced biological and behavioral phenotypes across generations. Based primarily in laboratory studies in animal models, the study of the transgenerational impact of nutritional, social, and toxicological experiences has revived notions of the inheritance of acquired characteristics described by Lamarck (1809; Skinner, 2015). Moreover, through use of advanced technologies within molecular biology and reproductive sciences, it has been possible to illustrate the unique pathways through which paternal versus maternal experiences can shape developmental outcomes in subsequent generations via epigenetic mechanisms. However, an important consideration within the framework of transgenerational epigenetic effects is the interplay that occurs among fathers, mothers, and offspring during reproduction. Interactive effects can only be revealed through an integrative study of parental and offspring influences that incorporates genetics, epigenetics, and the social environment.

This review will describe evidence of environmentally induced epigenetic consequences of maternal and paternal experiences, the implications of these effects for subsequent generations, and the critical importance of maternal–paternal–offspring interplay in predicting the transmission of phenotype. These studies highlight the need to integrate multiple routes of inheritance and the interactive effects of these pathways when considering developmental outcomes. This integrative view challenges traditional views of development

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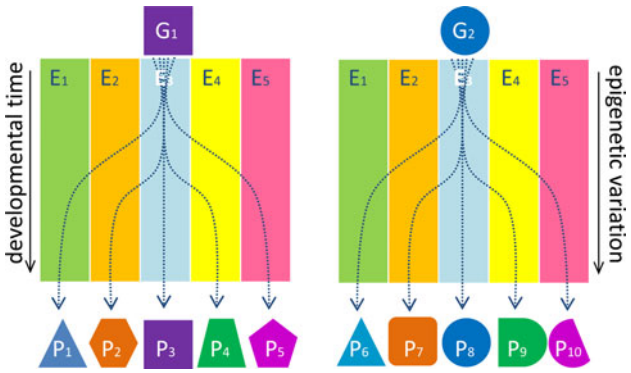

Figure 1. (Color online) Complex pathways linking genotype to phenotype. A single genotype (G_1 or G_2) has the capacity to generate multiple different phenotypes (P_1 to P_{10}) through interaction between genotype and environments (E_1 to E_5) experienced across developmental time. These interactions and the diversity of phenotypes that emerge may be the product of increasing epigenetic variation.

and places greater emphasis on the dynamic nature of development.

Environmental Epigenetics in Mothers and Offspring

The experience of mothers occurring during the periconceptual period (i.e., preconception and preimplantation), pregnancy, and postpartum can have an impact on offspring development. These experiences can have epigenetic consequences for the maternal and fetal/infant genome that shape developmental outcomes.

Periconceptual

In experiences occurring prior to conception of offspring, there is evidence for the impact of hormones and toxins on the epigenome of oocytes, which may account for disruption to genomic imprinting in offspring. Though most genes display biallelic expression, imprinted genes are characterized by monoallelic expression patterns due to epigenetic silencing of either the paternal or the maternal allele (Bartolomei & Ferguson-Smith, 2011; Keverne, 2009; see Figure 2). The maintenance of monoallelic expression of these genes is necessary to promote healthy growth and development (Biniszkiewicz et al., 2002; Wilkinson, Davies, & Isles, 2007). Superovulation procedures used within the process of in vitro fertilization (IVF), which involve maternal exposure to high doses of gonadotrophins, have been found to increase biallelic expression of imprinted genes in the placenta (Fortier, Lopes, Darricarrere, Martel, & Trasler, 2008) and increase the occurrence of epimutations (disruption to allele-specific DNA methylation patterns) in offspring tissues (de Waal et al., 2012). Superovulation is also associated with decreased genome-wide levels of DNA methylation and histone acetylation (H3K9, H3K14) within the maternal pronucleus of zygotes (Huffman, Pak, & Rivera, 2015). In addition to superovulation, other features of artificial reproductive technology, such as culture media and vitrification during cryopreservation, are associated with epigenetic disruption (Laprise, 2009) and may account for artificial reproductive technology-associated alterations in placental development (de Waal et al., 2015). Similarly, exposure of mouse oocytes and preimplantation embryos to bisphenol A (BPA), an endocrine disrupting chemical used in the manufacture of plastics (Welshons, Nagel, & vom Saal, 2006), results in reduced genome-wide DNA methylation levels within the placenta, abnormalities in placental development, and disruption to genomic imprinting in embryos (Susiarjo, Sasson, Mesaros, & Bartolomei, 2013). This early stage of development may be particularly susceptible to environmentally induced alterations in genomic imprinting, and it has been speculated that developmental abnormalities associated with periconceptual exposures are linked to these epigenetic effects (El Hajj & Haaf, 2013).

Prenatal

Maternal experiences occurring during pregnancy are associated with long-term neurodevelopmental outcomes in off-

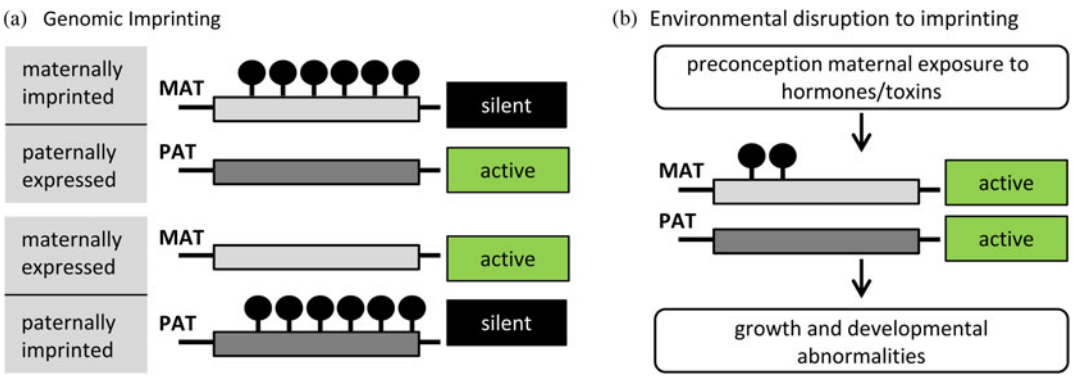

Figure 2. (Color online) Genomic imprinting and environmental disruption to imprinted genes. Imprinted genes refer to a subset of genes within the genome that display monoallelic expression patterns. a. In maternally imprinted/paternally expressed genes, the mother's gene copy is epigenetically silenced and only the father's gene copy is expressed. In paternally imprinted/maternally expressed genes, the father's gene copy is epigenetically silenced and only the mother's gene copy is expressed. b. Studies of maternal preconception/early embryonic exposure to toxins indicate a disruption to genomic imprinted in which the normally silent gene copy becomes transcriptionally active, resulting in developmental abnormality.

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spring, with implications for increased risk of depression and anxiety disorders (Davis & Sandman, 2012; Watson, Mednick, Huttunen, & Wang, 1999), and there has been increasing focus on the mechanisms (physiological and cellular/molecular) that account for these associations. Involvement of epigenetic mechanisms in these prenatal influences has been suggested by studies in both rodents and humans (Kundakovic et al., 2015; Monk, Spicer, & Champagne, 2012). In rodents, prenatal maternal exposure to BPA is associated with altered expression of DNA methyltransferases (enzymes necessary for the process of DNA methylation) within the hypothalamus of offspring and brain region-specific alterations in DNA methylation of the genes encoding estrogen receptor alpha (*Esr1*) and brain-derived neurotrophic factor (*Bdnf*; Kundakovic, Gudsnuk, et al., 2013, 2015). These BPA-associated effects are sex specific and the epigenetic impact on *Bdnf* is also observed in fetal cord blood samples in human newborns exposed to high versus low levels of BPA during gestation (Kundakovic et al., 2015). In rodents, maternal exposure to dietary manipulations during early pregnancy results in epigenetic alterations in offspring, including hypo- and hyper-DNA methylation in the brain (Sable, Randhir, Kale, Chavan-Gautam, & Joshi, 2015), altered histone acetylation, trimethylation and microRNA expression in the liver (Casas-Agustench et al., 2015; Suter et al., 2014), and altered expression of imprinted genes and DNA methyltransferase in the offspring cortex (Barski et al., 2007). The placenta also manifests epigenetic, gene expression, and functional variation associated with maternal dietary manipulations during pregnancy (Gabory et al., 2012). Fetal development is dependent on placental functioning during pregnancy, and this functioning is mediated by gene regulation and shifting placental epigenetic profiles (McMinn et al., 2006; Schroeder et al., 2013). Studies of prenatal maternal stress indicate epigenetic effects of gestational stress within the placenta with consequences for fetal development (Howerton, Morgan, Fischer, & Bale, 2013; Jensen Pena, Monk, & Champagne, 2012; Monk et al., 2016). Elevated placental DNA methylation within the gene encoding the 11-beta hydroxysteroid dehydrogenase type 2 enzyme (*Hsd11b2*), a protein involved in the inactivation of glucocorticoids, is associated with increased maternal stress in rodents and humans (Jensen Pena et al., 2012; Monk et al., 2016). Analyses of this epigenetic mark within the placenta and fetal neurodevelopmental measures indicates that elevated DNA methylation within *Hsd11b2* mediates the impact of maternal stress on impairments in offspring neurodevelopment (Monk et al., 2016; see Figure 3).

Postnatal

Gestational exposure to stress and BPA continue to influence the mother and the quality of mother–infant interactions during the postpartum period with associated epigenetic effects in offspring (Champagne & Meaney, 2006; Kundakovic, Gudsnuk, et al., 2013). In rodents, both gestational and postpartum exposure to stress results in reduced levels of pup licking–grooming (LG; Boccia & Pedersen, 2001; Ivy, Brunson, Sandman, & Baram, 2008; Moore & Morelli, 1979), a form of maternal care that is essential for physiological processes and neurodevelopment (Gubernick & Alberts, 1983; Meaney, 2001). Disruption to the quality of postpartum mother–infant interactions in rodents through prolonged maternal separation or disruption to nesting materials results in reduced maternal LG, decreased hypothalamic DNA methylation within the regulatory region of the vasopressin gene (Murgatroyd et al., 2009), increased hippocampal DNA methylation within the gene encoding the glucocorticoid receptor (*Nr3c1*; Kember et al., 2012; Kundakovic, Lim, Gudsnuk, & Champagne, 2013), decreased hippocampal levels of histone acetylation within the *Bdnf* gene promoter (Seo et al., 2016), increased cortical DNA methylation of *Bdnf* gene promoter (Roth, Lubin, Funk, & Sweatt, 2009), and modification of the expression of enzymes involved in histone modifica-

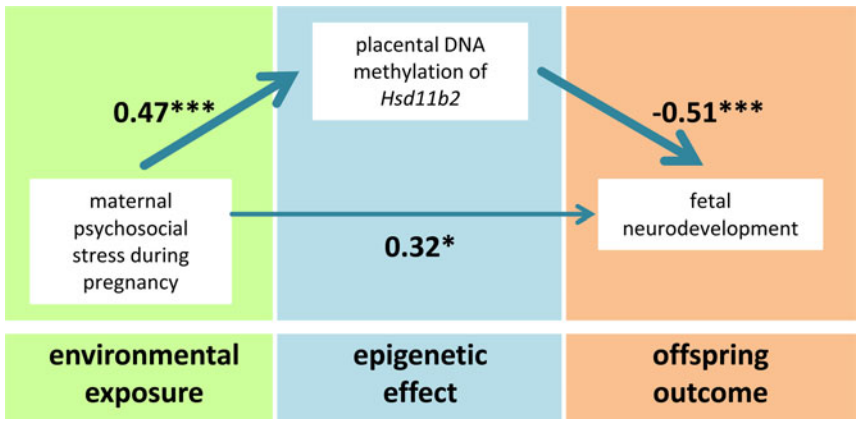

Figure 3. (Color online) Role of placental epigenetic changes in mediating the relationship between maternal stress during pregnancy and fetal neurodevelopment. Analyses of DNA methylation patterns within the placenta in women reporting variation in perceived psychosocial stress during pregnancy indicate that high perceived stress is a significant predictor of elevated placental DNA methylation of the 11-beta hydroxysteroid dehydrogenase type 2 (*Hsd11b2*) gene and that this epigenetic effect predicts poorer fetal neurodevelopment (Monk et al., 2016).

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tion within the cortex (Pusalkar et al., 2016). Though alterations in the quality of mother–infant interactions in response to postpartum adversity are only speculated to be the causal route through which these exposures exert epigenetic consequences for offspring, this association is supported by studies examining the epigenetic impact of naturally occurring variations in maternal LG in rodents. Exposure to low versus high levels of postnatal LG has been demonstrated to result in broad alterations in DNA methylation, histone acetylation (H3K9), and gene expression (McGowan et al., 2011; Weaver, Meaney, & Szyf, 2006). Epigenetic analyses of specific gene targets within the hippocampus of male offspring indicates that the experience of low versus high levels of LG during postnatal development results in increased DNA methylation and altered histone marks within *Nr3c1* and the genes encoding glutamate decarboxylase (*Gad1*) and Type I metabotropic glutamate receptor (*Grm1*; Bagot et al., 2012; Zhang et al., 2010). Within female offspring, hypothalamic expression of estrogen receptors is decreased in response to low postnatal maternal LG and associated with increased DNA methylation and altered histone marks within the *Esr1* gene. The role of mothers in shaping these outcomes is highlighted by cross-fostering studies, which indicate that it is the maternal phenotype of the postpartum rearing mother rather than the phenotype of the biological mother that is predictive of offspring outcomes (Champagne et al., 2006; Pena, Neugut, & Champagne, 2013; Weaver et al., 2004).

Environmental Epigenetics in Fathers and Offspring

In mammals, the developmental influence of mothers has been the primary focus of studies examining neurobehavioral and epigenetic outcomes in offspring. This bias is associated with the presumed role of mothers versus fathers in parental investment in offspring and the reliance of lab-based studies on species in which there is little or no involvement by fathers in reproduction postcopulation. Paternal postnatal care of offspring is only observed in 5%–10% of mammals (Woodroffe & Vincent, 1994), and among laboratory rodents, males will frequently display avoidance or infanticide toward pups (Svare, Kinsley, Mann, & Broida, 1984), which has further limited the broad study of paternal influences. However, there are mammalian species used in laboratory studies where biparental care is observed and associated with growth and neurodevelopmental outcomes in offspring (for review, see Braun & Champagne, 2014). Moreover, in species where exclusive paternal care is observed, the quality of the care provided can have epigenetic consequences. For example, in three-spined sticklebacks, father caretaking of offspring can reduce anxiety, buffer offspring from the presence of threat in the environment, increase fitness, and results in increased levels of DNA methyltransferase levels within the brain of offspring (McGhee & Bell, 2014). It is likely that the epigenetic consequences of postnatal paternal care will be increasingly evident in studies of species displaying exclusive paternal or biparental care and illustrate significant parallels to studies of maternal care and its developmental influence.

Although the postnatal period has not been the focus of studies of environmentally induced epigenetic variation in fathers, studies of preconceptual experiences have revealed the epigenetic sensitivity of sperm and the lasting consequences of fathers' experiences during this period for developmental outcomes in offspring. Exposure of adult male mice to the herbicide atrazine results in reductions in testosterone and sperm counts and increased histone trimethylation within genes involved in mitochondrial function and steroid metabolism (Gely-Pernot et al., 2015). Exposure to chronic stress in male mice is associated with increased microRNA expression in sperm (Rodgers, Morgan, Leu, & Bale, 2015). Among males fed a high-fat diet, altered patterns of DNA methylation and small noncoding RNA expression are observed in sperm, and these same patterns are also observed in the sperm of offspring (de Castro Barbosa et al., 2016). Epigenetic dysregulation in sperm is increasingly implicated as the primary mechanism through which the transmission of paternal effects across generations is mediated (Rodgers et al., 2015; Zamudio, Chong, & O'Bryan, 2008).

Multigenerational and Transgenerational Effects of Mothers and Fathers

The persistence across generations of the effects of parental experiences has been demonstrated in humans in studies of famine and trauma exposure (Kaati, Bygren, Pembrey, & Sjostrom, 2007; Yehuda et al., 2015) and may contribute to the observed familial transmission of psychopathology (Oquendo et al., 2013). However, evidence for this transmission and the mediating role of epigenetic mechanisms has been primarily derived from laboratory studies in animal models. These studies have typically focused on transmission via social interactions or transmission via the germline (see Figure 4).

Social transmission

The quality of early life experiences can have lasting consequences for adult behavior, and there is evidence to support the role of epigenetic modifications in these developmental effects (Weaver et al., 2004). In particular, these early life experiences can impact the quality of parenting, which has implications for the developmental experiences of the next generation of offspring. For example, variation in postpartum maternal LG in rodents alters gene expression within the hypothalamus of the developing brain of offspring, exerting an epigenetic impact on *Esr1* within the medial preoptic area (Champagne et al., 2006; Champagne, Weaver, Diorio, Sharma, & Meaney, 2006). Expression of *Esr1* within the medial preoptic ares is critically involved in estrogen sensitivity and adult maternal behavior (Ogawa et al., 1998; Ribeiro et al., 2012). Developmental manipulation of *Esr1* expression can also alter developing dopaminergic circuits involved in

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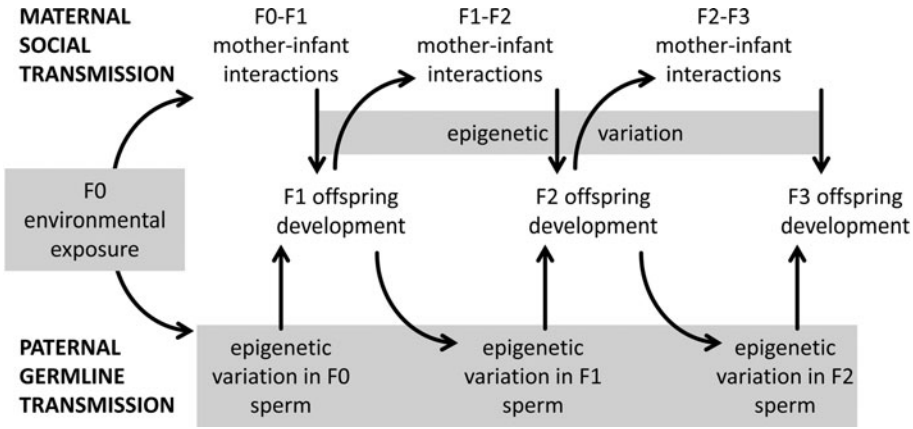

Figure 4. Complex mechanisms characteristic of maternal social versus paternal germline inheritance of environmentally induced phenotypes. An environmental exposure occurring in the parent (F0 generation) can have effects that persist across generations (e.g., to the grand-offspring [F3 generation]) via social transmission or through germline epigenetic inheritance. In maternal social transmission, the F0 environmental exposure influences the quality of mother–infant interactions (occurring prenatally and/or postnatally) between the F0 parent and their offspring (F1 generation). Through epigenetic variation, these interactions have developmental consequences for F1 offspring, resulting in variation in the quality of mother–infant interactions occurring between F1 parents and their offspring (F2 generation). This cycle then repeats to impact F3 development. In contrast, a paternal germline epigenetic inheritance involves an environmentally induced epigenetic change in F0 sperm that is recapitulated in the F1, F2, and F3 generations, altering development in each of these generations.

motivation and reward salience, which play a role in reproductive behavior more broadly (Numan, 2007; Pena & Champagne, 2015; Stolzenberg & Numan, 2011). These epigenetic and neurobiological effects of postnatal maternal care thus shape the maternal behavior of subsequent generations leading to a continuity of the quality of mother–infant interactions across generations. Due to the plasticity of maternal behavior, the life experiences of a female, such as stress or social support, can come to shape the future maternal behavior of offspring and grandoffspring (Champagne & Meaney, 2006, 2007; Curley, Davidson, Bateson, & Champagne, 2009). However, unlike a genetic route of inheritance, this transmission is experience dependent, such that variation in maternal care must be experienced during postnatal development for phenotypes to be recapitulated in the next generation (see Figure 4). This mechanism of transmission likely accounts for the observed intergenerational continuity of parental behavior observed in humans and primates (Benoit & Parker, 1994; Berman, 1990; Miller, Kramer, Warner, Wickramaratne, & Weissman, 1997). Though attributed primarily to mothers, the social transmission of parenting has also been observed via fathers in biparental species (Gleason & Marler, 2013) and thus related to the role of the parent in postnatal caregiving, rather than the sex of the parent.

Germline transmission

The influence of father's experience on offspring can be observed even under conditions when there is no direct paternal–offspring contact during the postnatal period (Anway & Skinner, 2006; Franklin et al., 2010; Gapp et al., 2014; Rodgers et al., 2015). This phenomenon is increasingly being attributed to the epigenetic alterations present within the sperm following paternal environmental exposures. These paternal epigenetic effects may also be recapitulated in subsequent generations, leading to a transgenerational inheritance of environmentally induced effects (see Figure 4). For example, maternal exposure during pregnancy to the pesticide vinclozolin or to a high-fat diet induces altered health and metabolism in subsequent generations via the patriline (descendants of prenatally exposed males; Anway, Cupp, Uzumcu, & Skinner, 2005; Anway & Skinner, 2006; Dunn & Bale, 2009, 2011). Altered DNA methylation levels are observed in the sperm of exposed males (F1 generation), as well as their offspring (F2 generation) and grandoffspring (F3 generation; Anway & Skinner, 2006). Transgenerational effects have also been observed involving altered histone modifications (Vassoler, White, Schmidt, Sadri-Vakili, & Pierce, 2013) and micro-RNA expression (Rodgers et al., 2015). The mediating role of sperm in this transmission is increasingly being demonstrated by studies involving IVF. For example, if males (F0 generation) experience an electric shock paired with a specific odorant, the F1 and F2 generation offspring of those males display sensitivity to that odorant and accompanying neuroanatomical changes within the olfactory system (Dias & Ressler, 2014). This effect is also observed when F1 generation offspring are generated with sperm of an exposed male using IVF. Although IVF can result in a general disruption to epigenetic outcomes (Laprise, 2009), these findings suggest that biological consequences of a parental experience can be transmitted via germ cells. In contrast to social transmission, these germline epigenetic effects do not appear to rely on a reexposure to the environmental event in order to be inherited. Rather, the epigenetic variation is "copied" much in the same way that DNA is copied when cells replicate within the developing organism.

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Interplay Between Mothers and Fathers in Shaping Development

Though the study of maternal and paternal influences on development has typically considered these influences separately and as independent predictors of neurobiological and behavioral outcomes, reproduction necessitates the union of mothers and fathers. Mate attractiveness has been found to directly influence reproductive investment in offspring with developmental consequences for offspring (Harris & Uller, 2009). For example, if male songbirds are made more attractive artificially (by placing a red ring around their legs), their female mates will alter investment of resources at the time of egg laying (Arnold et al., 2016). Food restriction of juvenile male birds can reduce attractiveness via effects on plumage coloration, suggesting that the environmental exposures of a male can influence mother–father interplay during reproduction (Naguib & Nemitz, 2007). Similarly, in laboratory mice, chronic social stress of males can result in decreased maternal care, particularly nursing and LG, of offspring sired by exposed males (Mashoodh, Franks, Curley, & Champagne, 2012). The phenomenon of differential allocation (Burley, 1988), which is variation in reproductive effort directed at offspring development as a function of mate attractiveness, may have divergent consequences for mating and offspring development dependent on whether male or female attractiveness has been altered (Limbourg, Mateman, & Lessells, 2013). This observation suggests that male versus female environmental exposures that impact health, behavior, and overall attractiveness may result in considerable phenotypic diversity in offspring due to complex interactions occurring at the time of mating. These mating-associated effects may also be attenuated or exacerbated by postnatal mother–father interactions. Within biparental species, fathers have been demonstrated to directly increase mother–infant interactions by physically placing mothers in contact with offspring (Libhaber & Eilam, 2002). In mice, the phenomenon of pairmate-dependent paternal behavior has also been observed, whereby males that normally would not contribute to postnatal care of offspring are stimulated to do so following sensory signals from mothers (Liang et al., 2014; Liu et al., 2013). Thus, bidirectional influences occurring between mothers and fathers and various stages of reproduction will be critical in shaping the early developmental experiences of offspring.

Parental interplay may be particularly important to consider in studies elucidating the transmission of the effects of paternal experiences across generations. Though it has been assumed that in nonbiparental species, where fathers have no postnatal interactions with offspring, the appearance of phenotypes in offspring that are predicted by father's experiences is evidence of a germline epigenetic transmission, the occurrence of mother–father interplay at mating challenges this assumption. Studies examining the transmission of paternal stress and anxiety-like behavior to offspring offer a suggestion of this interplay. Among males that experience chronic social stress, there is increased occurrence of anxiety-like behavior and depressive-like behavior in male offspring (Dietz et al., 2011). However, when IVF is used to generate offspring, these phenotypes are not completely transmitted to offspring, suggesting that mating associated in utero or postnatal maternal influences are necessary for the recapitulation of some paternally associated phenotypes. Studies of inbred (genetically identical) laboratory mice suggest that paternal locomotor activity levels and frequency of postnatal maternal care are predictive of locomotor activity levels in female offspring (Alter et al., 2009). Though postnatal maternal behavior was not found to mediate the paternal influence on female offspring, controlling for the duration of mating did reveal an influence of fathers on sons' behavior, indicating a moderating influence of mothers. Further, studies of the transgenerational effects of maternal separation in males suggest that phenotypic variation in offspring can be attributed to variation in postpartum maternal behavior (Schmauss, Lee-McDermott, & Medina, 2014). This transmission mechanism allows for effective intervention in propagating paternal-associated phenotypes through targeting of mothers and the quality of postnatal mother–infant interactions.

Inheritance of Acquired Characteristics With the Era of Epigenetics

Increasing evidence of transgenerational effects of parental experiences, particularly those implicating germline mechanisms, has encouraged a revival of Lamarckian notions of the inheritance of acquired characteristics (Skinner, 2015). In considering this revival, it is critical to revisit the fundamental components of Lamarck's theory of evolution (Lamarck, 1809). First, Lamarck posited that the "habits of life," referring to the behaviors needed to thrive and reproduce, result in altered developmental trajectories leading to altered characteristics of an organism. This notion captures the phenomenon of a dynamic developmental process that is responsive to the quality of the environment. Second, the more historically controversial Lamarckian notion was regarding the inheritance of these phenotypic changes. Lamarck suggested that when the environmental exposures that are driving the habits of life are sustained over time and repeated across several generations, the phenotypes that have emerged will be passed to descendants and preserved by heritability. The inheritance of acquired characteristics clashes with a DNA-centric notion of inheritance. However, within an expanded notion of inheritance that encompasses genetics, epigenetics, parental effects, and social/cultural transmission (Danchin et al., 2011), the idea that environmentally induced traits can be propagated across generations becomes a reasonable and highly likely scenario.

Though studies of the influence and transmission of parental experienced have typically examined exclusive maternal versus exclusive paternal exposures, Lamarck postulated the importance of phenotypes in both mothers and fathers in the inheritance of acquired characteristics. In *Philosophie Zoologique* (1809), Lamarck states:

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. . . in reproductive unions the crossings between the individuals which have different qualities or forms are necessarily opposed to the continuous propagation of these qualities and these forms. We see that in man, who is exposed to so many diverse circumstances which exert an influence on him, the qualities or the accidental defects which he has been in the way of acquiring, are thus prevented from being preserved and propagated by generation. If, when some particular features of form or any defects are acquired, two individuals under this condition should always pair, they would reproduce the same features, and the successive generations being confined to such unions, a special and distinct race would then be formed. But perpetual unions between individuals which do not have the same peculiarities of form would cause all the characteristics acquired by special circumstances to disappear.

Thus, in Lamarck's notion of the inheritance of acquired characteristics, the propagation of phenotypes across generations will be modulated by the degree to which these characteristics are manifested in both mothers and fathers. However, this is a phenomenon that is relatively unexplored within current studies of transgenerational epigenetic effects. Moreover, failure to account for this biparental contribution to the transmission of acquired characteristics may account for the variation and inconsistencies in phenotypic expression in offspring frequently observed in studies of parental epigenetic influence. These inconsistencies may also be contributed to by the mating paradigm frequently used in laboratory animal studies. Despite the acknowledged importance of sexual selection within mating systems and the emergence of phenotypic variation (West-Eberhard, 2014), reproductive pairings within the lab are by design and not a matter of choice. Among descendants within a paternally vinclozolin-exposed lineage, females show a preference for mates from a nonexposed lineage (Crews et al., 2007). The inclusion of mate choice within paradigms examining the transmission of epigenetic variation across generations may provide insight into the nuances of inheritance systems and their interplay.

Dynamic Developmental Legacies

Plasticity is a fundamental characteristic of development and central to the origins of epigenetics as a field of study. Expanded notions of inheritance and the dynamic process of gene regulation have contributed to the shift from a deterministic and DNA-centric view of development, in which phenotypes are programmed exclusively by genes, to a view of phenotypes as emerging through complex interactions between genes and environmental experiences in which there is bidirectional interplay among DNA, cells, the organism, and their environment (Laland et al., 2015; see Figure 5). Within this framework, it is important to view offspring as active participants in the developmental process. Studies in humans dissociating the effects of offspring genotype from the effects of variation in maternal in utero environment suggest that genotype of offspring can evoke differences in the quality of postnatal maternal care (Harold et al., 2013). During pregnancy, hormonal fluctuations in mothers can be induced through the interactions between fetal cells within the placenta and the maternal circulatory system, resulting in increased respiration, food intake, and glucose availability to facilitate offspring growth (Haig, 1993). Studies in rodents have identified particular sensory signals (e.g., acoustic and temperature) that can trigger the onset of postpartum maternal behavior (Stern, 1997). Though these examples of offspring-induced nurturance have typically been attributed to offspring genetic characteristics, environmentally induced epi-

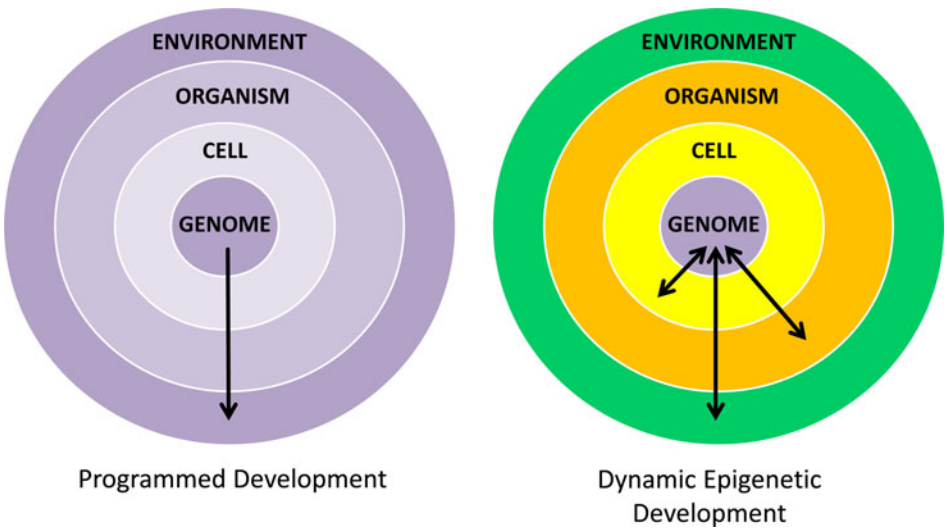

Figure 5. (Color online) Contrasting the framework of programmed versus dynamic epigenetic development. Traditional views of development view genes as deterministic of developmental outcomes through a unidirectional influence on the cells, organism, and the environments in which they inhabit. In contract, epigenetic development is characterized by bidirectional and dynamic interplay among the genome, cell, organism, and their environment. Adapted from "The Extended Evolutionary Synthesis: Its Structure, Assumptions and Predictions," by K. N. Laland, T. Uller, M. W. Feldman, K. Sterelny, G. B. Muller, A. Moczek, et al., 2015, *Proceedings of the Royal Society B: Biological Sciences, 282*, 20151019. Copyright 2015 by The Royal Society Publishing. Adapted with permission.

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genetic variation may also be capable of influencing mothers. Paternally expressed genes, genes in which there is monoallelic expression of the paternal gene copy (see Figure 2), are highly expressed in the placenta (Kumar, Leverence, Bick, & Sampath, 2012), are critical to placental function (Himes, Koppes, & Chaillet, 2013; Reik et al., 2003), and can also influence the quality of postnatal maternal behavior (Isles & Holland, 2005). Thus, epigenetic dysregulation of these genes through parental environmental exposures has the potential to disrupt mother–offspring interactions occurring prenatally and postnatally. Though disentangling the interactive effects of mothers, fathers, and offspring on development and the transmission of phenotypes poses a challenge both theoretically and methodologically, understanding of these interactions will be essential to continued advancement of knowledge regarding the role of epigenetics in development and the emergence of psychopathology.

Conclusions

Parental experiences can have a lasting impact on developmental outcomes in offspring and epigenetic variation induced by the environment provides a mechanistic link between parental exposures and offspring phenotypes. Evidence for the transmission of these phenotypes across generations has revived concepts within Lamarck's theory of the inheritance of acquired characteristics and generated a more integrative view of the concept of inheritance. These changing views have implications for the way in which development is conceptualized. Though genes play a critical and foundational role in the developmental process, the capacity of genes to be altered in their expression through the experiences of an organism argue that development is not programmed by genes: development is constructed through the bidirectional interactions between an organism and the environment (see Figure 5). Moreover, development occurs within the context of parental experiences that have an epigenetic legacy. Though challenges remain within the study of this dynamic epigenetic development, particularly regarding the reproductive interplay among mothers, fathers, and offspring, the complexity of this framework provides a more nuanced starting point for the study of developmental trajectories leading to both resilience and psychiatric risk.

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