Epigenetic Transgenerational Inheritance Across Species

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Abstract

Epigenetic activity is a normal mechanism by which organisms respond to the environment by changing gene expression. Epigenetic responses to environmental factors can be inherited to generations that were themselves never exposed to an inducing factor; a process called epigenetic transgenerational inheritance. Epigenetic transgenerational inheritance has been demonstrated to occur across a wide variety of eukaryotic phyla and species. Examples are given including plants, nematode worms, insects, crustaceans, quail, ducks, partridges, fish, frogs, rats, mice, Guinea pigs, domestic pigs, sheep, cattle and humans. This suggests that epigenetic transgenerational inheritance is a broadly conserved phenomenon, and likely has adaptive value for each species.

Glossary

Epigenetics Molecular factors and processes around DNA that regulate genome activity independent of DNA sequence, and which are mitotically stable.

Transgenerational epigenetic inheritance Germline (sperm or egg) transmission of epigenetic information between generations in the absence of any continued direct exposures or genetic manipulations.

Key Points

- Epigenetic transgenerational inheritance has been demonstrated to occur across a wide variety of eukaryotic phyla and species.
- Examples are given including plants, nematode worms, insects, crustaceans, quail, ducks, partridges, fish, frogs, rats, mice, Guinea pigs, domestic pigs, sheep, cattle and humans.
- This suggests that epigenetic transgenerational inheritance is a broadly conserved phenomenon, and likely has adaptive value for each species.

Introduction

Epigenetics is the molecular factors and processes around the DNA that regulate genome activity independent of DNA sequence, and that are mitotically stable (Skinner, 2011). Epigenetic mechanisms are crucial for normal biology and are some of the primary drivers of cell differentiation that produce all the different cell and tissue types in an organism (Klironomos *et al.*, 2013; Skinner *et al.*, 2014b). In addition, epigenetic activity is a normal mechanism by which organisms respond to alterations in the environment by changing gene expression (Aguilera *et al.*, 2010; Gomes and Pelosi, 2013). Epigenetic processes include DNA methylation, modifications to histone proteins, expression of non-coding RNA, and changes to chromatin structure.

It is possible for epigenetic changes and epigenetic responses to environmental factors to be inherited across generations (Anway *et al.*, 2005; Song *et al.*, 2013). Ancestral exposure to environmental factors or toxicants has been shown to promote changes in gene expression and disease frequency (Skinner, 2014). Transgenerational epigenetic inheritance can occur if epigenetic alterations and changes in an organism's phenotype are inherited through the germ line in generations that were themselves never exposed to an inducing factor like an environmental toxicant. Transgenerational epigenetic inheritance requires that epigenetic information or epigenetic changes are present in germ cells (i.e., sperm or eggs), as it is through germ cells that inheritance occurs (Fitz-James and Cavalli, 2022). This chapter reviews the diversity of organisms and species for which epigenetic transgenerational inheritance has been shown to occur (**Table 1**).

Overview

Epigenetic transgenerational inheritance phenomena have been shown in many plant species (Anastasiadi *et al.*, 2021; Furci *et al.*, 2019; Manning *et al.*, 2006). For example, cold temperature and drought can promote epigenetic transgenerational inheritance of flowering and growth characteristics. These processes involve heritable changes in DNA methylation (Quadrana and Colot, 2016; Song *et al.*, 2013).

In the nematode worm *C. elegans* epigenetic transgenerational inheritance has been shown to occur (Vaiserman *et al.*, 2017). For example, increased longevity that is associated with the histone modification H3K4me3 methylation can be transgenerationally inherited for up to three generations (Greer *et al.*, 2011). Similarly, specific changes in gene expression after an ancestor is exposed to heat shock can be epigenetically inherited for as many as 14 generations (Klosin *et al.*, 2017).

The model insect species *Drosophila melanogaster* has been used in a number of studies investigating epigenetic transgenerational inheritance (Grentzinger *et al.*, 2012). Interestingly, one of the first experiments to establish the potential for epigenetic transgenerational inheritance was performed by Conrad Waddington, who coined the term "epigenetics" (Waddington, 1942, 1953). In these studies it was found that heat shock induced wing structure changes persisted for more than seven generations. In more recent examples, it has been found that a high-sugar maternal fly diet can alter the larval body composition for the next two generations (Buescher *et al.*, 2013). Manipulations of protein levels in the diet of fruit flies can affect longevity and reproduction for three subsequent generations, and are associated with histone modifications (Xia and de Belle, 2016; Xia *et al.*, 2016).

Other arthropod species have also demonstrated epigenetic transgenerational inheritance. The brine shrimp *Artemia* is a genus of crustacean species that have shown the inheritance of an acquired immune resistance (Norouzitallab *et al.*, 2014). In these studies, *Artemia* were exposed to a bacterial pathogen that did not kill them, and to which they developed resistance. Three generations later the *Artemia* were still more resistant to that bacteria. This was associated with changes in DNA methylation and histone acetylation. In *Daphnia magna*, another crustacean species, it was shown that exposure to the toxicant 5-azacytidine resulted in decreased body length and reduced levels of DNA methylation in non-exposed subsequent generations (Vandegehuchte *et al.*, 2010). In the amphipod *Gammarus locusta*, exposure to the anti-cholesterol drug simvastatin resulted in a transgenerational decrease in growth rate and fecundity associated with transgenerational changes in gene expression.

Several species of fish have shown epigenetic transgenerational inheritance. Zebrafish exposed to the environmental toxicants benzo(*a*)pyrene (Knecht *et al.*, 2017), methylmercury (Carvan *et al.*, 2017) or dioxin (Baker *et al.*, 2014) have shown in their grand-offspring behavioral changes, visual defects, increased body mass, skeletal abnormalities and/or decreased fertility, some of which are associated with changes in DNA methylation. Medaka exposed to the endocrine disruptors bisphenol A (BPA) or ethinylestradiol produced grand-offspring and great-grand-offspring with reduced fertility (Bhandari *et al.*, 2015). The pipefish *Syngnathus typhle* has shown transgenerational inheritance of increased expression of immune response genes after grand-parental exposure to heat-killed bacteria, also associated with changes in DNA methylation or histone modifications (Beemelmanns and Roth, 2017). The Inland Silverside (*Menidia beryllina*) has shown transgenerational changes in DNA methylation in the F2 generation after F0 generation exposure to endocrine disrupting compounds such as bifenthrin, levonorgestrel and trenbolone (Major *et al.*, 2020).

Some bird species have shown evidence of epigenetic transgenerational inheritance. In a study with quail, eggs were injected with the environmental estrogen genistein (Carvalho *et al.*, 2023; Leroux *et al.*, 2017). In the great-grand offspring the age at which the first egg was laid was significantly greater in genistein-lineage quail compared to the control lineage. Also with quail, heat stress during egg incubation had a transgenerational effect on body weight (Carvalho *et al.*, 2023). Ancestral diet has been shown to have a transgenerational effect in ducks (Brun *et al.*, 2015). Ducks fed a methionine-deficient diet produced grand-offspring with altered weight gain and changes in metabolic parameters. Red-legged partridges (*Alectoris rufa*) exposed to triazole fungicides as F0 generation adults had transgenerational F2 generation descendants with changes in gene expression and changes in steroid levels present in eggs (Fernández-Vizcaíno *et al.*, 2024).

A study in *Xenopus tropicalis* frogs showed that exposure of males to the herbicide linuron resulted in changes to body morphology and plasma glucose levels in the transgenerational F2 generation, associated with changes in DNA methylation in brain and testis samples (Roza *et al.*, 2024).

In mammals most studies of epigenetic transgenerational inheritance have occurred in rodents (Skinner *et al.*, 2011). Examples of epigenetic transgenerational inheritance in rats include increased rates of reproductive abnormalities in great-grand offspring after exposure of pregnant rats to the environmental toxicant vinclozolin (Anway *et al.*, 2005) and transgenerational inheritance of altered behaviors (Gillette *et al.*, 2014), both associated with altered DNA methylation. Alterations in longevity and body weight have been seen in grand-offspring after non-pregnant grandmothers were fed a calorie-restricted diet (Araminaite *et al.*, 2014).

In mice, males who experience an enriched living environment had grand-offspring with changes in behavior and neuroendocrine parameters (Yeshurun *et al.*, 2017). Other examples of epigenetic transgenerational inheritance in mice include transgenerational increases in adult onset disease and changes in DNA methylation after ancestral exposure to vinclozolin (Guerrero-Bosagna *et al.*, 2012), and male diabetes resulting in increased rates of infertility in grand-offspring (Pavlinkova *et al.*, 2017).

Table 1 Epigenetic transgenerational inheritance across species

Species	*Exposure*	*Transgenerational phenotype*	*Generation*	*References*
Plant species	Cold, drought	Change in flowering, growth	F2 +	Quadrana and Colot (2016) and Song *et al.* (2013)
C. elegans (worm)	Heat shock, altered chromatin modifiers	Longevity, gene expression	F3, F14	Greer *et al.* (2011) and Klosin *et al.* (2017)
D. melanogaster (fly)	Heat shock, dietary protein and sugar	Wing changes, body composition, longevity	F2, F3, F7	Waddington (1953), Buescher *et al.* (2013) and Xia and de Belle (2016)
Artemia (brine shrimp)	Bacteria	Bacterial resistance	F3	Norouzitallab *et al.* (2014)
Daphnia magna	5-Azacytidine	Decreased body length	F2	Vandegehuchte *et al.* (2010)
Gammarus locusta	simvastatin	Decreased growth, fecunditiy	F2, F3	Neuparth *et al.* (2020)
Zebrafish	Benzo(*a*)pyrene, methylmercury, dioxin	Visual defects, increased body mass, skeletal abnormalities, decreased fertility	F2	Knecht *et al.* (2017), Carvan *et al.* (2017), and Baker *et al.* (2014)
Medaka (fish)	Bisphenol A (BPA), 17a-ethinylestradiol	Reduced fertility	F2, F3	Bhandari *et al.* (2015)
Pipefish	Bacteria	Increased immune gene expression	F2	Beemelmanns and Roth (2017)
Inland silverside (fish)	Endocrine disruptors	DNA methylation	F2	Major *et al.* (2020)
Quail	Genistein	Change in age of first egg laid	F3	Leroux *et al.* (2017)
Duck	Methionine-deficient diet	Altered weight gain	F2	Brun *et al.* (2015)
Partridge	Fungicides	Changes in gene expression and egg steroids	F2	Fernández-Vizcaíno *et al.* (2024)
Xenopus frog	Linuron	Morphology changes, blood glucose	F2	Roza *et al.* (2024)
Rat	Vinclozolin, calorie restriction	Increased disease rate, behavior changes, body mass	F2, F3, F4	Anway *et al.* (2005), Skinner *et al.* (2011), Gillette *et al.* (2014), and Araminaite *et al.* (2014)
Mouse	Cage enrichment, vinclozolin, diabetes	Behavior change, increased disease rate, infertility	F2, F3	Yeshurun *et al.* (2017), Guerrero-Bosagna *et al.* (2012), and Pavlinkova *et al.* (2017)
Guinea pig	Ethanol	Reduced fertility	F4	Stockard and Papanicolaou (1918)
Pig	Methyl donor diet	Decreased backfat	F2	Braunschweig *et al.* (2012)
Sheep	Methyl donor diet	Reproductive development, weight gain	F2	Braz *et al.* (2022)
Cow	Heat stress	Decreased milk production	F3	Laporta *et al.* (2024), and Weller *et al.* (2021)
Human	Calorie restriction	Increased diabetes, mortality	F2	Veenendaal *et al.* (2013), and Bygren *et al.* (2001)

Interestingly, a study in Guinea pigs from 1918 demonstrated transgenerational inheritance of decreased fertility and increased mortality for four generations after ancestral exposure to ethanol vapor, although this was not attributed to epigenetic inheritance at the time (Stockard and Papanicolaou, 1918).

The domestic pig is another mammal that has shown evidence of epigenetic transgenerational inheritance. Male pigs fed a diet high in methylating micronutrients had grand-offspring with a lower level of backfat (Braunschweig *et al.*, 2012). This change in carcass fat percentage was accompanied by differences in DNA methylation levels of selected genes in liver and muscle.

In sheep, it has been demonstrated that feed supplementation with a methyl donor in the paternal diet resulted in transgenerational changes in DNA methylation that were associated with changes in reproductive development and rates of weight gain (Braz *et al.*, 2022).

F0 generation cows exposed to heat stress while pregnant have been shown to produce great-grand-offspring (F3 generation) with transgenerational changes in milk and milk fat production and an increase in dystocia and stillbirths (Laporta *et al.*, 2024; Weller *et al.*, 2021).

Evidence of epigenetic transgenerational inheritance in humans comes from retrospective studies (Veenendaal *et al.*, 2013). For example, the Overkalix region of northern Sweden experienced periods of famine in the early 1900s, and the descendants of those people exposed to famine conditions as children 9–12 years of age were investigated (Bygren *et al.*, 2001). It was found that men whose grandfathers were exposed to famine had an increased risk of mortality due to diabetes, and similarly women whose grandmothers were exposed had increased risk.

Conclusions

Epigenetic transgenerational inheritance has been demonstrated to occur across a wide variety of eukaryotic phyla and species, including plants, nematode worms, insects, crustaceans, quail, ducks, partridge, fish, frogs, rats, mice, Guinea pigs, domestic pigs, sheep, cattle and humans. This suggests that epigenetic transgenerational inheritance is a broadly conserved phenomenon, and likely has some adaptive value for each species.

The question that then arises is why can environmental insults sometimes result in transgenerational inheritance of increased disease susceptibility, which is a maladaptive response? One possible answer may be explained by the predictive adaptive response hypothesis (Bateson *et al.*, 2014; Skinner *et al.*, 2014a). In this hypothesis an environmental stressor like famine may epigenetically promote an adaptive (thrifty) phenotype in progeny. If the current environment of those progeny has more than adequate nutrients, diseases like diabetes and obesity are promoted. Another possibility is that an environmental insult, such as exposure to a toxicant, may interfere with the normal molecular epigenetic machinery and result in stochastic and/or directed epigenetic changes that could be considered epimutations. If these epimutations occur in germ cells, then that can lead to transgenerational inheritance of a wider range of phenotypes in the progeny. Some of those phenotypes may be poorly adapted and develop disease. This would explain an increase in disease susceptibility in organisms whose ancestors were exposed to environmental insults. However, the increased phenotypic variation may also result in some individuals who are better adapted to an altered environment, facilitating natural selection (Skinner, 2015).

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