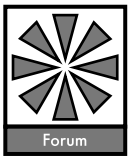

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Epigenetic effects of infection on the phenotype of host offspring: parasites reaching across host generations

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Parasite-induced changes in host phenotype are now well-documented from a wide range of taxa. There is a growing body of evidence indicating that parasites can also have trans-generational consequences, with infection of a host leading to changes in the phenotype of its offspring, though the latter are not parasitised. Several proximate mechanisms have been put forward to explain these 'maternal' effects, most involving hormonal or other physiological pathways, ultimately leading to offspring that are pre-adapted to the parasites they are most likely to encounter based on their mother's experience. Here, we propose that all these trans-generational effects on offspring phenotype must involve epigenetic phenomena. Epigenetics concerns the appearance and inheritance of seemingly new phenotypic traits without changes in the underlying DNA sequence. Since diet and other environmental factors experienced by a mother can affect gene expression in her offspring by turning genes 'on' or 'off' (for example, via DNA methylation), why couldn't parasites do it? Although epigenetic effects have not been explicitly invoked to account for trans-generational impacts of parasites on the phenotype of host offspring, the existing evidence is fully compatible with their involvement. We argue that epigenetic mechanisms must play a central role; we also discuss their evolutionary implications and suggest questions for future investigations in this new and exciting research direction.

Parasite-induced changes in host phenotype are now well-documented for a wide range of host and parasite taxa (Moore 2002, Thomas et al. 2005, Poulin 2007). In many of the best-known examples, these changes appear advantageous for the parasites. For instance, parasite-induced changes in host phenotype can result in the current host becoming more vulnerable to predation by the parasite's next host (Moore 2002, Poulin 2007). Alternatively, the altered host phenotype may cause the host to move to microhabitats where the parasite must go to complete its transmission cycle (Moore 2002, Poulin 2007). Although the proximate mechanisms by which parasites manipulate the behaviour, colour or morphology of their hosts have only been elucidated for a handful of cases, some sort of chemical interference with host neurochemistry, endocrine function or gene expression is thought to play an important role (Thomas et al. 2005). In other situations, phenotypic changes shown by parasitised animals are interpreted as host adaptations aimed at eliminating the infection or reducing its cost (Moore 2002).

To date, whether phenotypic changes are thought to benefit the host or the parasite, the assumption has mostly been that parasitism can directly modulate host phenotype, but, in the absence of vertical transmission (parent-to-offspring transmission), not directly influence the phenotype of the host's offspring. There is good evidence that many animals infected with harmful parasites produce fewer offspring, and sometimes smaller offspring if the mother cannot allocate sufficient energy to reproduction (Hakkarainen et al. 2007), but deeper effects on offspring phenotype are not expected as a direct consequence of the mother being parasitised. Recent developments in epigenetics combined with evidence from studies of trans-generational effects of parasitism suggest otherwise, however. Put simply, epigenetics concerns the appearance and inheritance of seemingly new phenotypic traits without changes in the underlying DNA (Jablonka and Lamb 1999, Jaenisch and Bird 2003, Fraga et al. 2005, Richards 2006). Several dietary components and other environmental factors experienced by a mother are now known to affect gene expression, but not DNA sequence, in her offspring. The classic example comes from studies on mice in which fur colour is affected by a single gene: a dietary supplement given to pregnant female mice has the effect of turning 'off' that gene in the embryos (Morgan et al. 1999, Waterland and Jirtle 2003). Because gene expression is thus permanently altered in the offspring, their phenotype (coat colour and associated traits) will differ from that expected solely from their genotype in the absence of the supplement. This process of genetic suppression is generally the outcome of DNA methylation or histone acetylation, both molecular mechanisms that mediate epigenetic phenomena (Jones and Takai 2001, Jaenisch

and Bird 2003, Richards 2006). For instance, a methyl group binding to a gene can silence its expression. Genes can be partially methylated, and the degree of methylation correlates roughly with how active the gene remains. Several environmental factors can cause DNA methylation and thus have epigenetic effects (Jaenisch and Bird 2003).

So why not parasites? They are just as important as diet and other environmental factors for host fitness in general. In addition, many parasites reproduce at a maximum rate during the host reproductive period (Møller 1997), which gives them plenty of opportunities to exert direct effects on the host's offspring. Furthermore, there is evidence that parasites can modulate gene expression in their host. For example, larval trematode parasites affect gene expression in their snail hosts (Coustau et al. 2003, Hertel et al. 2005). An infected snail is eventually castrated by trematode infection, but prior to castration it is reasonable to expect that such effects at the genomic level could also occur in the snail's embryos and translate into phenotypic alterations at the whole-organism level. Therefore all the ingredients are in place for a link between parasitism and epigenetics.

Here, we provide evidence for potential epigenetic effects of parasitism, often manifested as a 'maternal effect' in which infection of the mother alters the phenotype of her offspring. The evidence presented here comes from the literature, but our interpretation of these findings and their underlying cause often differs from that of the authors of the original studies. Surprisingly, no one has yet made an explicit link between the known trans-generational effects of parasites and the recent discovery of epigenetic mechanisms; we make this link here. We also touch upon some of the evolutionary implications of this phenomenon.

Parasitism and maternal effects

Perhaps the best-documented effect of maternal infection on offspring phenotype involves vertically transmitted sex-ratio distorters, such as the *Wolbachia* bacteria (Bouchon et al. 1998). Microsporidians provide another good example. These parasites invade the cytoplasm of the ova of their female crustacean hosts, and are thus transmitted from mother to offspring (Dunn et al. 1995, 2001). Because infected males cannot pass on the parasite to their offspring via sperm, they are dead ends with respect to transmission. Microsporidians are notorious for biasing the sex ratio of a mother's offspring to increase the proportion of female progeny, thus ensuring their continued transmission down the generations (Dunn et al. 1995, 2001). They often achieve this by feminising male offspring, for instance by suppressing the development or functioning of the androgenic gland during or after embryogenesis (Rodgers-Gray et al. 2004), turning genetic males into phenotypic females. This, however, is not a true maternal or epigenetic effect because the parasite infects the offspring as well as the mother, and can directly act on offspring phenotype. Vertically transmitted parasites will not be discussed any further and are excluded from all following examples.

Another well-known case of maternal effects of parasitism involves trans-generational priming of the immune system. In many plants, exposure to phytophagous insects (which are in many ways equivalent to parasites) has trans-generational consequences, with seedlings from parents subjected to herbivory displaying more resistant phenotypes (Agrawal 2001, 2002). In animal species ranging from insects to vertebrates, exposure of the mother to either actual infection or simply antigens from a parasite generally causes her offspring to display greater immunity against the same pathogen, compared to offspring of control mothers (Kristan 2002, 2004, Grindstaff et al. 2006, Moret 2006). In these cases, however, there is often a direct transfer of antibodies from mother to offspring, instead of, or in addition to, purely epigenetic effects.

The truly interesting cases of maternal effects of parasitism involve life history or behavioural changes in the offspring of infected mothers compared to those of uninfected mothers. These trans-generational phenotypic effects are not as easily attributable to substances such as antibodies passed down from the mother. Some of the best examples are summarised in Table 1. Although some studies have found no maternal effect of infection on offspring sizes (Willis and Poulin 1999), others report that offspring of parasitised mothers achieve larger initial sizes, higher growth rates, different internal morphology, or different body composition than those of unparasitised mothers (Sorci and Clobert 1995, Rolff 1999, Kristan 2004, Badyaev et al. 2006). These results can be interpreted as the outcome of adjustments of maternal investments in reproduction. In contrast, Sorci and Clobert (1995) suggested that in a relatively stable environment where infection levels incurred by a mother are a good indication of what her offspring are likely to experience, any 'information' passed on to the offspring that will allow them to adopt suitable life history traits will confer upon them a considerable selective advantage. They also suggested that stress-induced hormonal changes may be the proximate cause of these maternal effects. This mechanism is not incompatible with the epigenetic processes proposed here.

Table 1. Summary of maternal effects of parasite infection on offspring phenotype.

Host species	Parasite	Effect on offspring	Source
Locust, *Schistocerca gregaria*	Fungus	Different phase state (colour and behaviour)	Elliot et al. 2003
Damselfly, *Coenagrion puella*	Mite	Larger body size	Rolff 1999
Lizard, *Lacerta vivipara*	Mite	Altered dispersal or running speed	Sorci et al. 1994
Lizard, *Lacerta vivipara*	Mite	Higher growth rate	Sorci and Clobert 1995
Finch, *Carpodacus mexicanus*	Mite	Higher growth rate	Badyaev et al. 2006
Great tit, *Parus major*	Flea	Reduced dispersal	Tschirren et al. 2007
Mouse, *Mus musculus*	Nematode	Higher growth rate and altered internal morphology	Kristan 2002
Mouse, *Mus musculus*	Nematode	Altered internal morphology and body composition	Kristan 2004
Mouse, *Mus musculus*	Nematode	Greater exploratory behaviour	Rau 1985

Perhaps the most interesting maternal effects of parasitic infection are those involving changes in offspring behaviour. For instance, Sorci et al. (1994) found that sprint speed and the tendency to disperse in young lizards depend on whether or not their mother was infected by harmful mites during gestation. Similarly, Tschirren et al. (2007) found that in great tits, offspring of flea-infested mothers disperse shorter distances from their nest than those of uninfected mothers. A parallel experiment indicated that this maternal effect results from the lower concentrations of yolk androgens deposited in their eggs by flea-infested mothers compared to uninfected mothers (Tschirren et al. 2007). Elliot et al. (2003) found that offspring of desert locusts in their 'gregarious' phase were much more likely to be in the 'solitarious' phase state if their mother was infected by a fungal pathogen. The 'gregarious' and 'solitarious' phases are characterized by completely different morphologies, colouration and behaviour. Further experiments suggest that the altered phenotype of these offspring may be a consequence of the behavioural fever response adopted by the mother locust to combat the infection (Elliot et al. 2003). These findings are fully compatible with epigenetic effects, as altered gene expression in the offspring has to occur lower down the cascade of events initiated by either androgen transfer to eggs (great tits) or feverish body temperature (locusts) in the mother.

Even more intriguing are the results of Rau (1985), who studied the effect of the parasitic nematode *Trichinella spiralis* on offspring behaviour in mice. In Rau's (1985) experiment, all young born from a natural mother were transferred to a foster mother within one day of birth. Young mice born of an infected natural mother and reared by an infected foster mother were much faster to emerge from their cage into an open arena than offspring of uninfected natural mothers reared by uninfected foster mothers; young mice with only one mother, either the natural or foster one, that was infected displayed intermediate behaviour (Rau 1985). These results suggest that infection of the mother has both pre- and post-natal effects on offspring behaviour. Rau (1985) suggested that pre-natal effects may be the product of physiological stress induced by the parasite, whereas post-natal effects were ascribed to the poorer health of the mother, leading to fewer behavioural interactions with the pups and thus to the latter receiving less attention and stimulation. The pre-natal effects are also consistent with epigenetic mechanisms since the physiological impact of parasitism is not too different from that of diet, and the latter is known to mediate epigenetic effects in rodents (Morgan et al. 1999, Waterland and Jirtle 2003). With respect to post-natal effects, it is interesting to compare Rau's (1985) results with those of Weaver et al. (2004), who recently found that post-natal interactions between mother mice and their offspring have epigenetic effects. Using a similar cross-fostering experimental design to control for purely genetic differences, Weaver et al. (2004) found that high levels of pup licking and grooming result in altered DNA methylation profiles in the young mice. These changes in the epigenomic state of genes were also associated with differences in behaviour that persisted into adulthood. Put together, these studies show that the impact of a parasite can cross the trans-generational barrier: infection of a mother both before and after the birth of its offspring can lead to different patterns of gene expression, and therefore phenotypic alterations, in these offspring by causing certain genes to be switched 'on' or 'off'.

Infection itself may not always be necessary for trans-generational effects on host offspring. Sometimes, only the perceived risk of infection, for instance via detection of chemical cues from the parasite, may be enough to induce trans-generational phenotypic changes in offspring. This phenomenon has been documented for insects exposed to scents from hymenopteran parasitoids (Mondor et al. 2004), and could well apply to other host–parasite systems.

Recent proteomic studies of parasitised animals suggest that infection can lead to changes in the protein synthesis profile of the host, presumably as a result of altered gene expression (Biron et al. 2005a, 2005b). Some of these changes may be directly and actively triggered by the parasite, whereas others may be host responses to infection. The key point is that infection can lead to these changes, one way or the other. If this is possible within the host, then why not in its offspring if the host is producing or carrying young while infected?

Parasitism, epigenetics and evolution

We propose that some form of epigenetic phenomena must be involved in any trans-generational effect of parasitism. At some point in the chain of physiological events that lead to offspring of parasitised mothers displaying a different phenotype from what they would otherwise show, genes have to be either silenced or turned 'on', or up- or down-regulated, to implement the phenotypic change. Investigating where in the genome these epigenetic events take place could shed light on the phenotypic impact of specific genes.

It is important here to examine the distinction between maternal effects and epigenetic inheritance. The former can be seen as a special case of the latter, since epigenetic mechanisms can underlie most maternal effects. In the case of classical, or genetic, maternal effects, the mother's genotype influences the offspring phenotype whether or not the offspring inherit the maternal gene, whereas in the case of environmentally-induced maternal effects, the maternal genotype has an effect only if prompted by environmental factors (Mousseau and Fox 1998). We propose that parasitism is such a factor. The possible mechanism through which maternal effects are manifested in the offspring may be parasite-induced maternal products, such as stress hormones or fever compounds, affecting gene expression in the offspring. There is evidence that these parasite-mediated maternal effects can be sex-biased, with male and female offspring affected in different ways (Sorci et al. 1994, Badyaev et al. 2006), an observation that needs to be investigated further.

One issue that needs to be addressed briefly is whether these epigenetic, trans-generational effects are beneficial for the parasite or for the host. On the one hand, they could represent extreme examples of the extended phenotype (sensu Dawkins 1982) in which genes in the parasite genome have far-reaching effects on the phenotypes of its host's offspring. In the examples available to date, this scenario does not appear likely: finding explanations for the effects listed in Table 1 that are compatible with benefits for

the parasite is quite difficult and involves much speculation. On the other hand, epigenetic effects of parasitic infection could benefit the host by pre-adapting the offspring for the pathogens they are likely to encounter based on the parent's own experience. This kind of argument seems more compatible with the results of available studies.

Given the potential fitness benefits of adjusting offspring phenotype to local conditions by regulating gene expression, it is highly probable that the biochemical pathways that lead to methylation of specific genes under certain circumstances have themselves been shaped by natural selection. Here we must distinguish between different types of epigenetic effects: those that are transmitted through the germ line (Anway et al. 2005, 2006), and those that are somatic and transmitted via the developmental reconstruction of the mother's gene expression profile in the offspring (Weaver et al. 2004). Epigenetic changes affecting the germ line can be passed on down the generations, to the mother's grandchildren and their offspring. If parasite-induced epigenetic affects are of this type, parasitic pressure can lead to an evolutionary change in the host population. In humans, for instance, infectious diseases have been and continue to be a major cause of human mortality throughout the world. Because children with low birthweight are usually more susceptible to infections than others, natural selection should have operated on mechanisms (e.g. physiology, psychology, behaviour . . . and why not epigenetics?) that enable women to produce larger children when infection risks are extreme. This prediction was supported by a comparative analysis: all else being equal, birthweights significantly increase with the number of diseases present across human populations (Thomas et al. 2004). The role of epigenetics in evolution is rapidly gaining recognition (Jablonka and Lamb 1999, 2005, Newman and Müller 2000, Richards 2006, Crews et al. 2007), and the link highlighted here between parasitism and what may be epigenetic effects suggests yet another role for parasites in animal evolution.

Of course, trans-generational effects of infection on offspring phenotypes can have other proximate causes that may act jointly with any epigenetic pathways. For instance, in addition to maternal effects sensu stricto on developing offspring, embryos themselves could, in theory, perceive cues associated with the parasitic status of their mothers, and adjust their own developmental strategy accordingly (i.e. in a state dependant manner: Thomas et al. 2002). For instance, it could be expected that juveniles from parasitized mothers accelerate their developmental rate in order to leave their mother precociously, thereby avoiding infection-related consequences (e.g. higher predation risk associated with trophically transmitted parasites). From an evolutionary point of view, these considerations are relevant as they suggest that adaptive plastic responses of the progeny of parasitized hosts are not necessarily the outcome of maternal and/or parasitic effects. They can also be the direct product of natural selection acting on the offspring's genome.

The above consideration raises the issue of possible parent–offspring conflicts. These genetic conflicts of interest arise from the relative importance of a particular offspring for the fitness of its parents. From the parent's perspective, lifetime reproductive success depends more on lifespan than on success during a particular reproductive event, at least in iteroparous species. Conversely, the fitness of an offspring depends firstly on its own survival as a juvenile and only subsequently on its later reproductive success. If infection levels differ among reproductive events, heavily-parasitised parents should not necessarily 'allocate' maternal effects to current embryos, while the latter would be particularly in need of parental help. Similarly, mothers are expected to allocate immunity differentially to their offspring according to their reproductive value as influenced by the quality of their father (Saino et al. 2002). To date, very few studies of maternal effects and parasitism have explored the degree to which offspring phenotype could in fact be a compromise between parent and offspring strategies. What is needed to understand the resolution of this conflict is an evaluation of how costly it is for parents to provide their offspring with phenotypes to avoid and/or cope with infections.

The preceding scenario provides a potential ultimate explanation for intra- or interspecific variation in trans-generational effects of parasitism. What we are proposing here is that epigenetic pathways involving the turning 'on' or 'off' of genes may represent a general proximate mechanism for trans-generational modulation of host phenotype.

It is perhaps surprising that despite the few published studies of maternal or trans-generational effects of parasitism, there has been no previous attempt to link this phenomenon with epigenetics. Perhaps this paper will serve as incentive for the science community to turn to this problem. The first step would be to compare patterns of DNA methylation between control animals and animals infected by a common, preferably not-too-benign parasite. We can be reasonably confident that a difference would be found, and this finding would open the door to more fascinating questions. For example, is the extent of methylation proportional to the intensity of infection? Will different parasite species induce different methylation patterns in the same host species, i.e. would different parasite species affect different genes? Will the same parasite species induce similar patterns of methylation in different but related host species? How do parasitism and other factors, such as diet, interact to cause DNA methylation and epigenetic effects on offspring? Because of the reciprocal nature of the host–parasite relationship, it is also interesting to address the problem from the parasite perspective, and investigate whether host quality can result in epigenetic effects on the parasite's offspring (Little et al. 2007). We stand on the doorstep to a new research area, an important area that can yield profound insights into the maintenance and inheritance of phenotypic variability in natural populations.

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