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Interplay between paternal germline and maternal effects in shaping development: The overlooked importance of behavioural ecology

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Abstract

1. Environmental conditions can have a lasting epigenetic impact on development, and there is increasing evidence that these effects can be transmitted across generations. Evidence for parental transmission of epigenetic variation to offspring has been primarily focused on paternal epigenetic influences induced by a male's experience of nutritional, social and toxicological exposures.
2. There is an assumption in the literature that paternal influence on offspring in non-biparental species is mediated exclusively through epigenetic transmission via the germline. However, integration of concepts from behavioural ecology into the study of parental transmission of environmental effects reveals the importance of mating tactics and maternal–paternal interplay in shaping resource allocation towards offspring in considering the mechanism(s) of epigenetic transmission.
3. This paper describes the current state of knowledge regarding paternal epigenetic germline effects, the interplay between maternal and paternal influences and the importance of considering the complex nature of reproduction when predicting the transmission of phenotype across generations. Further, this paper highlights how incorporating concepts from behavioural ecology into the study of epigenetic transmission can refine predictions of phenotypes that emerge and create a more integrated notion of development and inheritance.
4. It is proposed that theoretical and methodological approaches that consider the impact of reproductive context, which include mating dynamics, fertility, variation in parental life history and assessment of maternal effects, could improve the predictions made within studies of paternal epigenetic effects on offspring development.

KEYWORDS

epigenetic transmission, fertility, intergenerational, mate choice, maternal, paternal, reproductive context, sperm

1 | INTRODUCTION

The plasticity of epigenetic modifications such as DNA methylation, post-translational histone modifications and expression of non-coding RNAs is increasingly recognized as a mechanism through which environments act to shape phenotypic outcomes. Despite historic assumptions that these gene regulatory pathways are highly stable and immutable, there is now an expansive literature

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describing the impact of a broad range of environmental exposures on epigenetic/epigenomic variation and the consequences of this variation for growth, physiology, neurodevelopment and behaviour. Though life span malleability of the epigenome has been observed, the persistence of early life-induced epigenetic changes into adulthood is a consistent finding within the study of behavioural and environmental epigenetics and illustrates the complementary properties of stability and plasticity that characterize epigenetic modifications (Ecker, Pancaldi, Valencia, Beck, & Paul, 2018).

Beyond the acquisition of epigenetic variation within the life span of an organism, there has been increasing focus on the role that epigenetic plasticity plays in the transmission of environmentally induced phenotypes from one generation to the next. The phenomenon of an intergenerational or multigenerational impact of environmental exposures has been observed across species such that the experience of parents may shape the development and phenotype of offspring, grand-offspring and their descendants. These phenotypic outcomes are also associated with the presence of epigenetic variation in offspring and their descendants. While it has been established that transmission of these environmental effects down the matriline involves behavioural and physiological pathways through which the experiences of mothers can shape the physical and social context of offspring development (Champagne, 2008), the mechanisms through which patrilineal transmission occurs has been more elusive. In species where there is significant involvement of fathers in the nurturing of offspring, it is possible for paternal experiences to impact offspring development through similar behavioural and physiological pathways to mothers (Gleason & Marler, 2013). However, paternal intergenerational and multigenerational effects have also been observed under conditions where paternal contact with offspring is limited or absent, suggesting that males may have alternative strategies for shifting phenotypic outcomes in their descendants (Curley, Mashoodh, & Champagne, 2011). It has been proposed that germline transmission of environmentally induced epigenetic variation accounts for these paternal effects, and there is increasing evidence from laboratory rodents supporting a germline transmission hypothesis (see Miska & Ferguson-Smith, 2016; Soubry, Hoyo, Jirtle, & Murphy, 2014).

The prospect of germline epigenetic transmission and of paternal transgenerational effects, whereby an environmental exposure in one generation becomes propagated across generations in the absence of any additional environmental exposure (Skinner, 2008), has led to increased speculation regarding the role of Lamarckian inheritance in phenotypic variation (Jablonka & Lamb, 2015). However, exploration of paternal epigenetic transmission may require careful integration with our understanding of reproductive biology and behaviour, ecological determinants of parenting and developmental trajectories in offspring and the interactive nature of maternal and paternal effects. To highlight this evolving area of research and advocate for a multidisciplinary framework when examining the mechanisms of paternal effects, this paper will describe the current state of knowledge regarding paternal epigenetic effects, the interplay between maternal and paternal influences and the importance of considering the complex nature of reproduction when predicting the transmission of phenotype across generations. The field of behavioural ecology has significant potential to enhance the predictions generated from ongoing research on paternal epigenetic effects and give context to the molecular insights emerging within this research.

2 | PATERNAL INTERGENERATIONAL TRANSMISSION OF ENVIRONMENTAL EFFECTS

The phenomenon of male environmental exposures being predictive of offspring phenotypes has been observed across species and taxa. In plants such as the *Campanula americana*, paternal exposure to high versus low levels of light increases pollen production in the parental generation and seed mass in the offspring generation (Etterson & Galloway, 2002). In the migratory locust, *Locusta migratoria*, paternal crowd rearing is predictive of a 10% increased egg weight (Chen et al., 2015). In three-spined sticklebacks (*Gasterosteus aculeatus*), paternal exposure to signals of predation risk is predictive of reduced offspring condition (smaller size and reduced activity levels; Stein & Bell, 2014). Increased emotionality and elevated plasma cortisol are observed in the offspring of nursery-reared male rhesus macaques (*Macaca mulatta*; Kinnally & Capitanio, 2015). In laboratory mice (*Mus musculus*), chronic wheel-running exposure in males is associated with offspring sensitivity to high-fat diet and altered expression of metabolic genes (Murashov et al., 2015). In humans, paternal smoking in adolescence is associated with increased risk of asthma in offspring (Accordini et al., 2018) and prepubertal age at onset of smoking in fathers is associated with elevated body fat in male offspring (Northstone, Golding, Davey Smith, Miller, & Pembrey, 2014). Overall, these studies highlight the broad range of environmental conditions that can result in a transmission from father to offspring of phenotypic variation. However, given the diverse approaches to mating, reproduction and offspring investment exhibited across these species, the mechanism(s) through which this occurs is also likely to be diverse. A focus on mammalian paternal germline effects will characterize the sections to follow—though there may be significant overlap in the effects described in mammals and the multigenerational potential of paternal influences in non-mammalian species.

3 | PATERNAL EPIGENETIC EFFECTS IN OFFSPRING

The phenotypic variation observed in offspring as a consequence of paternal environmental exposure extends to epigenetic variation in a broad range of tissues. These studies focus on environmentally induced epigenetic changes (primarily DNA methylation levels) that are occurring in genes that function within mechanistic pathways relevant to the phenotypes that are modified by exposure.

3.1 | Nutritional effects

Paternal nutrition prior to mating is predictive of altered DNA methylation, histone modifications and non-coding RNA expression in offspring. In rats (*Rattus norvegicus domesticus*), female offspring born to males fed a high-fat diet have DNA methylation changes in the interleukin-13 receptor alpha 2 (*Il13rα2*) gene in the pancreas (Ng et al., 2010). High-fat diet-induced obesity in male mice prior to mating is also associated with decreased expression of pancreatic microRNAs in male offspring (McPherson, Lane, Sandeman, Owens, & Fullston, 2017). In humans, paternal obesity is associated with reduced DNA methylation within imprinted genes, including insulin-like growth factor 2 (*IGF2*), mesoderm-specific transcript (*MEST*) and paternally expressed gene 3 (*PEG3*), in umbilical cord blood leucocytes of newborns (Soubry et al., 2015, 2013). In mice, offspring of males that are fed a low-protein diet during the post-weaning period have altered DNA methylation within the peroxisome proliferator-activated receptor alpha (*Pparα*) gene in hepatic tissue (Carone et al., 2010). In Agouti mice, prenatal exposure to a high methyl donor diet has been demonstrated to impact DNA methylation resulting in dramatic phenotypic changes (Morgan, Sutherland, Martin, & Whitelaw, 1999) and these epigenetic effects can also be observed in the offspring of male mice placed on a high methyl donor diet prior to mating (Ryan et al., 2018). Thus, pre-mating male diet can induce epigenetic changes in tissues and gene targets that shape metabolic outcomes in offspring (also see Dunford & Sangster, 2017).

3.2 | Toxicological effects

Direct exposure to toxins and drugs during development can have widespread epigenetic consequences. These effects can also be observed in offspring of exposed fathers. DNA methylation *Peg3* is increased in the cerebral cortex of offspring of alcohol-exposed male mice (Liang et al., 2014). Pre-mating cocaine exposure in male rats is associated with elevated histone acetylation within the brain-derived neurotrophic (*Bdnf*) gene promoter in the prefrontal cortex of their offspring (Vassoler, White, Schmidt, Sadri-Vakili, & Pierce, 2013). Male rats exposed *in utero* to the endocrine-disrupting chemical bisphenol A (BPA) sire offspring with hypermethylation within the *Igf2* gene in pancreatic tissue (Mao et al., 2015). Male exposure to the polycyclic aromatic hydrocarbon benzo[a]pyrene is associated with both up- and down-regulation of microRNAs in the developing embryos generated from exposed males (Brevik, Lindeman, Brunborg, & Duale, 2012). These studies suggest broad epigenetic consequences of paternal exposure to toxins that can generate multi-system effects of toxins on health and development in offspring.

3.3 | Stress exposure

Chronic exposure to stress—particularly unpredictable stress—can compromise health and well-being resulting in maladaptive phenotypes such as anxiety, impaired social behaviour and decreased cognitive ability (McEwen, 1998). These phenotypes and associated epigenetic changes can also be observed in the offspring of stressed fathers, with stress defined broadly as including social, physical and hormonal exposures. Exposure of male rats to chronic forced swim stress is associated with increased DNA methylation of the glucocorticoid receptor gene (*Nr3c1*) in offspring hippocampus (Niknazar et al., 2017). In humans, a similar increase in *NR3C1* DNA methylation is observed in blood samples from offspring of a trauma-exposed father, though only in cases where the mother was not trauma-exposed (Yehuda et al., 2014). The offspring of male mice that experience post-natal maternal separation are observed to have increased DNA methylation of loci within the methyl-CpG-binding protein 2 (*Mecp2*) and cannabinoid receptor type 1 (*Cb1*) genes in cortical tissue (Franklin et al., 2010). Paternal exposure to stress during *in utero* development has been found to reduce the expression of several microRNAs in the neocortex of male offspring (Morgan & Bale, 2011). These studies suggest that paternal stress impacts epigenetic variation in genes that shape stress reactivity in offspring and that these effects are likely to be sex-specific.

4 | PATERNAL TRANSGENERATIONAL TRANSMISSION OF ENVIRONMENTAL EFFECTS

The intergenerational phenotypic and epigenetic consequences of paternal experiences are a starting point for thinking about the potential of a germline transmission of paternal effects. A complementary strand of evidence to support a paternal germline hypothesis comes from work examining the multigenerational effects of paternal exposures suggestive of a transgenerational transmission. A critical methodological and theoretical issue within the context of this research is in distinguishing between an 'exposed' and 'non-exposed' generation of progeny (see Figure 1). For example, if a pregnant mammalian female is exposed to stress or a toxin, the developing embryo/foetus are exposed concurrent with the mother as are the primordial germ cells (PGCs) that will contribute to the creation of the subsequent generation of offspring. Using the typical nomenclature for designating generations, this prenatal exposure example would include an F0-exposed mother, F1-exposed oocyte/foetus and F2-exposed PGCs. The F3 generation would constitute the first generation not exposed to the stress or toxin, and the presence of a phenotype in this generation associated with F0 exposure is assumed evidence of a transgenerational transmission (Skinner, 2008). However, the generation number per se is not the defining feature of a transgenerational effect. For paternal exposures occurring in pre-mating males (F0), the F2 generation would be the first generation to not have direct exposure to the environmental manipulation. An issue that is typically not addressed when examining the persistence of parental effects across generations is whether an exposure in one generation can generate other types of exposures in subsequent generations. For example, if exposure of F0-F2 generations

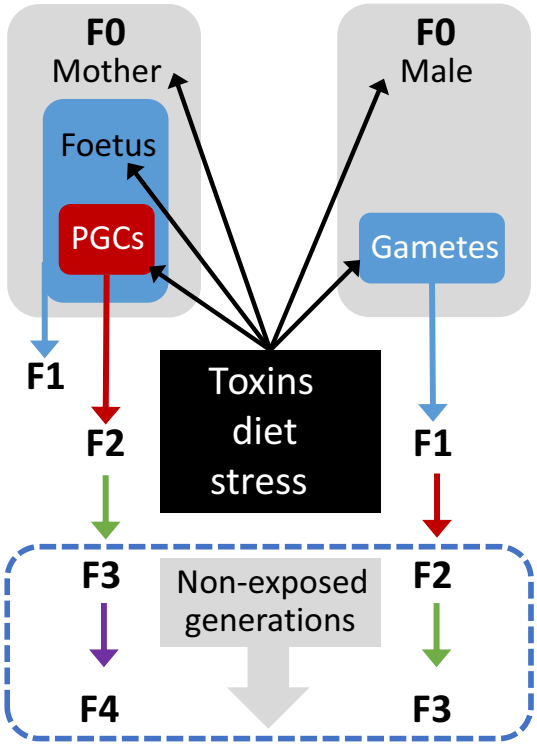

FIGURE 1 Generational transmission of paternal environmental exposures. Paternal effects can be observed among the descendants of males who are exposed in utero (left) or during their post-natal life span (right) to toxins, altered diet and social stress. The timing of exposure within the life span of the male will determine whether the F2 or F3 generation descendants of the male are the first generation to not be directly exposed to the environmental disruption. PGCs, primordial germ cells

to a stressor results in altered behavioural phenotypes that shape social/reproductive behaviour in F1-F2 generations, it may be possible for the behavioural effects to impact the environment of F2-F3 offspring with phenotypic and epigenetic consequences. The importance of considering these dynamic pathways will be highlighted in subsequent sections.

The phenomenon of paternal transgenerational effects is being increasingly demonstrated in experimental studies of targeted exposures. Maternal high-fat diet exposure in mice results in an increase in body size in descendants that persist to the F3 generation within the patriline (F1 exposed males) (Dunn & Bale, 2011, 2009). This F3 phenotype is accompanied by altered expression of imprinted genes in the liver and is only observed in female offspring (Dunn & Bale, 2011). A sex-specific impact of paternal exposures is also observed in longitudinal studies in humans examining the multigenerational effect of grandparental nutrition (Pembrey et al., 2006). Chronic social stress in male mice experienced during adolescence through to adulthood can induce social deficits and increased anxiety-like behaviour in female (but not male) offspring and grandoffspring through the patriline (Saavedra-Rodriguez & Feig, 2013). Descendants of pregnant female mice exposed to immune challenge display social and cognitive behavioural phenotypes that persist to the F3 generation via the patriline (Weber-Stadlbauer et al., 2017). In rats, F3 offspring generated from a vinclozolin-exposed male (exposure occurring to F1 male *in utero*) have impairments in reproduction, altered anxiety-like behaviour, stress sensitivity and increased disease risk (i.e. tumour formation, kidney disease, immune abnormalities) (Anway, Leathers, & Skinner, 2006). Taken together, these examples of the propagation of paternal effects beyond the offspring generation are suggestive of a modifiable yet potentially stable mechanism of transmission.

5 | PATERNAL GERM CELLS AND THE TRANSMISSION OF ENVIRONMENTALLY INDUCED EPIGENETIC VARIATION

The current focus of paternal effects research is on environmentally induced epigenetic changes in the sperm that may serve as the biological substrate of the transmission across generations of environmentally induced phenotypes. This focus is driven by several factors. First, within the mating systems used in laboratory-based studies of paternal epigenetic effects in progeny (typically in mice or rats), the post-exposure male is present only briefly during the mating period and has limited contact with the mating female and no contact with offspring. Second, due to the stability of some epigenetic characteristics of cells during mitosis and the occurrence of parent-of-origin effects on gene expression that are retained following meiosis (Ferguson-Smith, 2011), the potential for epigenetic changes in sperm to persist despite considerable epigenetic reprogramming occurring post-fertilization seems plausible (Borgel et al., 2010). Third, there is increasing evidence that some of the phenotypes observed in intergenerational studies of paternal effects can be recapitulated using artificial reproductive techniques such as in vitro fertilization (IVF) and embryo transfer, where sperm cells are generally thought to be the sole paternal contribution to the creation of offspring (Gapp et al., 2014; Grandjean et al., 2015; Rodgers, Morgan, Leu, & Bale, 2015). There is now a growing characterization of sperm profiles of DNA methylation, post-translational histone variation and non-coding RNAs that provide insights into the germ cell theory of paternal effects.

5.1 | DNA methylation

Altered DNA methylation in sperm has been found associated with a broad range of paternal exposures. Elevated *in utero* and post-natal exposure to a high folic acid diet in laboratory mice results in increased variation in the DNA methylation status of imprinted regions in the sperm genome in exposed males (Ly et al., 2017). In humans, paternal obesity is associated with both increased and decreased DNA methylation of imprinted genes in sperm (Soubry et al., 2016). Male alcohol exposure in rats is associated with decreased DNA methyltransferase expression in sperm (Bielawski, Zaher, Svinarich, & Abel, 2002) which may lead to genome-wide hypomethylation. Prenatal and post-natal exposure to BPA induces abnormal

expression and DNA methylation of the *Igf2* gene in sperm (Mao et al., 2015). Prenatal vinclozolin exposure in rats is associated with altered DNA methylation in the sperm of F1, F2 and F3 offspring (Anway, Cupp, Uzumcu, & Skinner, 2005), with particular effects of imprinted genes (Stouder & Paoloni-Giacobino, 2010). In humans, male exposure to organophosphates (flame retardants) is associated with altered DNA methylation within imprinted genes in sperm (Soubry et al., 2017). In mice exposed to early life post-natal maternal separation, DNA methylation changes (increases or decreases compared with controls) are observed in the brain-specific gamma isoform of protein kinase C (*Prkcc*), *Mecp2*, *Cb1* and corticotropin-releasing factor receptor 2 (*Crfr2*) genes in the sperm of F1-exposed males and similar changes are observed in the brain of F2 offspring (Bohacek et al., 2015; Franklin et al., 2010). The recapitulation of DNA methylation changes within target genes of sperm in the brain of the progeny of exposed males has also been observed as a consequence to odour fear conditioning in mice and may mediate the transmission of behavioural phenotypes related to the specific odorant-fear pairing (Dias & Ressler, 2014). Though genes linked to specific exposure–outcome pathways have been demonstrated to be impacted in sperm (e.g. Dias & Ressler, 2014; Franklin et al., 2010), it is evident that across species, there is a heightened susceptibility of imprinted genes to exposure-induced altered DNA methylation levels which may facilitate the occurrence of generational transmission (due to the ability of these genes to re-establish parental imprints during reproduction).

5.2 | Histones

The histone code—a complex map of post-translational modifications to the histone protein core in DNA—is a dynamic epigenetic mechanism through which changes in gene expression can be achieved. Within sperm, DNA is primarily packaged within protamines rather than histones, and at the time of fertilization, the protamines are replaced with maternally derived histones (Steger, Cavalcanti, & Schuppe, 2011). However, 'persisting histones' within sperm may have the potential to account for paternal intergenerational effects. The replacement of histones with protamines occurs over the process of sperm maturation, and the retention of histones occurs in specific genomic loci (Yoshida et al., 2018). The degree of histone retention may be impacted by paternal exposures. For example, in humans, smoking in males is associated with an elevated histone to protamine ratio in sperm (Hamad, Shelko, Kartarius, Montenarh, & Hammadeh, 2014). Histone (H3) retention is increased in the sperm of male mice exposed to a high-fat diet (Terashima et al., 2015). Within retained histones, there may also be histone modifications associated with exposure in sperm that have potential to shape developmental outcomes in offspring. Pre-conceptual cocaine exposure is associated with elevated histone acetylation within the *Bdnf* gene promoter in the testes and sperm of exposed males and in the prefrontal cortex of their offspring suggesting a highly targeted relationship between paternal exposure, epigenetic change in sperm and phenotypic outcome in offspring (Vassoler et al., 2013).

5.3 | Non-coding RNA

The gene regulatory role of non-coding RNAs is being increasingly appreciated, and these molecules may play a critical role in germline paternal effects. At the time of fertilization, the sperm transmits various cytoplasmic RNAs (e.g. mRNAs, microRNAs and piwi-interacting RNAs [piRNAs]) to the oocyte that plays critical roles in the early (and perhaps later) stages of development (Champroux, Cocquet, Henry-Berger, Drevet, & Kocer, 2018; Yuan et al., 2016). In humans, paternal smoking induces changes in the microRNA content of sperm (Marczylo, Amoako, Konje, Gant, & Marczylo, 2012). In mice, irradiation leads to upregulation of microRNAs from the miR-29 family in the testes of exposed males (Filkowski et al., 2010). Paternal stress applied during adolescence or adulthood in mice has been shown to elevate levels of specific microRNAs in the sperm (Rodgers, Morgan, Bronson, Revello, & Bale, 2013). Exposure to chronically elevated glucocorticoid levels in mice alters sperm microRNA profiles across multiple generations (Short et al., 2016). In male mice exposed to chronic social instability and human males reporting elevated levels of early childhood adversity, there are reduced levels of expression of microRNAs 449 and 34 (Dickson et al., 2018)—suggesting a conserved biological response to stress. Altered expression of piRNAs in sperm has been associated with early life social stress in mice (Gapp et al., 2014) and with exposure to undernutrition in sheep (Guan et al., 2015). Transfer RNAs (tRNAs) fragments (28–34 nucleotides, generated from the 5′ ends of tRNAs) play a critical role in translation and have been found to be altered in expression in sperm following exposure of male mice to a high-fat diet (Chen et al., 2016) or a low-protein diet (Sharma et al., 2016).

While the profiling of sperm cells extracted from exposed males provides some insights into the potential of environmentally induced epigenetic changes in the germline transmission of paternal effects, these profiles are only a first step. The mere presence of epigenetic changes in sperm is only suggestive of epigenetic plasticity in cells and is consistent with the general notion that gene regulatory mechanisms can be dynamically altered. The next step in building a paternal germline transmission hypothesis is to establish that the sperm from exposed males and the epigenetic variation in those sperm are capable of inducing phenotypic changes in the progeny of those males. In vitro fertilization and embryo transfer studies indicate that the sperm (and associated seminal fluids) of males exposed to social stress (Dietz et al., 2011), fear conditioning (Dias & Ressler, 2014) and chronic food restriction (Mashoodh, Habrylo, Gudsnuk, Pelle, & Champagne, 2018) is predictive of developmental outcomes in offspring. Foundational studies of the transmission of epimutations in mice illustrate the role of sperm RNAs in this transmission (Rassoulzadegan et al., 2006). Injection of RNA purified from the sperm of male mice exposed to post-natal social stress into the oocyte of a non-stressed female results in behavioural phenotypes in offspring indicative of a paternal stress effect (Gapp et al., 2014). Similarly, injection of microRNAs that are differentially expressed in sperm of male mice exposed to chronic stress into a zygote results in

a stress phenotype in offspring (Rodgers et al., 2015). Injecting up-regulated tRNA fragments that have been isolated from the sperm of male mice placed on a high-fat diet into a normal zygote leads to emergence of a glucose intolerance phenotype in F1 offspring (Chen et al., 2016). Though the phenotypes that emerge in these germ cell manipulation studies may not reproduce intergenerational phenotypic outcomes with a high fidelity to those generated using natural mating, it is clear that the informational content of sperm can be altered by the environment and shape offspring characteristics.

6 | ENVIRONMENTAL EXPOSURES AND THE REPRODUCTIVE SUCCESS OF MALES

The study of paternal germline effects has integrated high-resolution profiling and germ cell manipulation to characterize the epigenetic and transcriptional state of sperm cells and the zygotes generated from these cells. However, in addition to this molecular perspective, it is also important to consider the broader reproductive context of these epigenetic changes. Sperm counts are decreased following exposure to stress, nutritional and toxicological exposures in males. In humans, there has been growing concern regarding increasing infertility related to reduced semen quality and analyses of global trends indicate that sperm concentration and total sperm count have decreased over the past four decades (Levine et al., 2017). A systematic review of the literature has indicated that male obesity in humans is associated with decreased fertility, decreased likelihood of success using assisted reproduction technology (ART) and abnormal sperm morphology (Campbell, Lane, Owens, & Bakos, 2015). In animal studies in the laboratory, manipulation of environmental variables considered likely candidates of fertility effects in humans (Gabrielsen & Tanrikut, 2016) supports the hypothesis that male experiences impact spermatogenesis and post-mating reproductive success. Developmental exposure of mice to elevated dietary folic acid levels results in decreased sperm counts and decreased post-mating implantation success (Ly et al., 2017). Chronic exposure to BPA in mice is associated with reduced quality and quantity of sperm through altered gene expression and reduced meiotic progression of sperm cells (Zhang et al., 2013). Pattern and levels of histone retention and increased sperm histone to protamine ratio—factors altered by environmental exposures—are associated with infertility and recurrent pregnancy loss (Hammoud et al., 2011; Mohanty, Swain, Goswami, Kar, & Samanta, 2016).

The presence of these more global characteristics of sperm function raises a number of questions regarding the mechanisms of paternal germline effects in offspring. If sperm count and motility are acutely or chronically diminished by an exposure, mating success is likely to be significantly diminished resulting in reduced likelihood of producing offspring to base the study of intergenerational and transgenerational effects. If a recovery period is used to allow sperm counts to rise sufficiently for successful mating and implantation, then it is likely that the duration of this recovery period will influence outcomes in offspring through a variety of processes, including sperm morphological, genomic and epigenomic integrity. The degree to which any given environmental exposure impacts overall sperm quantity and quality is unknown and of additional importance is the variability of effect within a given sperm cycle. Variable quality of sperm would be predicted to impact intra-ejaculate sperm competition with potential consequences for offspring outcomes (Wigby & Chapman, 2004). Under conditions where a vast majority of sperm are impacted at an epigenetic and morphological level and there is a smaller pool of healthy sperm to engage in competition, what determines the path to successful mating and how will these early cellular and physiological characteristics contribute to embryogenesis? If there is variability in the effects of an environmental exposure on sperm, what are the specific characteristics of a sperm cell that will contribute to its success in generating viable offspring and a transgenerational impact? It would be predicted that sperm that have morphological and genetic defects would be less successful. If this is the case, what conditions lead to a dissociation between morphological and genetic integrity and epigenomic changes? Answers to these questions may provide more depth of insight into the processes where an environmentally induced change in sperm can be epigenetically transmitted to offspring.

7 | BEYOND SPERM: ROLE OF MATE QUALITY AND SELECTION IN OFFSPRING DEVELOPMENT

Exposure to nutritional, toxicological and social environmental challenges can have enduring effects on male physiology and behaviour. In concert with the observed deficits in sperm counts and morphology (Crean, Adler, & Bonduriansky, 2016), these phenotypic effects in males serve as a multisensory cue to mate quality. Competition between mates in natural populations of animals is a defining characteristic of most species and a driver of social organization in group-living males and females (Clutton-Brock & Huchard, 2013). Social hierarchies are hypothesized to occur as a consequence of competition over resources, including mating opportunities (Kuse & De Fries, 1976). Dominant social status, size and physical ornamentation have been associated with mate choice dynamics, though since there is often co-occurrence of multiple phenotypic traits in reproductively successful individuals, it not always clear what trait is the perceived signal in a mating dyad (Charlton, 2013). Beyond successful mating, offspring generally benefit from being the descendants of attractive mates. Genetic factors can contribute to male attractiveness/social dominance, and offspring can either directly inherit these genetic benefits or experience indirect genetic effects on the social context of development with phenotypic advantages for their own growth and reproductive success (Schneider, Atallah, & Levine, 2017). In addition to the paternal genetic and resource investments that might accompany male attractiveness and influence offspring development, the attractiveness of a male mate is predicted to influence the level

of maternal investment in offspring. These maternal adjustments in reproductive effort can come in the form of 'differential allocation' (DA) or 'reproductive compensation' (RC). The differential allocation hypothesis (DAH) predicts that when mating with high-quality males (typically attractive), females should increase their investment in offspring if the cost of reproducing is high (Haaland, Wright, Kuijper, & Ratikainen, 2017). However, increased maternal investment may also occur when a female mates with unattractive or non-preferred males as a form of reproductive compensation that helps buffer offspring from the disadvantageous characteristics they may inherit from their father (Gowaty et al., 2007). There is evidence in support of the occurrence of female reproductive investment adjustments related to male mate quality in species such as birds where the level of investment can be quantified more easily. Female zebra finches, *Taeniopygia guttata*, mated with more attractive males, achieved artificially by placing red ring bands on the males, lay heavier eggs and feed their chicks more frequently (Burley, 1988; Rutstein, Gilbert, Slater, & Graves, 2004). The prediction of whether DA or RC will occur is challenging and likely dependent on variables relating to the context of reproduction (energetic costs, resource availability, likelihood of future mating opportunities) and the characteristics of the female (age, health) (Harris & Uller, 2009).

Within the literature on paternal epigenetic effects in offspring, there is evidence indicating that exposed males are less attractive as potential mates and evidence that females adjust their reproductive investment in the offspring sired by exposed males. Mate preference tasks indicate that F3 male rats from vinclozolin-exposed lineages are less preferred as mates (Crews et al., 2007) as are male mice exposed *in utero* to food restriction (Meikle, Kruper, & Browning, 1995) and male rats exposed to either high-fat diet (Korgan, O'Leary, King, Weaver, & Perrot, 2018) or predator odours (Korgan et al., 2016). When female mice are presented with urine from food-restricted or control-fed male mice, they exhibit preference for the control-fed males (Mashoodh et al., 2018). In these examples, females can clearly distinguish between males, dependent on the environmental exposure history of the male. In some cases, this ability to discriminate males is also associated with altered reproductive investment. Female rats mated with high-fat diet-exposed males engage in reduced post-natal maternal behaviour towards their offspring, including decreased licking/grooming and arched back nursing (Korgan et al., 2018). Female rats rearing offspring from predator odour-exposed males engage in elevated licking/grooming and arched back nursing compared with females rearing offspring of non-exposed males—though this effect is only observed when females are rearing pups in a semi-naturalistic environment (Korgan et al., 2016). Increased post-natal maternal care is also observed when female mice are mated with males that have experienced social enrichment (compared with isolation-reared males) or males that have been exposed to food restriction in adulthood (Mashoodh, Franks, Curley, & Champagne, 2012; Mashoodh et al., 2018). Though it is challenging to determine the level of prenatal maternal investment in mammals, female mice mated with food-restricted males gain more weight during pregnancy, suggestive of increased gestational food intake (Mashoodh et al., 2018). Thus, the impact of paternal exposures that are known to influence offspring outcomes can also be observed at the level of maternal investment by female mates and these reproductive adjustments illustrate both DA and RC. Olfactory, auditory, physiological and/or behavioural cues may contribute to this discrimination and reproductive shift—though as in the broader literature, the specific feature of males or of the mating interaction that mediates this effect has yet to be determined.

A critical consideration within the design of studies examining the transmission of paternal effects across generations is the mating strategy. Male exposures to nutritional, toxicological and social challenges impact their mate quality and females generally prefer mating with non-exposed males. Yet, the breeding designs used in most laboratory studies of paternal effects eliminate the capacity of females to choose their mate. The lack of choice and forced mating with non-preferred males introduces additional variables that may impact maternal and offspring outcomes. In Gouldian finches, *Erythrura gouldiae*, females mated with less attractive non-preferred males have elevated stress hormone levels (Griffith, Pryke, & Buttemer, 2011). In mice, females mated with a preferred male give birth to larger litters and these offspring are more socially dominant, better nest builders and have reduced mortality rates compared with the offspring of females who mated with non-preferred males (Drickamer, Gowaty, & Holmes, 2000). These changes in maternal and offspring outcomes are associated with female preference for a male during a free choice preference test rather than specific qualities of the male. Importantly, laboratory studies of paternal germline epigenetic effects typically occur in the absence of free mate choice and force mating with non-preferred mates. The effects of these manipulations may have significant consequences for the interpretation of causal mechanisms and for the relevance of the findings to natural populations. Thus, comparison of paternal effects of male environmental exposures that emerge within a forced mating versus a free choice mating design would allow greater depth of understanding of the potential impact of this factor.

8 | PATERNAL EFFECTS ON MOTHERS

The impact of paternal phenotypes on maternal reproductive investment creates an indirect pathway for the influence of fathers on offspring development. The gestational nutritional environment and quality of social interactions that occur during the post-natal period in mammals that are shifted by fathers can have lasting effects on growth, neurobiology and behaviour (Gluckman, Hanson, Cooper, & Thornburg, 2008; Meaney, 2001). In addition to impacting the perceived mate quality, exposed males may trigger post-mating adaptations in the female reproductive tract. Both the sperm and seminal plasma derived from males exposed to a low-protein diet (compared with control diet) impact preimplantation uterine immunological responses, cell signalling and vascular remodelling responses in females (Watkins et al., 2018). Paternal exposures may

also impact placental function resulting in potential disruption of the transfer of resources from the mother to the developing foetus. In mice, F1 embryos generated from the sperm of males fed a high-fat diet pre-mating have altered placental gene expression and DNA methylation (Binder et al., 2015). These prenatal effects are sex-specific such that *Pparα* and caspase-12 (*Casp12*) gene expression are significantly decreased in male placentas, and global DNA methylation levels are elevated in female placentas of high-fat diet-exposed fathers. Paternal obesity in mice is associated with altered expression of imprinted genes in the placenta, including *Peg3*, *Peg9*, *Peg10* and the *Slc38a2* gene that encodes for a sodium-coupled neutral amino acid transporter (Mitchell et al., 2017). Female mice mated with a food-restricted male have increased hypothalamic expression of *Peg3* and other genes involved in post-natal maternal care which may facilitate the paternal effects on maternal post-natal reproductive investment (Mashoodh et al., 2018).

It is likely that paternal environmental exposures influence multiple facets of maternal–infant interplay during the prenatal and post-natal period, however, the degree to which these influences mediate paternal effects on offspring development needs further investigation.

9 | MATERNAL MODULATION OF PATERNAL EFFECTS ON OFFSPRING

The role of mothers in the expression of paternal effects in offspring may also be modulatory. Within intergenerational studies in mice, offspring of males exposed to chronic social defeat stress have offspring that exhibit heightened anxiety- and depression-like behaviours (Dietz et al., 2011). When offspring are conceived through IVF, there is incomplete transmission of these paternal effects, indicating that maternal interactions with the male at the time of mating were contributing to the expression of some of the paternally induced phenotypes in offspring. Though paternal food restriction in mice increases prenatal and post-natal maternal investment in offspring by female mates under natural mating conditions, this adjustment to reproductive investment is not observed when offspring are generated using embryo transfer (Mashoodh et al., 2018). Offspring of these food-restricted fathers display increased recognition memory only if maternal investment is increased. When mothers do not adjust their reproductive investment, offspring of food-restricted fathers exhibit impairments in recognition memory (see Figure 2). In studies of the intergenerational and transgenerational transmission of the Kit paramutation phenotype, maternal microRNAs and piRNAs in the oocyte have an inhibitory effect on the likelihood of germline transmission of the paramutation (Yuan, Oliver, Schuster, Zheng, & Yan, 2015). Transmission of variations in paternal exploratory behaviour to offspring in isogenic mice is modulated by the duration of time spent with the female mate during the breeding period such that the expression of paternal effects is lessened if there is prolonged post-conception interactions (Alter et al., 2009). The multigenerational effects of endocrine-disrupting chemicals on F3 generation offspring are impacted by altered F2 maternal behaviour, highlighting the complexity of phenotypic transmission in these exposure lineages (Krishnan et al., 2018). Overall, it is clear that although evidence supports the occurrence of paternal germline effects, the direction and magnitude of impact of these germline effects will be dependent on the context of reproduction—which in mammals is shaped primarily by the mother.

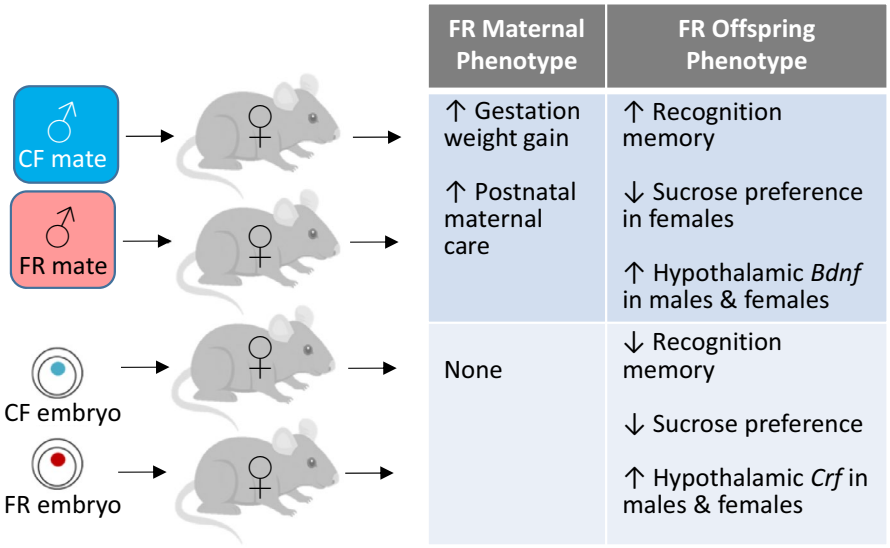

FIGURE 2 Association between altered reproductive investment by females and outcomes in offspring of food-restricted fathers. Female mice mated with food-restricted (FR) males engage in increased reproductive investment in offspring via increased gestational weight gain and increased post-natal maternal care. Among offspring of these matings (compared with offspring of control-fed [CF] males), there are phenotypic outcomes that include improved recognition memory. Embryo transfer using the sperm of CF or FR males indicates that females do not increase their reproductive investment under these conditions and offspring of FR males display impairments in recognition memory (Mashoodh et al., 2018)

10 | A DYNAMIC REPRODUCTIVE PROCESS: INTEGRATING CONTEXT

The prospect of paternal germline epigenetic transmission of the effects of environmental exposures has reinvigorated the study of non-genomic inheritance. The impact on offspring and their progeny of variations in ancestral conditions of life provide a novel perspective on the origins of physical and behavioural traits that complements and interacts with DNA-based phenotypic variation and contributes to a more inclusive theory of inheritance (Danchin et al., 2011). However, simple mechanistic explanations of this phenomenon may lack predictive utility and limit integration of findings with the broader theoretical and empirical literature on environments, parental effects, reproduction and offspring fitness. Perhaps the most critical variable that needs to be integrated into this research is a more nuanced perspective on context. To approach the topic of context in a meaningful way requires careful consideration of the ways in which context is generally viewed within behavioural ecology—with both a theoretical and methodological consideration of past, present and predicted future environments and reproductive opportunities. Exposure to environmental challenges has both absolute meaning and relative meaning. *Does the environmental exposure indicate a persistent or recurring change in the context of growth, development and reproduction?* Adaptations to the environment will depend on how these changes are experienced within the life history of an organism. Propagation of these adaptations to future generations through the patriline will depend on the life history and traits of the exposed male, the life history and traits of their female mate and the dynamic interactions that occur between mating pairs as well as between parents and offspring during reproduction (see Figure 3). In mammals, these interactions may be difficult to characterize due to the evolution of internal fertilization and gestation. However, there are increasing tools available to probe the physiological and behavioural dynamics of reproduction in mammals, and if combined with the molecular profiling, these approaches could generate more integrative hypotheses and models of paternal effects. This is an important first step in improving the design of studies that examine paternal epigenetic inheritance. Though using approaches such as IVF and embryo transfer are critical for demonstrating, under controlled reproductive conditions, the likelihood of a germline transmission, these approaches must be accompanied by studies that add reproductive 'variability' back into the model in a systematic way. Simple questions could include the following: (a) What is the impact on paternal effects when the prenatal environment is modified? (b) What is the impact on paternal effects when the post-natal environment is modified? (c) How do both maternal and paternal life history variables (e.g. age, reproductive history) impact the transmission of paternal effects? Addressing these questions theoretically and methodologically requires integration of knowledge that spans beyond a molecular understanding of epigenetic mechanisms.

Rather than being constrained to a unidirectional mode of generational transmission that characterizes very simple DNA-based inheritance systems, the growing literature on paternal epigenetic effects and the interplay between mothers and fathers that predict offspring phenotypes highlights the need for a more dynamic and multidisciplinary approach. Expertise in reproductive biology, genomics, molecular biology, neuroendocrinology, behavioural ecology and evolutionary theory needs to be combined and leveraged to create models that not only predict the phenomenon of paternal effects but also generate a framework for understanding the broader context of when and why these effects may occur. This framework could potentially provide insights into the complex array of factors that predict the breadth, direction and fidelity of paternal influences across generations. This complexity of the inheritance of acquired

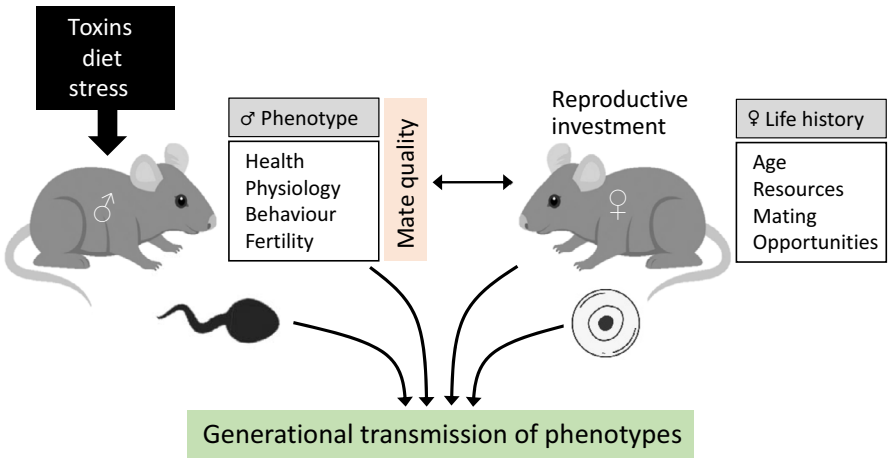

FIGURE 3 Complex interplay between males and females influences the transmission of phenotypes to offspring following paternal exposures. Though male germ cells can acquire and transmit biological changes resulting from exposure to environmental challenges, prediction of the phenotypes transmitted to offspring requires consideration of the phenotypic changes in males that impact their mate quality and fertility, the level of reproductive investment by female mates, the life history of the mating female and the capacity of the female gametes to moderate biological information deriving from the male

characteristics was certainly appreciated by Lamarck who described the role of context and the critical importance of both males and females in the propagation of environmentally induced adaptations (Lamarck, 1809). The challenge in the current era will be to oscillate between the molecular and broader ecological lens in ways that capture the nuances of an epigenetic Lamarckian revival.

DATA AVAILABILITY STATEMENT

There are no data included in this manuscript.

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