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REVIEW ARTICLE

Paternal Influences on Offspring Development: Behavioural and Epigenetic Pathways

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Although mammalian parent–offspring interactions during early life are primarily through the mother, there is increasing evidence for the impact of fathers on offspring development. A critical issue concerns the pathways through which this paternal influence is achieved. In the present review, we highlight the literature suggesting several of these routes of paternal effects in mammals. First, similar to mothers, fathers can influence offspring development through the direct care of offspring, as has been observed in biparental species. Second, there is growing evidence that, even in the absence of contact with offspring, fathers can transmit environmentally-induced effects (i.e. behavioural, neurobiological and metabolic phenotypes induced by stress, nutrition and toxins) to offspring and it has been speculated that these effects are achieved through inherited epigenetic variation within the patriline. Third, fathers may also impact the quality of mother–infant interactions and thus achieve an indirect influence on offspring. Importantly, these pathways of paternal influence are not mutually exclusive but rather serve as an illustration of the complex mechanisms through which parental influence is achieved. These influences may serve to transmit traits across generations, thus leading to a transgenerational transmission of neurobiological and behavioural phenotypes.

Key words: paternal care, biparental, epigenetic, neurodevelopment, maternal

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Introduction

Development is a dynamic process involving an interplay between genes and the environment that can lead to diverse phenotypic outcomes. In mammals, the process of development typically occurs within the context of mother–infant interactions occurring during both the prenatal and postnatal period. During this time, disruptions to these interactions can have profound consequences for offspring development (1). Prenatal maternal stress (2), nutrition (3) and exposure to drugs/toxins (4,5) can have lasting neurobiological, physiological and behavioural effects, which may increase the risk of physical and psychiatric dysfunction in offspring. During the postnatal period, withdrawal of maternal care, in the form of prolonged maternal separation (6) or deprivation (7), can also have long-term consequences, particularly involving the development and reactivity of the hypothalamic-pituitary-adrenal (HPA) response to stress. Even variations in maternal care within the normal range can alter stress reactivity, fear responses, affect, cognition and social/reproductive behaviour in offspring (8,9). These studies highlight the dependence of offspring on species-specific mother–infant interactions and the divergent developmental trajectories that can emerge when there is augmentation or disruption to that early-life experience.

The focus of mammalian studies of parental care and its effects has been primarily on the mother, whereas the role of fathers in shaping development has received more limited attention. However, in humans, cultural influences and economic conditions are leading to changes in the view of fathering and the father's actual involvement in infant care (10). There is an increasing involvement of fathers in various aspects of childcare and, in experimental studies of paternal care in animals, fathers provide similar levels of parenting as mothers, which, in some species, is characterised by a unique behavioural style (11). This unique approach to parenting may contribute to social development and emotion regulation, particularly the capacity to function adaptively within the social milieu (12–14). Although maternal and paternal dimensions of parental care may differ, it is important to attain a more thorough understanding of the mechanisms and impact of paternal behaviour to establish how

these dimensions act synergistically in creating a parenting system that enhances offspring development.

Experimental approaches to the study of the influence of mammalian fathers on offspring have relied on species in which biparental care is evident (15). Only 5–10% of mammals display paternal care (16), which has further limited the broad study of paternal influences. Amongst laboratory rodents, the majority of species that are used display limited paternal care and, in some cases, are infanticidal toward neonatal pups (17). However, in biparental rodent species, such as California mice (*Peromyscus californicus*), prairie voles (*Microtus ochrogaster*), Mandarin voles (*Lasiopodomys mandarinus*), Djungarian hamsters (*Phodopus sungorus*), Mongolian gerbils (*Meriones unguiculatus*) and degus (*Octodon degus*), there are survival benefits associated with paternal care and there is increasing evidence for the neurobehavioural impact of fathers on offspring (18–20).

Although paternal care of offspring is observed in a limited number of mammalian species, paternal influences have been demonstrated more broadly and can occur even in the absence of genetically transmitted variation (21). For example, in CD-1 laboratory mice (*Mus musculus*), exposure of males to stress can alter the behaviour of offspring and grand-offspring, even though males are absent during the postnatal period and thus have no direct contact with offspring (22). Similar paternal programming effects have been shown after exposure of males to pesticides (23), alcohol (24) and variation in the nutritional environment (25). The occurrence of these paternal effects has raised the possibility of epigenetic inheritance, whereby epigenetic variation (i.e. DNA methylation, post-translational histone modifications, small noncoding RNAs) induced in the male germline is transmitted to subsequent generations with consequences for a broad range of phenotypes (metabolism, behaviour, neurobiology). This epigenetic route of paternal influence may also interact with the quality of mother–infant interactions, leading to an indirect pathway through which fathers influence offspring (26). Within behavioural ecology, there are established theoretical frameworks to account for reduced or enhanced maternal investment (i.e. increased maternal care) in offspring dependent on mate quality (27,28). Moreover, both genetic and epigenetic variation in males can alter mate choice in females (29,30), suggesting that paternally-induced maternal effects on offspring may be an important consideration in shaping offspring development. In this review, we highlight the literature illustrating the influence of fathers on offspring from the perspective of: (i) direct paternal care; (ii) epigenetic transmission; and (iii) paternally-induced variation in mother–infant interactions. Although not mutually exclusive, these divergent routes of paternal influence demonstrate the complex pathways through which fathers can shape developmental outcomes in offspring and the importance of further research on the unique strategy whereby paternal effects are established.

Influence of paternal care on offspring development

In humans, although it is typical for the mother to be the primary caregiver, the influence of fathers on child development is still apparent. Absence of the father exposes children to a range of developmental risks and results in lower adult psychological adjustment and a greater risk for psychopathology (31,32). Deprivation of paternal care (typically as a result of absence of the father) predicts higher rates of conduct disorders, delinquency, substance abuse and violence in adolescence (33). Paternal absence may result in HPA hyperactivity and increased sensitivity to stressors, leading to increased susceptibility to disease (34,35). Although these associations are compelling, it is important to note that socio-economic and cultural factors coinciding with paternal absence may confound the interpretation of these findings. These confounds highlight the importance of animal models when studying the impact of fathers. In mammals, paternal behaviour has been reported in a number of primate and rodent species (15,36).

Parental behaviour can be categorised into direct and indirect investment in offspring survival and development (37). In rodents, direct investment can take on the form of huddling, pup licking/grooming, nursing, retrieval of pups to the nest and parent–offspring play. Indirect investment includes the acquisition of nutritional resources and feeding, nest-building and cleaning, maintenance of the territory and defence against intruders. Studies focussing on the quality of paternal behaviour in several biparental species, including California mice, prairie voles, Djungarian hamsters and degus, indicate that with the exception of lactation/nursing, fathers display the same parental behavioural repertoire towards pups as the mother. However, there may be differences in the interactional styles of mothers compared to fathers. For example, compared to mothers, human fathers appear to engage more in challenging physical activities and unpredictable, arousing play, and this unique paternal style contributes to children's attachment security and also may be important for helping the child to develop appropriate emotional control mechanisms and reduce aggressive behaviour (38). In animals, the paternal parent engages in playing and socialising, including mutual sniffing, nosing, greeting, wrestling and scent marking, which contributes to the social development and social integration of his offspring. Furthermore, a father's directed care towards his offspring may be elevated when the offspring are exposed to stressors (12,39,40).

Although the majority of studies evaluate paternal and maternal care in isolation from one another, there is some evidence that maternal and paternal parents 'team up' and display complementary parenting styles (36,41–43). For example, when the female nurses the pups, the male may engage in indirect forms of parental care, such as protection of the mother from intruders. In social voles (*Microtus socialis guentheri*), it has been observed that the male parent physically 'forces' the female parent to move towards or remain in the nest (44). Thus far, few studies have systematically analysed whether and in which way parents influence each other's parental activities. In outbred ICR laboratory mice, it has been demonstrated that the maternal parent communicates to the paternal parent to stimulate pup care (45). In gerbils, the presence of the father stimulates physical contact between pups and both parents, and offspring are more rapid in their physical and behavioural development, including earlier eye opening, in father-present rearing environments (46). Thus, the overall quantity of parental care may be altered by the presence of the father. In degus, the

quantification of paternal–offspring interactions reveals that paternal care comprises approximately 37% of total parent–offspring interactions (47,48). In prairie voles and degus, it has been shown that pups that are reared by a single mother (i.e. in a rearing condition where the father was removed and the mother rears her pups alone) receive less parental nurturing (e.g. licking/grooming) than biparentally reared pups (47–49). Prairie vole and degu dams are not observed to compensate for reduced paternal care in father-absent rearing conditions, leading to a semi-deprived social environment for the pups (47,50). In prairie voles, the absence of the father leads to reduction in maternal presence in the nest and an early weaning of offspring, as indicated by an earlier onset of eating solid food and spending time outside the nest (51).

Influence of paternal care on behavioural phenotypes

Although paternal care may only be evident in a limited number of species, fathers contribute significantly to offspring survival (52) and behavioural development through parental investment. These effects may be particularly evident when considering the development of social behaviour and anxiety-like responses. Amongst California mice, paternal behaviour influences the development of aggression and associated hypothalamic brain regions (53,54). The experimental stimulation of paternal pup retrieving behaviour results in reduced attack latency in both male and female adult offspring, whereas reducing huddling and grooming has no effect on this behavioural trait. In California mice, the presence of the father exerts a greater influence on social contact between the members of the litter than on physical growth (20). In biparental Mandarin voles, paternal deprivation inhibits the development of social recognition in female and male offspring and alters social behaviour later in life (55). In California mice, paternal deprivation leads to sex-specific abnormalities in social and reward-related behaviours (56). Father-deprived male and female offspring show impaired social interactions with another father-deprived animal. In females, this social deficit is also observed when tested with a nonfather-deprived animal and is associated with a sensitised locomotor response to amphetamine (56). Father-absent rearing conditions are also associated with increases in anxiety-like behaviour in offspring (49) and recent studies in marmosets indicate that reduced paternal care leads to increased HPA reactivity (57), a finding that suggests parallels to the impact of reduced maternal care on stress and anxiety-like behaviour (9).

Parental behaviours and pair-bonding are likewise regulated by paternal behaviour. In the prairie vole, paternal deprivation is associated with reduced alloparental behaviour in female offspring and both male and female offspring that have experienced paternal deprivation require longer cohabitation periods than biparentally reared offspring to form partner preferences (58). Male Mongolian gerbils reared without paternal care display lower parental responsiveness, including reduced nest attendance and a lower rate of grooming of pups. In addition, these father-deprived males groom their female mates less frequently than males raised in biparental contexts (59). Collectively, these behavioural consequences of paternal behaviour may lead to the transmission of variation in parental behaviour across generations, whereby the experience of paternal care shapes the neural substrates of parental behaviour, thus transmitting the phenotype behaviourally to offspring and even grand-offspring (53,60).

Paternal care and the developing offspring brain

The developing brain is shaped by a cascade of experiences occurring during both prenatal and postnatal development. During these periods, mother–infant interactions can induce long-term neurobiological effects that persist into adulthood and account for the behavioural variation that emerges (1,2,9). In biparental species, the presence (or absence) of paternal care can likewise induce effects on neural development. In degus, paternal deprivation is associated with reduced excitatory spine synapses in the orbitofrontal cortex, which is involved in sensory integration, planning and decision-making, and expectation of reward and punishment (47). An imbalance between excitatory and inhibitory synapses is also evident in the anterior cingulate cortex of father-deprived degus (47,61). Father-deprived degu offspring display fewer spine synapses in the somatosensory cortex (48), which emphasises that somatosensory stimulation, provided through body contacts with the father (licking/grooming and huddling), is essential for the synaptic development of this sensory cortex. In California mice, paternal deprivation has been found to alter synaptic density and glutamatergic receptor subtypes in the hippocampal formation. Offspring raised under conditions of low paternal care have increased NR2A and decreased NR2B mRNA (subunits of the N-methyl-D-aspartate receptor) and postsynaptic density protein 95 protein expression in the hippocampus (39). More recently, it was shown that, in the medial prefrontal cortex of this species, paternal deprivation leads to sex-dependent changes in dopaminergic and glutamatergic neurotransmission in pyramidal neurones that are paralleled by behavioural changes (56). Pyramidal neurones in the prelimbic and anterior cingulate regions of female offspring raised without the father present have a decreased response to dopaminergic stimulation, whereas the physiological response to NMDA receptor stimulation is elevated in both male and female father-deprived offspring.

Paternal deprivation may have consequences for homeostatic synaptic plasticity, whereby neurochemical, physiological and structural changes within neurones and synapses are induced to maintain an appropriate balance of excitatory and inhibitory activity within the central nervous system. In light of the decreased density of excitatory spine synapses observed in the orbitofrontal and somatosensory cortices of father-deprived degus, the 'homeostasis' hypothesis would predict that this effect would be compensated or counterbalanced by a reduction in inhibitory neuronal systems (62). However, in the orbitofrontal cortex, juvenile father-deprived degus display elevated numbers of inhibitory neurones (characterised by the Ca-binding protein CaBP-D28K), which primarily inhibit dendritic input (63). This increase of inhibitory tone is also manifest in an increased density of neurones that primarily serve to inhibit the axonal output of pyramidal neurones, expressing the Ca-binding protein parvalbumin (PARV). Thus, amongst father-deprived degus, the excitatory input of orbitofrontal neurones is not counterbal-

anced by reducing inhibition but rather amplified by increased inhibition (63). By contrast, a 'homeostatic' regulation of excitatory and inhibitory activity appears to occur in the amygdala, where the presumed increased dendritic input is paralleled by enhanced inhibition of dendritic and axonal activity. The density of inhibitory GABAergic neuronal subpopulations is also significantly altered in the hippocampus and nucleus accumbens of father-deprived degus (63,64). In the hippocampal formation, paternal deprivation results in elevated CaBP-D28k-positive neurones in the CA1, CA3 and dentate gyrus (DG) and an increased density of PARV-positive neurones in the DG and CA1 in juvenile offspring. The PARV-positive neurones in the nucleus accumbens are elevated in paternally deprived juvenile degu offspring, possibly indicating a dampened activity and reduced output (63).

Paternal deprivation studies have also illustrated the effects of paternal care on the development of catecholaminergic systems. In degus, paternal deprivation results in increased dopaminergic innervation of prefrontal cortical regions, indicating a dopaminergic 'hyper-innervation' caused either by enhanced fibre ingrowth and/or local sprouting or by suppressed pruning (65). This neurobiological change may have implications for a variety of behavioural outcomes, including impulsivity, aggression and alterations in motivated behaviour (66,67). Dopaminergic/noradrenergic innervation of limbic areas is also altered by paternal deprivation. A biphasic, age-dependent impact of paternal care on the maturation of dopaminergic innervation is observed in the core region of the nucleus accumbens of male degus, with a juvenile increase and a significant reduction in adult father-deprived degus (65). In Mandarin voles, paternal deprivation induces sex-specific changes in dopamine receptors in the nucleus accumbens. Although paternally deprived female offspring show a reduced expression of dopaminergic D1 and D2 receptor mRNA, these receptor mRNA levels are up-regulated in male offspring (68). Taken together, this specific sensitivity of the nucleus accumbens core region in response to paternal deprivation indicates that the availability of dopamine is altered in father-deprived animals. This may affect reward-evoked dopamine release and thus impair emotional and cognitive functioning. The hippocampal formation of father-deprived juvenile degus shows an elevated density of dopaminergic (CA1) and noradrenergic (DG) fibres (65). Norepinephrine plays a role in selective attention, general arousal and stress reactions, and has been implicated in learning and memory, addiction and affective disorders (69). Thus, the up-regulation of noradrenergic fibres in the DG of juvenile father-deprived animals, together with the increase in presumptive dopaminergic fibres in the CA1 region, may be indicative of cognitive and emotional dysfunction.

The HPA and hypothalamic systems regulating social and reproductive behaviour have been demonstrated to be particularly sensitive to early-life rearing experiences comprised primarily of mother–infant interactions, and these same systems are modulated by paternal care. In degus, the density of corticotrophin-releasing factor (CRF)-expressing interneurones is affected by paternal deprivation in an age- and region-specific manner (12,64). Paternal deprivation induces an elevated density of CRF-containing neurones in the orbitofrontal cortex and in the basolateral amygdala of juvenile male degus, whereas a reduced density of CRF-expressing neurones is seen in the DG and stratum pyramidale of the hippocampal CA1 region, and in the medial (but not lateral) bed nucleus of the stria terminalis (BNST) (64,70). With the exception of the CA1 region and the BNST, these deprivation-induced changes are no longer evident in adulthood, which suggests a transient change that, in later life, might be normalised by other socio-emotional experiences. In Mandarin voles, paternal deprivation reduces the expression of oestrogen receptor α in the BNST, medial preoptic area, ventromedial hypothalamic nucleus, medial amygdala, nucleus accumbens and arcuate hypothalamic nucleus (55,71). In addition, reduced oxytocin receptor expression in the medial amygdala and nucleus accumbens (in both males and females) and reduced serum oxytocin concentrations (only in females) is observed in father-deprived voles (55). In California mice, offspring reared by fathers that have been stimulated to display increased pup retrieval display more vasopressin-immunoreactive neurones in the dorsal BNST, whereas the opposite is observed in the ventral BNST (54). The experimental reduction of paternal grooming induces elevated vasopressin-immunoreactive in the paraventricular nucleus and increased corticosterone. These neuroendocrine changes may account for the increased anxiety-like behaviour and impaired social interactions observed in father-deprived offspring and may contribute to the transmission of these behavioural phenotypes to subsequent generations.

Paternal epigenetic inheritance

Although offspring development in biparental mammals is altered by paternal care and the deprivation of this care can lead to behavioural and neurobiological dysfunction, paternal effects on offspring can emerge even in species that are not biparental and where there is no contact between fathers and their progeny. Importantly, this phenomenon occurs in isogenic species and thus is unlikely to be attributed to inherited genetic variation. The influence of paternal characteristics or life experiences on offspring may also persist across multiple generations, indicating a transgenerational inheritance. Taken together, these observations have generated hypotheses regarding the role of epigenetic mechanisms in these inherited phenotypes (26).

Although genome-wide epigenetic re-programming occurs during the post-fertilisation phases of development (72), it has been observed that, at certain loci within the genome, there may be 'maintenance' of epigenetic variation that presumably escapes re-programming erasure. For example, variations in the DNA methylation status of an intracisternal-A particle (IAP) element, a long terminal repeat retrotransposon, can result in phenotypic variability that is heritable. This has been demonstrated elegantly in studies in which the IAP is inserted into either the agouti gene (*Avy*) or the the *AxinFu* allele (73–75). Imprinted genes, which exhibit parent-of-origin expression patterns, can also retain epigenetic marks across generations leading to epigenetic silencing of one of the parental alleles. Small RNAs (e.g. microRNA, piRNA) may also be transmitted across generations, suggesting the trans-

mission of multiple types of epigenetic marks (76,77). The possibility of inherited epigenetic information leading to phenotypic variation in offspring has led to increasing investigation of the epigenetic mechanisms that may contribute to the transmission of environmentally-induced characteristics. Although there is certainly potential for epigenetic transmission through both mothers and father, the inability to dissociate oocyte, *in utero* and postnatal maternal influences from germline epigenetic variation has turned the focus of much of this work to paternal transgenerational effects. Here, we highlight the literature exploring the impact of paternal nutrition, toxicological exposures and social environments on offspring development.

Paternal nutritional effects

In humans, the impact of maternal nutrition on offspring development and disease risk has been demonstrated in longitudinal studies following women who were pregnant during the World War II Dutch Famine (3) and there is emerging evidence for lasting epigenetic alterations in offspring that were exposed to this nutritional deprivation during foetal development (78). Evidence of the impact of paternal nutrition has also emerged suggesting that the nutritional exposures of grandparents can influence the metabolic function of grandchildren. In humans, archival data indicate that food availability during the pre-pubertal phase of grand-fathers is associated with an increased risk of cardiovascular disease, diabetes and mortality in grandsons (79,80). These data are highly suggestive of a paternal transgenerational epigenetic effect, leading to increased focus on the development of rodent models in which the mechanism of these effects can be established.

In laboratory rodents, offspring and grand-offspring of rat dams fed a low protein diet during gestation have elevated hypertension and, amongst both offspring and grand-offspring, there is a decrease in DNA methylation within the regulatory region of the glucocorticoid and peroxisome proliferator-activated receptor alpha (*Pparα*) genes (81–83). Amongst mouse dams that have been fed a high-fat diet from pre-conception to weaning, increased body length and reduced insulin sensitivity have also been observed in offspring (F1) and grand-offspring (F2) (84). Moreover, the transmission of these effects to F3-generation female offspring has been observed through the patriline (85). In rats, males that are fed a high-fat diet in adulthood produce female offspring that exhibit impaired pancreatic function (e.g. reduced insulin secretion and glucose tolerance) and this phenotype is associated with changes in the expression of genes associated with insulin regulation and glucose metabolism, as well as altered DNA methylation in the interleukin 13 receptor alpha 2 (*Il13rα2*) gene in pancreatic tissue (25). In mice, males that are fed a low-protein diet produce offspring that have altered DNA methylation within the enhancer region of *Pparα* gene in hepatic tissue (86). Hepatic expression of several microRNAs involved in cell proliferation and growth are likewise altered in offspring of male mice fed a low-protein diet (86). Collectively, these studies point toward a paternal epigenetic transmission of nutritional exposures that may be a significant predictor of disease risk in descendants.

Drugs and toxins

Although paternal pre-conception alcohol exposure in rats had previously been demonstrated to induce phenotypes in offspring comparable to foetal alcohol syndrome, even in the absence of any direct contact between fathers and offspring, the mechanism that could account for these effects was unclear (24). However, one of the most compelling examples of paternal epigenetic inheritance derives from toxicological studies. Prenatal exposure to the pesticide vinclozolin induces a transgenerational effect via the patriline (i.e. males exposed *in utero*) that impacts neurobiology, behaviour and health, and coincides with epigenetic marks that persist across generations (23,87,88). In rats, F3-offspring generated from a vinclozolin exposed male have impairments in reproduction, altered anxiety-like behaviour and increased disease risk (i.e. tumor formation, kidney disease). These patriline effects of *in utero* vinclozolin exposure induce DNA methylation changes in sperm that persist to F3-generation males (89). Global screens of DNA methylation of sperm reveal multiple differentially methylated sites in gene promoters in the male germline.

Revisiting the phenomenon of paternal alcohol exposure from the perspective of epigenetic inheritance has revealed that male alcohol consumption induces decreases in DNA methyltransferase levels in sperm, which may then lead to altered genome-wide DNA methylation and gene expression profiles (90). Male rats that are exposed to alcohol during *in utero* development exhibit later life deficits in pro-opiomelanocortin (POMC) function, and these deficits are associated with increased DNA methylation of the *Pomc* gene (91). These changes in DNA methylation are also observed in the sons (F2) and grandsons (F3) of alcohol-exposed males. In rodents, paternal cocaine exposure before mating can induce multiple phenotypic changes in offspring, including reduced body weight, impaired cognitive performance, increased indices of hyperactivity and depressive-like behaviour, as well as reduced cocaine self-administration (92–94). Offspring of cocaine-exposed males also have elevated levels of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex and this paternal effect may be achieved by altered histone acetylation levels within the *Bdnf* gene that are present in the testes and sperm of exposed males, as well as the prefrontal cortex of their offspring. MicroRNAs may also serve as a route of paternal transmission of drug and toxin exposure-induced effects because smoking, irradiation and benzo[a]pyrene exposure in males can induce altered microRNA levels in sperm and, in some cases, these epigenetic changes are observed in offspring (95–97).

Social experiences

The experience of variation in the social environment during both early and later phases of development can induce lasting changes in brain and behaviour and there is increasing evidence for the role of epigenetic changes as mediators of these effects (98) and for the paternal transmission of social experiences. Amongst male mice, maternal separation experienced during postnatal development induces social deficits (99) and altered anxiety- and depressive-like behaviours that persist across generations (100,101). These

transgenerational behavioural outcomes are associated with altered serotonergic function present in the offspring of maternally-separated males. Amongst male mice that experience postnatal maternal separation, there is increased sperm DNA methylation in the DNA binding protein gene, methyl CpG binding protein-2 (*Mecp2*) and in the cannabinoid receptor type 1 (*Cb1*) gene, as well as decreased methylation in the corticotrophin releasing factor receptor 2 (*Crfr2*) gene (101). These epigenetic changes persist in the cortex and sperm of the offspring of these males, suggesting that there may be incomplete erasure of DNA methylation marks in these target genes at the time of post-fertilisation genomic reorganisation. Moreover, the paternal transmission of epigenetic variation may occur even when variation in the social environment occurs in later life. In male mice, chronic social stress (achieved through instability of social hierarchy) experienced during adolescence through to adulthood can induce social deficits and increased anxiety-like behaviour in offspring and grand-offspring, and this transgenerational effect is only observed through the patriline (22). Chronic social defeat, which is used as a model of stress-induced psychopathology, can similarly lead to increased anxiety and depressive-like behaviour in exposed males and their offspring (102).

Paternal influence on mothers

The possibility that male experiences before conception can lead to epigenetic changes in the germline that are transmitted to subsequent generations has generated increasing excitement in the fields of neuroscience, epigenetics and genetics. This phenomenon may also have implications for evolutionary theory and public health. Moreover, this route of paternal influence provides the vast majority of mammalian species that do not engage in biparental behaviour with a mechanism whereby fathers can shape developmental outcomes in offspring. However, as with all new discoveries, this excitement should be tempered with an increasing appreciation of the complex routes through which parental influence can be achieved. In mammals, development occurs within an *in utero* and postnatal environment consisting of intense mother–infant interactions, and dissociating those influences from inherited epigenetic variation from fathers poses a significant methodological challenge. Artificial reproductive techniques, including *in vitro* fertilisation (IVF), offer an effective experimental strategy, and in humans are being increasingly applied to help understand the impact of inherited genetic, *in utero* and postnatal influences on the risk of psychiatric dysfunction (103,104). The use of IVF in the context of studies of the effect of paternal chronic social defeat stress in mice suggests that, although some phenotypes (i.e. depressive-like behaviour) are recapitulated in offspring when IVF is used, other phenotypes (i.e. anxiety-like behaviour) are not. Although the failure to observe epigenetic transmission following IVF could be associated with the epigenetic disruption that can occur during the IVF process (105), there is also the possibility that maternal factors contribute to the paternal influence on offspring development.

The influence of fathers on mothers is apparent in studies of biparental species, where father absence leads to reduced maternal care and father presence stimulates contact between both parents and offspring (47–49). In humans, the father can provide a source of social-emotional support for the mother (106), thus influencing mood, affect and the quality of mother–infant interactions. In cases where there is marital dissatisfaction, interpersonal violence or paternal drug use, fathers could lead to impaired mother–infant interactions through increased maternal stress exposure and environmental instability (107). However, the transmission of the effects of paternal chronic social stress to offspring that have been observed in mice, which are rendered incomplete following IVF, occur in the absence of any contact between father and offspring. Moreover, these studies were conducted in a mouse strain that does not exhibit a biparental rearing strategy (102). In the case of these and other comparable paternal effects, insights may come from a more indepth understanding of the dynamic adjustments in reproductive investment that are predicted and, in some instances, demonstrated as a function of mate preference or quality.

Maternal investment in offspring growth and development can be shifted in response to mate quality, resulting in either 'differential allocation' or 'reproductive compensation'. The differential allocation hypothesis suggests that females paired with a high-quality (typically attractive) male should increase their reproductive investment in offspring, particularly if the cost of reproducing is high (27,108). Alternatively, if females are paired with an unattractive or nonpreferred male, the compensation hypothesis predicts that these females would increase their investment towards offspring to compensate for any disadvantages they may inherit from their father (28). Support for both of these hypotheses has emerged across a wide variety of species (109,110). Interestingly, particularly in the context of environmentally-induced paternal influences, the level of a female's reproductive investment appears to be based on observed phenotype or perceived quality that is not attributable to genetic differences between potential mates. In laboratory inbred mice, females that are mated with males that have experienced social enrichment across their lifespan show elevated levels of postnatal maternal nursing and pup licking/grooming towards their offspring (111). Similarly, female zebra finches can be induced to lay heavier eggs and have offspring with larger growth rates, if they are paired with males that have been artificially made more attractive, and the female offspring of these males lay larger eggs in bigger clutches than those of unattractive fathers, indicating that these changes in maternal investment have multigenerational consequences (112,113). The ability of females to detect and form a preference for males that differ in nutritional, toxicological and social experiences is a critical factor within this theoretical framework, and it would appear that, in the case of paternal *in utero* food restriction (114) and vinclozolin exposure (29), female mate preferences are shifted towards males from non-exposed lineages.

Future directions

Although the study of parental influence on offspring development has traditionally focussed on the mother, the increasing appreciation of the study of biparental species as a more relevant model for developing translational research approaches and the evolving study of epigenetic inheritance through the male germline have

shifted focus to fathers. With this shift comes a more integrated understanding of parent–offspring interactions with the potential to better account for the origins of variation in offspring physiology, metabolism, neurobiology, behaviour and disease risk. One of the significant challenges for future research on paternal influences will be creating experimental paradigms that capture the complex and diverse pathways through which fathers can influence their progeny. Although it is possible that epigenetic inheritance has evolved as a mechanism for non-monogamous species that do not invest in paternal care to exert influence over their offspring, it is likely the case that paternal care, inherited epigenetic variation and paternal influences on mothers serve as complementary and interacting routes of parental influence. Although the controlled conditions of laboratory studies have their utility in elucidating mechanism, incorporating more ecologically relevant conditions in the study of paternal influence will be essential in furthering our understanding of the dynamics of the rearing environment, the cascade of developmental events that stem from variations in paternal care, the environmental conditions inducing epigenetic variation in fathers that is transmitted to subsequent generations, and the moderating influence of mothers on this transmission.

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