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REVIEW ARTICLE

Epigenetic paternal effects as costly, condition-dependent traits

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Abstract

It is now recognized that post-copulatory traits, such as sperm and ejaculate production can impose metabolic costs, and such traits are therefore expected to exhibit condition-dependent expression, whereby, low condition individuals experience a greater marginal cost of investment compared to high condition individuals. Ejaculates are especially costly in species where males invest in offspring quality through nutrient-rich spermatophores or other seminal nuptial gifts. However, recent evidence shows that, in species where males do not provision females or offspring, males can still influence offspring development through paternal effects mediated by epigenetic factors, such as non-coding RNAs, DNA methylation and chromatin structure. Because such epigenetic paternal effects do not involve the transfer of substantial quantities of resources, such as nutrients, the costs of conferring such effects have not been considered. Here we argue that if selection favours paternal investment in offspring quality through epigenetic factors, then the epigenetic machinery required to bring about such effects may also be expected to evolve strongly condition-dependent expression. We outline indirect evidence suggesting that epigenetic paternal effects could impose substantial metabolic costs, consider the conditions under which selection may act on such effects, and suggest ways to test for differential costs and condition-dependence of these effects. Incorporating epigenetic paternal effects into condition-dependent life history theory will further our understanding of the heritability of fitness and the evolution of paternal investment strategies.

Epigenetics and life history

Recent evidence shows that males across many taxa, including nematodes, insects, fish, and mammals, can influence offspring development and quality through epigenetic factors transferred in the sperm and/or semen (reviewed in Crean and Bonduriansky 2014; Rando 2016; Wang et al. 2017). These epigenetic factors can include small non-coding RNAs (ncRNAs), DNA methylation, and chromatin structure, and all these factors can alter gene expression in developing embryos (e.g., Milekic et al. 2015; Grandjean et al. 2015; Skinner 2016; Klosin et al. 2017).

Modifications of the methylation pattern or differences in chromatin structure of the paternal haploid genome in sperm can in some cases be retained throughout offspring embryonic development or even into adulthood, affecting important aspects of offspring phenotype and fitness (Guerrero-Bosagna et al. 2010; Manikkam et al. 2012; Vassoler et al. 2012; Kelly 2014; Klosin et al. 2017), and non-coding RNAs (such as miRNAs or tsRNAs) can be transferred to the zygote in the sperm and/or seminal fluid and can also alter gene expression in the offspring (Gapp et al. 2014; Stoeckius et al. 2014; Rodgers et al. 2015; Marré et al. 2016). Moreover, changes in multiple types of epigenetic factors often appear to be involved in paternal effects on offspring fitness. For example, high-fat diets in mice can alter the expression of miRNAs, methylation patterns, and chromatin structure in the paternal germline (Fullston et al. 2013; Duale et al. 2014; Barbosa et al. 2016), and these can then up- or down-regulate gene expression in offspring (affecting genes involved in metabolism, insulin secretion and glucose tolerance, and embryo development) and cause significant reductions in offspring health (e.g., Ng et al. 2010; Binder et al. 2012a, b; Fullston et al. 2013; Mitchell et al. 2017). While these well-characterised paternal effects act to reduce offspring fitness, there are many examples of non-genetic paternal effects that have the potential to increase offspring fitness by enhancing

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offspring survival and/or reproductive success (e.g., Bonduriansky and Head 2007; Zajitschek et al. 2017; Crean et al. 2013; Delcurto et al. 2013; Jensen et al. 2014; Evans et al. 2017). Paternal effects with both negative- and positive-effects on offspring fitness can be mediated by similar epigenetic mechanisms. Yet, despite their potential importance, there has been little to no incorporation of epigenetic paternal effects into life history theory.

A central idea in life history theory is that persistent directional selection on fitness-enhancing traits can lead to trait exaggeration and thereby drive up the metabolic cost required to produce the trait. Therefore, the amount of metabolic resources available to an individual (i.e., its condition) is expected to determine the expression of such a costly trait, resulting in condition-dependent trait expression (Andersson 1982; Nur and Hasson 1984; Grafen 1990; Iwasa et al. 1991; Kotiaho 2001; Cotton et al. 2004). Individuals that have fewer metabolic resources (i.e., are in low condition) are less able to invest in costly traits compared to individuals that have more metabolic resources (i.e., are in high condition)—that is, low condition individuals experience a higher marginal cost of trait expression. This theory has been extensively applied to secondary sexual traits, such as displays and weaponry (Moller and Delope 1994; Mappes et al. 1996; Kotiaho 2000; Judge et al. 2008) and, more recently, to post-copulatory traits, such as sperm quality and quantity (reviewed in Fitzpatrick and Lüpold 2014; Lüpold et al. 2016; Godwin et al. 2017) and ejaculate size and composition (Eberhard and Cordero 1995; Linklater et al. 2007; Perry and Tse 2013; Friesen et al. 2015; Bretman et al. 2016; Wigby et al. 2016). All these traits are important for male reproductive success and can therefore be exaggerated by selection.

Selection can also favour paternal investment in offspring quality (Maynard Smith 1977; Clutton-Brock 1991; Sheldon 2002; Requena and Alonzo 2017). The costs and condition-depedence of paternal investment have been examined in species where males directly provision their offspring through paternal care (reviewed in Clutton-Brock 1991; Badyaev and Hill 2002; Kelly and Alonzo 2009), or confer nutrient-rich spermatophores or other types of glandular nuptial gifts to females (Gwynne and Simmons 1990; Michaud et al. 2013; Mirhosseini et al. 2014). Such seminal provisioning is typically associated with the production of very large ejaculates that are expected to require substantial investment of resources and to impose substantial metabolic costs. However, such obvious forms of paternal investment are lacking in most species (Eberhard 1997).

More recently, it has been recognised that paternal investment may extend beyond parental care and nutrient provisioning, with calls to generalize the definition of parental investment beyond a 'nutrition-centric' view to include any investment in an offspring that reduces the parent's ability to invest in future offspring (Royle et al. 2012; also see Trivers 1972). If the molecular mechanisms that mediate the transmission of epigenetic factors from fathers to their offspring are costly to build, maintain and deploy, then epigenetic paternal effects are encompassed by this definition of paternal investment. Below, we argue that epigenetic paternal effects that enhance offspring fitness are indeed likely to be costly, and that such effects should be incorporated into life-history theory as condition-dependent paternal investment traits. In addition to behavioural and nutritional provisioning, males may increase offspring survival and/or reproductive success through investment in molecular processes that shape the epigenome in the paternal germ-line and determine the nature of the epigenetic factors transferred to offspring via the sperm and seminal fluid. This can then provide variation for selection to act on, with the fitter offspring surviving to confer the ability to invest in offspring through such epigenetic molecular mechanisms. Selection for enhanced offspring fitness through epigenetic inheritance may then further drive up the metabolic cost of molecular investment, resulting in strongly condition-dependent investment, like that observed in other fitness-enhancing traits (Moller and Delope 1994; Rowe and Houle 1996; Kotiaho 2000; Perry and Rowe 2010).

Obviously, epigenetic factors transmitted through the germ-line can also mediate maternal effects (reviewed in Aiken et al. (2016)). However, because maternal effects can occur via a wide range of mechanisms, such as the egg cytoplasm, the intrauterine environment, or post-partum provisioning (Champagne 2008), the role of germ-line epigenetic factors can be difficult to establish and such factors are unlikely to constitute a major component of total maternal investment. By contrast, in species where males do not provide parental care or nutritional resources, epigenetic paternal effects are likely to comprise a large share of total paternal investment. We therefore focus our discussion on paternal effects mediated by epigenetic factors.

Is epigenetic machinery costly to build and maintain?

Several lines of evidence suggest that the cost of maintaining a 'good' epigenetic profile could be substantial, and individuals that are unable to invest in maintaining a good epigenome are likely to produce lower quality offspring. First, changes in chromatin structure, RNA synthesis, DNA methylation and some de-methylation require energetic and material investment in tightly regulated molecular processes. Such processes include histone acetylation, RNA synthesis, and the expression and deployment of DNA

methyltransferases (DNMTs) and methyl-CpG-binding domain (MBD) proteins. All these processes require ATP to provide energy to build and deploy (Gaal et al. 1997; Amiott and Jaehning 2006; Wellen et al. 2009; Bhutani et al. 2011; Horvath 2013). Therefore, individuals that do not have substantial metabolic reserves may be less able to invest in these metabolic pathways.

The most extensively studied of these epigenetic factors is DNA methylation. In mammals and plants, it has been shown that newly synthesised DNA lacks methylation until maintenance methyltransferases (DNMT1) restore methylation patterns through some type of memory mechanism (Okano et al. 1999; Saze et al. 2003; Kato et al. 2007). Horvath (2013) proposed that a substantial amount of energy is needed to maintain epigenetic stability during the stressful period of development when the rate of cell division is high. This may explain why we see such pronounced effects of males' developmental environment on their subsequent capacity to influence the development of their offspring (Bonduriansky and Head 2007; Burdge et al. 2007; Kaati et al. 2007; Bonduriansky et al. 2016). Horvath (2013) also suggested that constant energy expenditure may be required to maintain epigenetic stability throughout adult life, given that DNMTs need to be deployed to maintain existing methylation patterns. Any perturbations such as stress or exposure to toxins may therefore lead to epigenetic dysregulation.

If both the establishment and maintenance of epigenetic machinery are costly, then environmental conditions both during development and during adult life may be expected to affect the epigenome. Such costs may be expected to apply to the maintenance of the epigenome in the soma as well as the germ-line, where epigenetic changes resulting from environmental perturbations can be transmitted to offspring (Lambrot et al. 2013; Guerrero-Bosagna and Skinner 2014; Kitamura et al. 2015). This could explain why both juvenile and adult environments are sometimes found to influence paternal effects on offspring fitness (Ducatez et al. 2012; Adler and Bonduriansky 2013; Braun and Champagne 2014; Fricke et al. 2015; Macartney et al. 2017). However, some paternal effects could be programmed during a specific ontogenetic phase. For example, if the epigenetic machinery involved in such effects is built during embryonic development, then the nutrient abundance or stress experienced by males during a specific sensitive phase of development could largely determine the paternal effects they will confer as adults if environmental perturbations also disrupt epigenetic regulation of the germ line (e.g. Bonduriansky and Head 2007; Kaati et al. 2007; Macartney et al. 2017).

Hypomethylation and (to a lesser extent) hypermethylation of some sites occur with age throughout the mammalian genome—a process known as the 'epigenetic clock' (Bellizzi et al. 2012; Horvath 2013; Marttila et al. 2015; Milekic et al. 2015; Breitling et al. 2016). Changes in chromatin structure and RNA transcriptional dysfunction have also been shown to increase with age (reviewed in Ashapkin et al. 2017), and several studies have shown that these epigenetic changes to DNA methylation, chromatin structure and RNA synthesis can be accelerated by stress and toxins (Dick et al. 2014; Duale et al. 2014; Horvath et al. 2014; Beach et al. 2015; Boks et al. 2015; Gao et al. 2016). These changes in epigenetic regulation probably reflect negative effects of age and stress on the epigenetic maintenance system (Bellizzi et al. 2012; Horvath 2013; Breitling et al. 2016). Such epigenetic dysregulation has been demonstrated to occur in the germ-line, as well as the soma (e.g. Lambrot et al. 2013; Duale et al. 2014; Milekic et al. 2015; Rodgers et al. 2015), suggesting that some age- and stress-induced epigenetic changes can be transmitted to offspring through transgenerational epigenetic inheritance (Miller et al. 2010; Danchin et al. 2011; Seong et al. 2011; Jenkins and Carrell 2012; Soubry 2015). Just as individuals that are in high condition can prevent or repair genetic mutations better than individuals in low condition (Agrawal and Wang 2008; Skinner et al. 2015; Skinner 2016), males in high condition may be better able to protect or repair the epigenome of their soma and germ-line from age- and stress-induced dysregulation, and thereby produce offspring of higher quality.

In addition to the energetic costs of investing in protection and repair of the epigenome, the ability to synthesize epigenetic factors can be limited by access to certain biochemicals. For example, methylation requires methyl groups, which are derived from dietary methionine—an amino acid that can be limited by the availability of certain foods (Grandison et al. 2009), and dietary glucose appears to play an important role in histone acetylation which influences chromatin structure (Burdge and Lillycrop 2010). Therefore, access to specific dietary nutrients, as well as metabolic energy can influence and limit the expression of epigenetic factors, and thereby affect the maintenance and repair of the epigenome.

Selection on epigenetic paternal effects

As with investment in other forms of paternal provisioning, selection for males to invest in offspring quality through epigenetic paternal effects will only occur under certain conditions (Kokko 1999; Kokko and Jennions 2008; West and Capellini 2016; Requena and Alonzo 2017). Selection may occur directly through female mate choice, if females discriminate among males based on an honest signal of paternal epigenetic investment. While male sexual signals typically exhibit condition-dependent expression, some

components of the male phenotype may specifically reveal male epigenetic quality and such signals should be investigated in the future. Females could evolve preferences based on these signals, and such signaler-receiver coevolution could be prevalent in non-resource-based systems where conventional forms of paternal investment are lacking (Crean et al. 2016).

Selection may also occur indirectly, if the epigenetic paternal effect enhances offspring fitness, such that offspring are more likely to inherit and pass on genetic alleles that cause the development of the required epigenetic machinery. The fitness gains from any form of paternal investment will depend on paternity certainty, which reflects the likelihood of female re-mating and the risk of cuckoldry (i.e., the use of resources provided by one male to enhance the quality of another male's offspring) (e.g. Wickler 1985; Gwynne 1988). When the risk of cuckoldry is high, selection may instead favour males that invest in traits that enhance mating success. However, if paternal investment is conferred through factors transferred within the sperm and associated with paternal DNA (for example, via DNA methylation, chromatin structure, and sperm-borne ncRNAs), the risk of cuckoldry will be negligible or absent as the epigenetic factors are tied directly to fertilisation. Therefore, paternal investment mediated by sperm-borne epigenetic factors may be more likely to evolve than other mechanisms of paternal investment (Bonduriansky and Day 2013). Paternal investment though epigenetic factors may therefore be taxonomically widespread.

In particular, males of some species can confer their condition to offspring through epigenetic factors (Bonduriansky and Crean 2017), with high condition males producing better quality offspring relative to low condition males (e.g. Bonduriansky and Head 2007; Delcurto et al. 2013; Evans et al. 2017; Zajitschek et al. 2017). For example, such condition-transfer effects have recently been reported in the guppy *Poecilia reticulata*, where epigenetic factors attached to the sperm of fathers reared on a high-quantity diet produced larger offspring and probably enhanced juvenile survival (Evans et al. 2017). Such effects have also been demonstrated in the neriid fly, *Telostylinus angusticollis*, where fathers reared on a nutrient-rich diet produce larger offspring (Bonduriansky and Head 2007), likely through epigenetic factors (Crean et al. 2014).

While larger body size may be advantageous across a wide range of environments, males of some species may also anticipate the environment that their offspring are likely to experience and produce offspring that are better suited to that environment ('anticipatory effects') (Marshall and Uller 2007; Burgess and Marshall 2014). For example, Crean et al. (2013) and Jensen et al. (2014) demonstrated anticipatory effects of male environment in a broadcast spawning ascidian (*Styela plicata*) and marine tubeworm (*Hydroides diramphus*) respectively, most likely through epigenetic changes to the sperm. Both condition-transfer and anticipatory effects can enhance offspring fitness, providing an indirect benefit to the father and generating positive selection on the cellular and physiological mechanisms involved in the paternal effect. Both condition-transfer and anticipatory effects are also likely to be costly for males, requiring the synthesis, maintenance and deployment of epigenetic factors that alter offspring development.

Conversely, epigenetic paternal effects can be detrimental. As mentioned previously, stressed or senescent individuals can undergo epigenetic dysregulation (Jirtle and Skinner 2007; Horvath 2013), and transmit some of these epigenetic changes to their offspring (e.g. Rassoulzadegan et al. 2006; Manikkam et al. 2012; Weyrich et al. 2016). This can then result in offspring with decreased health and increased susceptibility to disease (Miller et al. 2010; Danchin et al. 2011; Seong et al. 2011; Jenkins and Carrell 2012; Rando 2012; Soubry 2015). Marshall and Uller (2007) suggest that such 'transmissive' effects occur due to physiological constraints on the expression of reproductive traits. Therefore, selection should favour males that are able to overcome such physiological constraints by investing more metabolic resources in maintaining a healthy germline epigenome to produce healthier offspring. High condition individuals possess more metabolic resources and may therefore be better able to prevent transmissive effects by investing in costly molecular mechanisms that protect or repair the epigenome.

Predictions and empirical tests

There is currently a dearth of empirical and theoretical work directly exploring the costs and condition-dependence of investment in epigenetic factors, including the molecular machinery involved in non-genetic paternal effects. Two important questions that require empirical research and that are key to furthering our understanding of the evolution and ecology of paternal effects mediated by epigenetic factors are: (1) Under what conditions does selection favour male ability to influence offspring quality through transmission of beneficial epigenetic factors via the germ-line and/or through suppression of detrimental epigenetic effects?; and (2) does investment in epigenetic paternal effects result in life-history trade-offs similar to the trade-offs that limit investment in other costly reproductive traits?

To address question (1), it is necessary to determine whether males that confer positive epigenetic effects through their germ-line have higher fitness than males that do not confer such effects, and whether variation in the ability to confer such paternal effects is heritable. If both

conditions are met, then the ability to confer such epigenetic effects to offspring may be expected to evolve. It would also be interesting to determine whether females preferentially mate with males that produce better quality offspring via such epigenetic effects, given that female preferences could contribute to selection on males to confer such effects (Bonduriansky and Day 2013; Bonilla et al. 2016; Head et al. 2016). For example, a model by Bonduriansky and Day (2013) showed that paternal condition-transfer effects in species where males do not provide conventional forms of paternal provisioning could drive the evolution of costly female mate choice. Such female preferences could drive increased male investment in offspring quality. Importantly, given the potential for epigenetic paternal effects, the evolution of paternal investment can occur in species where opportunity for conventional forms of paternal investment (such as paternal care or nutrient-laden nuptial gifts) is lacking. For example, such effects can evolve in species such as guppies (Evans et al. 2017) and neriid flies (Bonduriansky and Head 2007) or in broadcast spawning species (Crean et al. 2013; Jensen et al. 2014), where males transfer small ejaculates and do not interact with their offspring.

Regarding question (2), if investment in offspring quality through epigenetic factors carries a substantial metabolic cost, then such investment may be predicted to respond to variation in the availability of metabolic resources, and to trade-off against investment in other costly fitness components, as predicted by life history theory (Stearns 1989; Zera and Harshman 2001; Roff and Fairbairn 2007). For example, we might expect to see a decline in offspring quality with increased mating (or an increase in other costly life-history traits that may trade-off with investment in offspring) due to a reduction in the ability to maintain the synthesis and/or maintenance of epigenetic factors in the germ-line. We may also expect to see a steeper decline in offspring quality in low condition individuals compared to high condition individuals if investing in these factors is condition-dependent. This has been demonstrated in males that produce spermatophores: in such species, depletion of male stores through repeated mating can reduce spermatophore size (Rutowski 1979; Marcotte et al. 2007; Michaud et al. 2013) and alter offspring development (Michaud et al. 2013; Mirhosseini et al. 2014). However, such reductions in offspring quality have not yet been demonstrated in species where paternal effects on offspring performance are mediated by epigenetic factors. We may also expect to see a trade-off with other life-history traits, such as somatic maintenance and lifespan, as observed in males that transfer costly spermatophores (Mishra and Omkar 2006; Perry and Tse 2013). However, in order to directly test for costs of investment in epigenetic factors, and determine whether investment is condition-dependent (i.e., whether investment involves differential marginal costs to high condition vs. low condition males), male condition and the expression of the epigenetic factors that mediate paternal effects will need to be manipulated (as suggested by Kotiaho (2001) in relation to the costs and condition-dependence of secondary sexual traits).

Epigenetic factors could be manipulated by creating 'knockout' lines for particular RNAs, administering oligonucleotides or synthesized RNAs, or by using CRISPR-Cas based tools (e.g. Vasudevan et al. 2007; McDonald et al. 2016; Abudayyeh et al. 2016). These approaches may allow researchers to experimentally up- or down-regulate the expression of specific epigenetic factors involved in paternal effects or epigenetic regulation systems such as DNMT1s that maintain epigenetic integrity, and then measure how males of different condition respond to changes in such factors. For example, if the expression of an epigenetic factor is upregulated, we may expect males of low condition to suffer a steeper decline in other life-history traits because of the higher marginal costs of investment in the epigenetic machinery. We may also detect an exaggerated decline in other life-history traits if the epigenetic machinery is upregulated in older individuals, since older individuals may suffer a larger marginal cost of maintaining epigenetic integrity relative to young individuals. These effects are likely to interact, such that the effect of old age is accentuated by low condition. Such experiments would make it possible to test for differential costs of investment in epigenetic paternal effects, and potentially make it possible to quantify such costs.

Conclusion

Establishing to what extent paternal effects transmitted through epigenetic factors function as costly and condition-dependent life-history traits requires additional theoretical and empirical work, and will necessitate overcoming some practical challenges. Progress will require an understanding of when investment in the epigenetic machinery occurs (i.e., are the key epigenetic systems built during juvenile development, or during the adult stage?), knowing what epigenetic factors are involved in influencing offspring quality in specific study species, as well as the ability to manipulate individual condition and investment in epigenetic factors that mediate paternal effects. Although, the technology available for direct manipulation of epigenetic mechanisms is currently limited, it is progressing at a rapid rate (e.g., Frye et al. 2016; McDonald et al. 2016; Abudayyeh et al. 2016; Pulecio et al. 2017). And while we have focused on the most widely studied epigenetic factors (DNA methylation, ncRNAs and chromatin structure), the sperm and semen also contain many other non-genetic factors (such as cytoplasmic and accessory-gland proteins) that are not

conventionally regarded as forms of nutrient provisioning or categorized as instances of transgenerational epigenetic inheritance, but that could nonetheless influence offspring development.

Understanding the differential costs and condition dependence of non-genetic paternal effects mediated by epigenetic factors will make it possible to extend life history theory to encompass this poorly understood facet of male reproductive strategies. Understanding such effects will also shed light on a potentially important component of variation in offspring performance, and a potential factor in the evolution of female mate choice. Moreover, epigenetic paternal effects could provide a valuable opportunity to investigate the costs of building, maintaining and deploying various types of epigenetic machinery—a question that remains almost entirely unexplored.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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