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Multigenerational Epigenetic Inheritance: Transmitting information across generations

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Abstract

Inherited epigenetic information has been observed to regulate a variety of complex organismal phenotypes across diverse taxa of life. This continually expanding body of literature suggests that epigenetic inheritance plays a significant, and potentially fundamental, role in inheritance. Despite the important role these types of effects play in biology, the molecular mediators of this non-genetic transmission of information are just now beginning to be deciphered. Here we provide an intellectual framework for interpreting these findings and how they can interact with each other. We also define the different types of mechanisms that have been found to mediate epigenetic inheritance and to regulate whether epigenetic information persists for one or many generations. Epigenetic inheritance is entering an exciting phase, where mechanistic understanding of how non-genetic information is transmitted and deciphered by subsequent generations to maintain essential environmental information without permanently altering the genetic code. A more complete understanding of how and when epigenetic inheritance occurs will advance our understanding of numerous different aspects of biology ranging from how organisms cope with changing environments to human pathologies influenced by a parent's environment.

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Keywords

Transgenerational Epigenetic Inheritance; Intergenerational; DNA methylation; histone methylation; small RNAs; non-genetic; non-Mendellian; epigenetics

Introduction

Since the original observations of the inheritance of traits in pea plants by Gregor Mendel in 1865 [1], and their rediscovery in 1900 [2–4], a vast majority of all traits in eukaryotic organisms have been found to follow Mendelian inheritance patterns and are transmitted via DNA [5]. For almost equally long, but perhaps less appreciated, it has also been known that some traits do not follow Mendelian inheritance patterns and can be influenced by the environment or signaling pathways in previous generations. For example, original studies in 1909 by Mary Isabel McCracken [6], and in 1924 and 1925 by K. Watanabe [7] and Yositiro Umeya [8], respectively, reported that external temperature affected the ovaries of female silk moths (*Bombyx mori*) in a way that influenced whether her offspring would enter a hibernating diapause state. Later studies demonstrated that this heritable trait was controlled via a diapause hormone which is released from the mother's somatic cells (the suboesophageal ganglion) and transmitted via blood [9] to oocytes [10–12]. These studies of diapause in *B. mori* collectively described the first animal trait known to be controlled by somatic cell experiences in a previous generation. Of particular note, the experimental blood transfusions in *B. mori* by Yositiro Umeya [8] are conceptually identical to Francis Galton's early experiments on the inheritance of coat color in rabbits using blood transfusions [13]. Galton's experiment ultimately was influential in refuting Charles Darwin's theory of germules [14] and impacted the acceptance of August Weismann's "Weismann barrier" which suggested that information could not be transmitted from somatic cells to germ cells [15]. However, the conclusions reached by Umeya [8] and later confirmed by others [10–12] were the exact opposite of those reached by Galton and Weismann, and indicated that some traits were in fact controlled by factors present in the blood moving to germ cells.

The findings of McCracken, Watanabe, and Umeya never received the same level of scientific attention and interest as those of Galton and Weismann. Nonetheless, similar observations to those in *B. mori* of a parent's environment affecting traits in their offspring have since been observed in studies of diverse organisms ranging from nematodes to mammals [16]. These studies include numerous examples where a parent's exposure to particular environmental stresses can promote adaptive changes in offspring. These consistent observations of non-genetic inheritance across diverse evolutionary taxa suggest that such effects might represent a fundamental aspect of biology. Despite its potential importance in biology, non-genetic inheritance remains poorly understood and a better understanding of such effects and the mechanisms that mediate them could significantly advance our understanding of both biological and medical sciences.

To date, a growing body of literature has painted a complex picture of both the phenomena and mechanisms underlying non-Mendelian inheritance. Non-Mendelian effects have been reported to be transmitted anywhere from one to an indefinite number of generations; they

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sometimes, but not always, occur in response to environmental stimuli; and they play an as-yet-unknown role in biology with estimates ranging from rare occurrences observed in organisms with short generation times [17] to pervasive effects that are potentially found in all eukaryotic species [18]. Because the molecular mechanisms underlying non-Mendelian inheritance are just beginning to be deciphered, a non-overlapping patchwork of mechanisms have been proposed even within a single species.

Here, we review the current state of research into multigenerational effects, encompassing both intergenerational effects (lasting 1–2 generations) and transgenerational effects (lasting 3+ generations), with a particular focus on the molecular mechanisms that mediate the transmission of such effects via germ cells. In addition, we highlight how different evolutionary pressures are likely to favor the evolution of intergenerational or transgenerational effects and how such pressures might explain why organisms may have evolved separate mechanisms to mediate each type of effect. We propose that this type of thinking and categorization of multigenerational effects might help avoid some of the problems that have led to significant confusion in the field, such as the term transgenerational having a different definition in studies performed in different species. Furthermore, this categorization will allow us to better estimate how common different types of effects might be, what molecular mechanisms might be most likely to underlie newly observed examples of non-Mendelian inheritance, and if the molecular mechanisms underlying one multigenerational effect are likely to mediate similar multigenerational effects in other organisms.

What are intergenerational and transgenerational effects?

In mammals, transgenerational effects, particularly those that occur in response to the environment, are defined as any phenotypic or molecular effect that persists for 3 or more generations through the female line or 2 or more generations through the male line [19]. By contrast, effects that only persist for 1 or 2 generations are for the most part referred to as intergenerational effects [19]. Whether a phenotype is intergenerational or transgenerational was originally determined by whether the genetic material for the subsequent generations was present at the time of exposure to the altered environment. This often differs between different species, so caution must be used to identify whether the germ cells were present at the time of exposure. The original distinction between these two terms lay in the fact that intergenerational effects could, in principle, be caused by the effects of the parent's environment/physiology directly on the developing embryo/fetus or on germ cells but transgenerational effects could not be due to direct exposure. However, mechanistic investigations of multiple different intergenerational effects have since discovered mechanisms of intergenerational regulation that are not due to the direct effects of the environment on germ cells or F1 embryos [12, 20–23]. In some cases, these mechanisms are initiated and maintained using similar mechanisms as transgenerational effects such as the transmission of small RNA molecules via germ cells [24, 25]. Nonetheless these effects remain described as intergenerational effects. Thus, the currently used definition of intergenerational has evolved to refer mainly to the duration a phenotypic effect persists for rather than the potential mechanism by which the effect is mediated (Figure 1). By comparison, for a phenotype to be considered transgenerational, none of the

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individuals genetic material can be present at the time of the environmental insult (Figure 1). Thus, transgenerational effects predominantly refer to phenotypic effects that persist for three or more generations. For the purposes of this review, and for comparing effects across species, we will define all effects that only persist for a single generation (parent-offspring effects) as intergenerational regardless of species or timing of germ cell development. We will also define all effects that persist three or more generations as transgenerational. Observations of multigenerational effects lasting for specifically two generations will be discussed on a case-by-case basis with considerations for species and line of transmission.

Why do organisms maintain non-genetic information across generations?

The question of why organisms transmit non-genetic information across generations has been asked since Alexander Brink first reported transgenerational epigenetic inheritance in maize in 1956 [26]. If we were to anthropomorphize evolution, epigenetic inheritance exists to transmit environmental information to the descendants without modifying the heritable material of DNA and therefore permit future generations to revert back to a “normal” state when the environmental insult has passed. In addition to the question of why information is maintained at all, there also remain significant questions related to why organisms maintain certain types of information for differing numbers of generations. A better understanding of these outstanding questions in the field is likely to significantly enhance our ability to compare different multigenerational effects across species. In an effort to advance this understanding, here we break known multigenerational effects into three distinct types of responses based on the duration of their inheritance – intergenerational effects, transient transgenerational effects, and permanent transgenerational effects.

Intergenerational effects

Intergenerational effects refer, most commonly, to the effects of a parent’s environment on their offspring and can be both adaptive and deleterious from the perspective of the offspring. For the purposes of this review, we focus on adaptive intergenerational effects, as these are the most likely to be mediated by active mechanisms that evolved to mediate a heritable biological function rather than the toxic side effects of various biological or chemical insults.

Adaptive intergenerational effects are commonly observed throughout evolution and can lead to substantial and sometimes dramatic changes in organism development and physiology. For example, in the pea aphid *Acyrthosiphon pisum*, parental exposure to certain stresses can lead to the development of wings in offspring in addition to many additional behavioral and physiological changes [27–29]. The development of wings allows offspring to fly away from stressful conditions, but comes at the expense of fecundity [28]. Such trade-offs are commonly observed for intergenerational adaptive effects and likely explain why these forms of plasticity are only observed in response to specific environmental stimuli and are lost or erased within one generation of removal from the triggering environmental stress. Similar observations of intergenerational adaptations to stress, including observations of trade-offs, have been observed in diverse taxa ranging from plants to mammals including *Arabidopsis* responses to pathogen infection [30], *C. elegans* responses to osmotic stress,

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social environment, and multiple types of pathogen infections [22, 23, 31–33], *Daphnia* helmet formation in response to predators [34], the overwintering response of *Bombyx mori* [11], and the response of red squirrels to food and territory availability [35] among many other examples. Furthermore, intergenerational adaptive changes in response to nutrient stress, and their deleterious tradeoffs, have been hypothesized to underlie observations of fetal programming in humans and possibly contribute to multiple human metabolic pathologies including Type 2 diabetes [36].

Studies of the tradeoffs of intergenerational adaptations and mathematical modelling of intergenerational adaptive effects suggest that intergenerational adaptive effects are likely to evolve in any scenario where (1) the environment is variable, (2) a parent's environment is predictive of their offspring's future environment, (3) the benefits of the adaptation outweigh the costs [37]. These conditions are likely common for most organisms in response to one or more stresses, and thus intergenerational adaptive effects might similarly be common. In addition, despite the potential benefits of intergenerational adaptations to stress, the costs of these adaptations might promote their loss or active erasure when the environment changes, potentially explaining why most intergenerational adaptations do not persist for more than one generation [38].

Transgenerational effects

Like intergenerational effects, transgenerational effects can also be both adaptive and deleterious. However, unlike intergenerational effects, both adaptive and deleterious transgenerational effects are likely to be mediated by epigenetic mechanisms, as transgenerational effects cannot usually be due to the direct exposure of an organism to any particular stress or condition. Furthermore, experimental studies of transgenerational effects suggest that there might be at least two different types of transgenerational effects that may or may not be mechanistically related. Here we describe these two types of transgenerational effects as permanent transgenerational effects that persist indefinitely and transient transgenerational effects that occur in response to a specific set of conditions but are ultimately lost after a varying number of generations.

Permanent transgenerational effects

Some of the original observations of transgenerational epigenetic inheritance come from studies of paramutation in maize [26]. Paramutation-like phenomena have since been described in several species and in each case represent the transmission of epigenetic information that can be maintained for an indefinite number of generations [39–42]. Studies of the molecular mechanisms underlying permanent transgenerational effects have almost exclusively identified epigenetic mechanisms that regulate the silencing of transposons, repetitive elements, and foreign DNA, and most known examples of paramutation involve the silencing of a transposon or repetitive element that indirectly affects the expression of a nearby gene [39–42]. Permanent transgenerational effects are likely to evolve in response to conditions that do not change or when a stress is permanently present by virtue of being integrated into the host genome, such as the presence of a transposon. These types of effects are unlikely to occur in response to environmental stimuli that can change between generations.

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Transient transgenerational effects

In contrast to permanent transgenerational effects, transient transgenerational effects have been reported to persist for anywhere from three to approximately ten generations and are often reported in response to environmental stimuli or stresses [43–65]. Initial studies of the mechanisms underlying transient transgenerational effects that occur in response to the environment have identified similar mechanisms to those that regulate permanent transgenerational effects, such as small RNAs [41, 43, 44, 46, 47, 52, 58, 60, 66], DNA methylation [53], and histone modifications [59, 60]. The mechanisms that prevent transient transgenerational effects from persisting permanently in most organisms remain unclear, but recent work in *C. elegans* suggests that H3K9 methylation and the chromodomain protein HERI-1 antagonize the transgenerational inheritance of small RNA silencing and in the absence of either the putative histone methyltransferase MET-2 or HERI-1, animals can inherit a normally transient transgenerational effect permanently [51, 67]. Similarly, transgenerational inheritance of elevated H3K4me2 is also antagonized by regulators of H3K9 methylation [63, 68, 69]. Collectively, these results suggest that H3K9 methylation might play a role in preventing transient transgenerational epigenetic inheritance from becoming permanent silencing. It will be important, in future studies, to deduce whether there are common or unique mechanisms that set the transgenerational clock and prevent epigenetic effects from persisting indefinitely.

Unlike intergenerational responses to environmental stimuli, modelling of transient transgenerational responses to environmental stimuli has found that they are more likely to evolve when a parent's environment is not predictive of their offspring's environment [70]. While in most cases a parent's environment is highly likely to be predictive of their offspring's future environment, there are certain cases where the opposite is true. For example, in certain cyclical environments such as the changing of seasons, and in organisms with short generation times, information about a great-grandparent's environment could be more predictive of an individual's future environment, such as the coming of winter, than their parent's. Alternatively, in highly variable environments it could be more useful to average the environments of multiple previous generations rather than use the input of parental environment alone. Consistent with this hypothesis, several studies have demonstrated that the exposure of multiple successive generations of animals to pathogens results in offspring with more robust multigenerational adaptations to these pathogens [31, 55].

These differences in the pressures favoring intergenerational vs transient transgenerational effects are predominantly due to the costs of maintaining information about the environment across many generations and the potential costs of adapting to one particular stress which can come at the expense of being able to adapt to other stresses [32]. Transient transgenerational effects, particularly adaptive ones, need to avoid costs that occur in mismatched environments that do not match the stress that triggered the transgenerational effect, or have benefits to the organism that outweigh any potential costs. These differences in the pressures favoring transient transgenerational effects, when compared to intergenerational effects, raises the possibility that different molecular mechanisms might evolve to mediate these two types of multigenerational effects.

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Consistent with the hypothesis that different evolutionary pressures favor intergenerational vs transgenerational effects, some organisms have evolved parallel mechanisms to elicit separate intergenerational or transgenerational responses to the same stimuli. For example, the nematode *Caenorhabditis elegans* can elicit both intergenerational and transgenerational responses to the presence of dsRNA [24, 25, 43, 44, 66, 71]. To accomplish these two separate types of inheritance, different mechanisms have evolved that are spatially separated in different tissues to mediate intergenerational vs transgenerational dsRNA-directed gene silencing. Specifically, the argonaute NRDE-3 mediates intergenerational gene silencing in somatic tissues for somatically expressed genes [25] while the argonaute HRDE-1 mediates transgenerational gene silencing in germ cells for genes expressed in germ cells [43]. The observations that these two argonautes function in different tissues to carry out intergenerational silencing in somatic cells and transgenerational silencing in germ cells in response to the same dsRNA stimuli suggests that *C. elegans* has evolved separate argonautes to mediate intergenerational vs transgenerational inheritance and that the tissues in which intergenerational and transgenerational silencing occur in might also be separate. It will be interesting, in future studies, to determine how specific small RNAs are selected to transmit information intergenerationally or transgenerationally. Is the inheritance of small RNAs simply dictated by when and where the small RNAs are expressed or are the specific small RNAs which are destined to be inherited marked by specific chemical modifications [72] or potentially sequestered into special subcellular compartments to be transmitted to descendants [73, 74]? Identifying these mechanistic determinants of small RNA inheritance will help to distinguish why the phenotypic consequences of some small RNAs are not inherited at all, some are intergenerationally inherited, and some are transgenerationally inherited.

Comparing the mechanisms that mediate multigenerational effects

Analyses of the mechanisms underlying multigenerational effects have often grouped intergenerational and transgenerational effects together. This is in part because similar general mechanisms can mediate both types of multigenerational effect, such as small RNAs and histone modifications. If, however, different evolutionary pressures favor the evolution of different types of multigenerational effects then further insight might be gained by comparing the mechanisms underlying these phenomena separately. Here we consider the mechanisms underlying intergenerational and transgenerational effects separately. We also examine the gaps that remain in our mechanistic understanding of these types of effects and to what extent similar mechanisms might underlie the many observations of intergenerational or transgenerational effects that have been observed across different species.

Mechanisms underlying intergenerational effects

Hormone signaling to oocytes

As was observed in *B. mori*, hormone signaling to oocytes has also been shown to play an important role in *C. elegans* response to osmotic stress. Specifically, parental exposure of animals to mild osmotic stress protects offspring from future exposure to osmotic stress [22]. This intergenerational adaptation is regulated by insulin-like signaling to

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oocytes, with reduced signaling resulting in an increase in the expression of the glycerol-3-phosphate dehydrogenase GPDH-2 in offspring [22]. GPDH-2 subsequently increases glycerol production which, in turn, promotes resistance to osmotic stress [22]. It will be interesting, in future studies, to elucidate the mechanisms by which insulin-like signaling to oocytes causes gene expression and metabolic changes. Nonetheless, the strong evolutionary conservation of insulin signaling throughout metazoans and recent observations in mammals demonstrating that maternal dietary stress can affect oocytes in a way that modifies insulin sensitivity and metabolism in offspring [75] suggest that intergenerational effects in other organisms might also be regulated by insulin signaling to oocytes. Identifying such mechanisms will be critical to our future understanding of how hormone signaling to oocytes can affect offspring, how common such effects might be, and if such effects play a role in human pathologies linked to maternal environment such as Type 2 diabetes.

Small RNA-based intergenerational mechanisms

RNAi silencing of a subset of genes can be passed from parents to offspring via germ cells in *C. elegans* [24, 25, 43, 44, 66, 71]. For almost all such genes that are expressed in somatic cells this silencing lasts for only a single generation [25, 71], suggesting that RNAi silencing in somatic tissues is inherited intergenerationally in *C. elegans*. Genetic studies of the factors that regulate the intergenerational inheritance of RNAi silencing found that some genes were required for the initiation of RNAi silencing, such as the RNA helicase RDE-1 and the RNA binding protein RDE-4 [24], while others were required for the maintenance of RNAi silencing, such as the 3'–5' exoribonuclase MUT-7 and the MUT-7 interacting protein RDE-2 [24, 76]. Later studies found that the nuclear RNAi pathway mediates the inheritance of RNAi silencing across generations and that the argonaute NRDE-3 specifically mediates the intergenerational silencing of genes expressed in somatic cells [25]. Collectively, these studies demonstrated that a dedicated NRDE-3 dependent mechanism has evolved to mediate the intergenerational inheritance of RNAi silencing in somatic tissues and this inheritance is transmitted via germ cells in these animals.

In addition to RNAi inheritance, various tRNA fragments and miRNAs have also been reported to mediate the transmission of information about the environment from parents to offspring via germ cells in mammals [20, 21, 77–84]. The abundance of many of these RNAs, in particular tRNA fragments, have been shown to be responsive to different environmental conditions [20, 21, 83, 85]. Furthermore, injection of total sperm RNA or purified RNA fragments into either oocytes or zygotes recapitulates some of the effects of a father's environment on offspring [20, 21, 42, 82–84]. These findings provide strong evidence that such RNA populations mediate some of the effects of a parent's environment on offspring. However, the mechanisms by which these RNAs exert their effects on long-term offspring health and physiology remain unclear.

Histone modifications and DNA methylation-based intergenerational mechanisms

Early forays into *in vitro* fertilization in mice revealed that having two sets of only maternal or only paternal chromosomes were not viable [86–88], suggesting that each sex had to contribute one set of chromosomes for viability and that the chromosomes coming from different sexes were not identical. Subsequent discoveries of maternally (*Igf2)* and

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paternally (*H19* and *Igf2r*) imprinted and C5-cytosine methylated (5mC) genes [89–95], and demonstration that the C5-cytosine methyltransferase DNMT1 was required for maintenance of imprinted gene expression [96] found that DNA cytosine methylation could mark, and epigenetically silence, gene expression of critical genes inherited from parents. The presence of 5mC in monoallelic imprinting control regions allows for consistent expression of critical genes from a single parental allele. The precise method by which DNA cytosine methylation at critical imprinting control regions, in a parent-of-origin specific manner, escapes the canonical epigenetic erasure that occurs upon fertilization is still being deciphered [97–99]. DNA cytosine methylation has also been demonstrated to regulate imprinting in *Arabidopsis* [100]

The demonstration that methylated histones can be retained through cell divisions [101] and that the polycomb complex, a complex responsible for methylating histone H3 on lysine 27 (H3K27) [102–105], can be retained on the chromatin through DNA replication [106, 107], has suggested potential mechanisms by which histone methylation could escape erasure or facilitate the immediate reapplication of histone modifications through cell divisions and potentially across generations. Similarly, mutational analyses combined with fluorescent labelling experiments in *Drosophila*, have demonstrated an asymmetric inheritance of histones in the germline [108, 109] which could provide mechanistic support for how histone modifications could transmit through cell divisions. Several recent reports have also demonstrated a DNA methylation independent imprinting which is driven by inheritance of maternal histone H3 lysine 27 trimethylation (H3K27me3) and brief histone H2A lysine 119 ubiquitination (H2AK119ub1) [110–115]. Interestingly, some elegant work in *C. elegans* and *Drosophila* has further supported the inheritance of H3K27me3 across generations [116, 117], suggesting that inherited histone methylation could be a conserved process of transmitting non-genetic information to descendants. This does not appear to be restricted to H3K27me3 as fluorescent labeling experiments have also demonstrated the inheritance of H3K36me3 from parents to their children in *C. elegans* [118]. While paternal inheritance of histones is rarer in mammals, due to the replacement of histones with the more compactable protamines, in *C. elegans* histones are retained in paternal sperm and have been suggested to retain high levels of H3K27me3 and H3K36me3 and lower levels of H3K4me3 [119]. This paternal inheritance of modified histones correlates with repression of a neuronal fate in early germ cells [120]. Whether modified histones or DNA themselves are the transmitted material or something else is transmitted to cause the altered reacquisition of histone methylation/acetylation remains to be determined.

Interestingly, there are examples where genetic deletion of the enzymes necessary for these DNA and histone modifications eliminate certain intergenerational phenotypes arising from environmental stresses raising the possibility that these altered histone modifications themselves are transmitted from parents to their children. The naïve progeny of *Arabidopsis* which are exposed to the pathogenic bacteria *Pseudomonas syringae* have reduced DNA methylation [121], decreased seed production, and increased resistance in response to alternative pathogenic bacteria [30]. Elimination of DNA cytosine methyltransferases *drm1, drm2*, and *cmt3* eliminates the inherited resistance to the alternative pathogenic bacteria [30]. Similarly, naïve progeny from *Arabidopsis* ancestors which were repeatedly exposed to elevated salinity display altered DNA methylation and increased resistance to hyperosmotic

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stress. This increased resistance to elevated salt is dependent on the presence of both DNA demethylases and DNA methyltransferases [122], suggesting that intergenerational inheritance is dependent on inheriting the appropriate levels of DNA methylation.

Correlations of changes in DNA and histone modifications in response to parental diet span the evolutionary tree [123–127]. For instance, naïve children of *Drosophila* fathers fed a high-sugar diet display inherited obesity correlated with elevated H3K9me3 and H3K27me3 [127]. These heritable obesity phenotypes are dependent on the presence of the H3K9 and H3K27 methyltransferase machinery [127]. Similarly, *Drosophila* fed a high-fat diet have reduced cardiac function correlated with elevated H3K27me3 which is transmitted to naïve descendants [128]. Overexpression of the H3K27me3 demethylase dUTX or chemical inhibition of the H3K27 methyltransferase EzH2 protect against the heritable heart defects [128]. The importance of H3K27 methylation in intergenerational inheritance is further highlighted by experiments in genetically wildtype *M. musculus* descendants of the H3K27me3 demethylase Utx which display increased DNA methylation and increased susceptibility to cancer relative to wildtype descendants from wildtype parents [129]. Chromatin modifications can be elicited in different manners. Exposure of *Drosophila* to heat stress can activate the transcription factor dATF-2 which binds to the H3K9me3 binding protein HP1 [130]. Heat stress causes dATF-2 phosphorylation and disruption of heterochromatin which can be epigenetically inherited [130]. Interestingly, repeated generational exposures to elevated temperature dulled the epigenetic phenotype suggesting that repeated exposures to the same stimuli can alter transgenerational responses to stress. A similar observation of multigenerational adaptation to repeated exposures was detected from exposure *of C. elegans* to pathogens [55]. Together these data raise the exciting possibility that modified histones and DNA can transmit environmental information to their naïve descendants to regulate intergenerational phenotypes.

Maternal provisioning

There are many known mechanisms by which changes in maternal provisioning of resources to offspring result in changes in offspring phenotype. This includes many examples of adaptive effects such as the transfer of antibodies from mother’s to offspring in mammals [131], changes in yolk provisioning affect several offspring phenotypes in *C. elegans* including starvation resistance [132, 133], and changes the deposition of hormones into eggs in birds [134]. In many cases, these adaptive intergenerational provisioning effects achieve the same biological goals as intergenerational effects that are transmitted via germ cells. A comprehensive discussion of all of the possible intergenerational effects mediated by changes in provisioning is outside the scope of this review, but we note that these types of effects likely play as large of a role in biology as effects transmitted via germ cells. In addition, and similar to intergenerational effects mediated via germ cells, the molecular mechanisms by which altered maternal provisioning can affect the long-term health and physiology of offspring remain poorly understood and future studies of these effects are likely to substantially advance our understanding of diverse aspects of biology.

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Notable examples of intergenerational effects that occur via unknown mechanisms

An especially notable example of intergenerational effects in humans is the observation of many different changes in metabolism and physiology in children conceived during the Dutch Hunger Winter [135, 136] and the Great Chinese Famine [137, 138]. These observations fit broadly within the emerging field of fetal programming – studies of how the *in utero* environment affects long-term health and physiology [36]. Fetal programming has been linked to several major pathologies including Type 2 diabetes and cardiovascular disease and stressful environments appear to cause similar changes in offspring physiology in diverse species of mammals [139–144]. The mechanisms by which fetal programming occur are poorly understood but are likely related to the mechanisms that regulate intergenerational effects in other organisms. In support of this hypothesis, recent studies of a model of fetal programming in mice found that the effects of a mother's high-fat diet on offspring obesity and insulin resistance can be transmitted via oocytes [75]. Fetal programming involving both fetal adaptations to stressful maternal or *in utero* environments comes at the expense of long term health [36]. These observations resemble the tradeoffs observed in intergenerational adaptive effects observed in other non-mammalian organisms. Future studies of the mechanisms underlying fetal programming will be critical for our understanding of the role these intergenerational effects play in human disease and if they are evolutionarily related to intergenerational effects observed in non-mammalian systems.

Mechanisms underlying transgenerational effects

Small RNA-based mechanisms

Observations of transgenerational epigenetic inheritance that are mediated by small RNAs have been reported in multiple different taxa including yeast, plants, and nematodes. In general, many observations of small RNA-based transgenerational epigenetic inheritance function to silence repetitive elements, transposons, and foreign DNA present in the genome (reviewed in [145–148]). For example, observations of paramutation in maize were one of the first known examples of transgenerational epigenetic inheritance [26], and it was later observed that paramutation in maize occurs due to the silencing of a tandem repeat sequences present in certain isolates of this species via a mechanism that requires small RNA biogenesis via RNA-dependent RNA polymerases [149–151]. Observations of paramutation have been reported in animals and were also found to silence transposable elements via a mechanism that depends on PIWI-interacting RNAs (piRNAs) [40]. These RNA-based silencing of repetitive and foreign elements largely represent permanent transgenerational effects.

Multiple studies have also reported transient transgenerational epigenetic effects in response to environmental stress that require small RNA-dependent machinery [45–50, 52, 55, 58, 60, 152]. These transient transgenerational effects have predominantly been reported in *C. elegans* and appear to converge on the PIWI-like argonaute PRG-1 [45, 58, 60], which is a core regulator of piRNA function in *C. elegans*, and/or the germline nuclear-localized argonaute protein HRDE-1 [47, 52, 152, 153] which functions to silence the expression of various retrotransposons, cryptic loci, foreign DNA and certain coding genes specifically in germ cells [43, 44, 66, 154, 155]. However, several other argonaute proteins have also

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been proposed to regulate transgenerational effects in *C. elegans* including CSR-1 [66], PPW-1 [156, 157], WAGO-1 [66], and WAGO-4 [158]. These effects often also require the production of small RNAs by the RNA-dependent RNA polymerase RRF-1 [159].

Despite piRNA and endo-siRNA mediated silencing by PRG-1 and HRDE-1 frequent association with permanent transgenerational epigenetic silencing, recent studies suggest that PRG-1 and HRDE-1 might also mediate transient transgenerational silencing under certain conditions. For example, exogenous uptake of dsRNA [43, 160], transgenic expression of the Flock House Virus [46], starvation [45, 47], heat stress [152], and bacterial infection [58, 60] have all been reported to transgenerationally alter animal gene expression or physiology via PRG-1 and/or HRDE-1 dependent mechanisms. These transgenerational effects often persist for between 3 and 5 generations after which they reset via a mechanism dependent on the H3K9me1/2 methyltransferase MET-2 [51] and the chromodomain containing protein HERI-1 [67]. These findings suggest that MET-2 and HERI-1 might be dedicated molecular factors that separate the targets of PRG-1 and HRDE-1 into permanently silenced and transiently silenced targets.

Despite a growing body of literature indicating that small RNAs play an important role in regulating transient transgenerational epigenetic effects in *C. elegans* and yeast, there remain several outstanding questions about the mechanisms underlying these observations. For example, how certain environmental stresses initiate transgenerational epigenetic effects via small RNAs are poorly understood. In cases involving bacterial pathogens, *C. elegans* ingest dsRNAs produced by bacteria that in turn guide the silencing of *C. elegans* genes involved in a pathogen response [58]. However, the molecular mechanisms by which stresses such as heat or starvation might elicit similar small RNA-dependent changes is still unclear. Similarly, the extent to which these transgenerational epigenetic effects represent stress-specific responses or a general stress response and the extent to which similar small RNA-dependent transgenerational effects might occur in organisms lacking RNA-dependent RNA polymerases, such as humans, remains unknown. Future studies of these effects will be critical in elucidating the role small RNAs play in transgenerational effects more broadly.

Histone modification-based mechanisms

The realization that insufficient folate in the diet of pregnant women correlated with increased anemia, placental abruption, neural tube defects, and abortions [161] led to trials to supplement folate which substantially prevented neural tube defects [162, 163]. The success of these trials has led many countries to enrich grain products with folic acid, which has reduced the incidence of neural tube defects by 19–55% [164]. Folates' importance stems from its role in the one-carbon pathway where it is required to synthesize methionine which can be subsequently converted to S-adenosylmethionine which donates methyl groups to DNA, RNA, lipids, and proteins [165]. The importance of this pathway not only in intrauterine health for the offspring, but transgenerational viability was demonstrated by a hypomorphic mutation of a folate metabolism gene, *Mtrr*, in mice. Loss of *Mtrr* in ancestors was demonstrated to cause intrauterine growth retardation, developmental delay, and congenital malformations of the neural tube, heart and placenta for four generations of wild type descendants [166]. These experiments raised the possibility that insufficient

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methylation of a variety of different substrates could have transgenerational consequences on the health of descendants.

A number of studies have pointed toward histone methylation playing an essential role in transgenerational epigenetic inheritance. Genetic mutation of enzymes that regulate H3K4 methylation have been revealed to elicit transgenerational epigenetic phenotypes independent of the mutation. For instance, mutation of an H3K4 trimethylation complex in *C. elegans* causes a ~20–30% extension in lifespan [167], which is transmitted for three generations to genetically wild-type descendants [64]. This H3K4 trimethylation complex regulates other transgenerational phenotypes in *C. elegans*, mutation of this complex causes a progressive sterility and transgenerational misregulation of genes [168–170]. Additionally knock-out of the members of the H3K4 methyltransferase complex in *D. discoideum* eliminate the inheritance of active transcriptional states [171]. Conversely, knockout of the H3K4me1/2 demethylase *spr-5* in *C. elegans* causes a transgenerational progressive decline in fertility [172] and a transgenerational extension in lifespan [173]. In mammals, overexpression of the human H3K4me1/me2 demethylase, LSD1, in mice results in heritable effects on development and survival [174]. Collectively, these studies point to the importance of H3K4 methylation for regulating transgenerational epigenetic inheritance.

In addition to H3K4 methylation, several other histone methylation marks have been linked to transgenerational effects in multiple different species. For example, in *C. elegans* a heat stress can elicit transgenerational effects on gene expression [175], and this effect is associated with decreased heritable levels of H3K9me3 [59]. Interestingly, deletion of the putative H3K9 methyltransferase, SET-25, eliminates the transgenerational change in gene expression of a heat shock inducible transgenerational reporter [59]. H3K27me3 has also been implicated in transgenerational inheritance in *Drosophila*. A series of studies have created transgenic lines linking a region where both H3K4 and H3K27 methyltransferases bind to lacZ reporters and drivers of eye color [176]. Using this reporter line the authors have demonstrated that transient activation of this reporter can be transgenerationally inherited corresponding with heritably altered H3K4me3, H3K27me3, and H3 and H4 acetylation levels that are dependent on the H3K27 methyltransferase machinery [176–178]. These heritable histone modifications are not restricted to methylation. Due to the prevalence of preacetylated histones in the pool of free histones, histone acetylation is a prime candidate for transmitting non-genetic information. Indeed, increases in histone acetylation correlate with an intergenerational adaptation to maternal sensing of pheromones in *A. friebergensis* [179]. Therefore, both traditionally activating histone methylation marks, such as H3K4me and histone acetylation, and traditionally repressive histone methylation marks, including H3K9me3 and H3K27me3, have been correlated with changes in heritable epigenetic information.

Complicating the mechanistic understanding of the consequence of manipulating histone modifying enzymes is the fact that none of these epigenetic cues exist in isolation, they all communicate with each other to reinforce an epigenetic signature. Therefore identifying what the heritable cues are and what is the cause of each phenotype is complicated. For instance, elimination of the H3K4me1/me2 demethylase *spr-5* in *C. elegans* causes a transgenerational accumulation of H3K4me2 but a transgenerational decline in H3K9me3

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and increase in H3K36me3 [63], and manipulation of the H3K9me and H3K36me regulatory machinery can eliminate or exacerbate the transgenerational phenotypes of *spr-5* mutant worms [63, 68, 180]. Similarly the transgenerational effects on lifespan of the H3K4 trimethyltransferase complex can be eliminated by genetic manipulation of the H3K9me2 methylation machinery [69]. In mice, overexpression of the H3K4me1/me2 demethylase LSD1 causes an increase in H3K4me3 in the first generation descendants [181]. These examples highlight how difficult it is to distinguish causal non-genetic cues transmitted across generations from those which are subsequently altered in response to the initial change.

DNA methylation-based mechanisms

While DNA methylation can be inherited through cell divisions [182] and is essential for maintenance of imprinting, as discussed above, it's role in transgenerational epigenetic inheritance is less well delineated in animals. In mammals, under basal conditions, while the majority of DNA cytosine methylation is erased between embryonic day 8.5 and 13.5 [183, 184], intracisternal A particle retrotransposons (IAPs) retain 5mC [185, 186]. Interestingly an IAP inserted upstream of the agouti gene to produce viable yellow (A^{vy}) mutations result in yellow coat color, increased tumor incidence, and adult onset obesity [187] which can be regulated and inherited in an epigenetic manner through the maternal line retention of 5mC [188]. Another IAP retrotransposon inserted upstream of axin-fused ($Axin^{fu}$) that is regulated by DNA cytosine methylation causes kinked tails in mice, has been shown to transmit the 5mC state and kinked tail epigenetically through both the paternal and maternal lineages [189]. While these examples of DNA methylation regulating transgenerational epigenetic phenomena in mammals are relatively rare under basal conditions [190], it still remains to be determined whether extreme environmental manipulations, which can elicit transgenerational epigenetic inheritance phenotypes, and which have been shown to alter epigenetic alleles [191–194], can cause DNA methylation to be retained transgenerationally in regions other than IAPs.

While cytosine methylation is relatively prevalent in metazoans DNA N6-adenine methylation (6mA) [195, 196] is an epigenetic modified base which is much more prevalent in bacteria and protists [197]. A number of recent reports have suggested that this rarer DNA methylation occurs in metazoans [198–204]. However, a number of groups have had difficulty detecting this rare modification in metazoans [205–208]. This discrepancy could be due to the relative scarcity of 6mA in metazoans, the sensitivity of detection methods, and that its importance might only be revealed under specific circumstances [207, 209]. Interestingly, 6mA has been shown to increase in response to specific stresses and tracks with transgenerational epigenetic inheritance [53, 198, 210]. Whether 6mA exists and plays an important role in transmitting non-genetic information across generations will have to be further tested through site specific directed methylation and demethylation of adenines.

Contrary to the relatively rare DNA cytosine methylation retention in animals, DNA methylation retention in plants to regulate transgenerational epigenetic silencing of transposable elements is relatively prevalent [211–218]. The prevalence of DNA methylation transgenerational epigenetic inheritance in plants is presumably due to the limited DNA

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methylation reprograming that occurs [219]. Therefore, different organisms might rely more heavily on one epigenetic mode over another depending on which epigenetic cues are more prevalent or less tightly erased upon fertilization. For example small RNAs, which are essential for the basic immune response in *C. elegans* [220, 221], and therefore have an outsized importance, have been repeatedly identified in regulating transgenerational epigenetic inheritance in *C. elegans* while, DNA methylation, which is much more prevalent in plants and is not actively erased upon fertilization, plays a consistent role in regulating epigenetic inheritance in plants.

Crosstalk of epigenetic cues

As we mentioned earlier, chromatin modifications do not exist in isolation and oftentimes communicate with each other to reinforce non-genetic signatures. This modification cross talk is also prevalent in the communication between different epigenetic inheritance substrates. For instance, the RNAi machinery has been demonstrated to physically interact with histone modifying enzymes and binding proteins to help reinforce a repressed chromatin state across virtually all species tested [155, 222–230]. The RNAi machinery is required for the establishment and/or maintenance of heterochromatin characterized by H3K9 methylation in *S. pombe* [223, 224, 226], *C. elegans* [155], *A. thaliana* [222], and mammals [225] and H3K27me3 in *C. elegans* [230] and mice [227]. Reciprocally, studies in *S. pombe* and *C. elegans* have demonstrated that the establishment of H3K9 methylation by small RNAs is required for the long-term maintenance of RNAi silencing, especially across generations [44, 231]. These findings suggest that small RNAs and H3K9 methylation interact, as feedback loops, to maintain silencing at certain genomic loci. However, in *D. melanogaster* Dicer 2 and Argonaute 2 are associated with euchromatic loci [229] suggesting that there might be some species specific divergence with these crosstalk pathways.

Similarly to RNAi and histone modifications, DNA methylation is also important for directing histone methylation and vice versa, through the physical interaction between modifying enzymes and the alternative epigenetic modification [232–237]. Furthermore, many other signaling and metabolic pathways might also interact with these classical epigenetic pathways to mediate multigenerational effects in ways that are as-yet-unknown. For example, recent studies have found that differential deposition of lipids into germ cells can trigger transgenerational changes in histone methylation patterns [238]. These feedback loops are important for maintaining a variety of transgenerational phenotypes [60, 230] and thus make it more difficult to identify the initiating signal, what is transmitted from parents to their children, and what is mediating the phenotypic consequences. It is likely that these intercommunicating networks are essential for most, if not all, epigenetic inheritance paradigms, and that perturbance of any node of this network will elicit disruptions in other interconnected epigenetic pathways.

Conclusions and Future Directions

While we have mostly focused on DNA methylation, histone methylation, and small non-coding RNA as potential carriers of heritable non-genetic information other mechanisms of inheritance clearly exist. We have not been able to give sufficient attention to the inheritance

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of prions and other maternally inherited proteins as well as the microbiome which have both been extensively investigated. Additionally other putative carriers of non-genetic information which have not been studied but could readily transmit epigenetic information across generations include lipids, which are frequently used as cell to cell and organism to organism communication molecules and other RNAs which have diverse roles in virtually every aspect of biology. Epigenetic inheritance is in an exciting era of both discovery of new inter and transgenerational epigenetic inheritance phenomena as well as at the cusp of identifying the molecular mechanisms underlying these amazing and complex biological processes. Time will tell whether these diverse epigenetic cues coalesce into a common epigenetic signaling mechanism or whether a network of independent and sometimes interconnecting nodes of epigenetic information can be transmitted from ancestors to their descendants.

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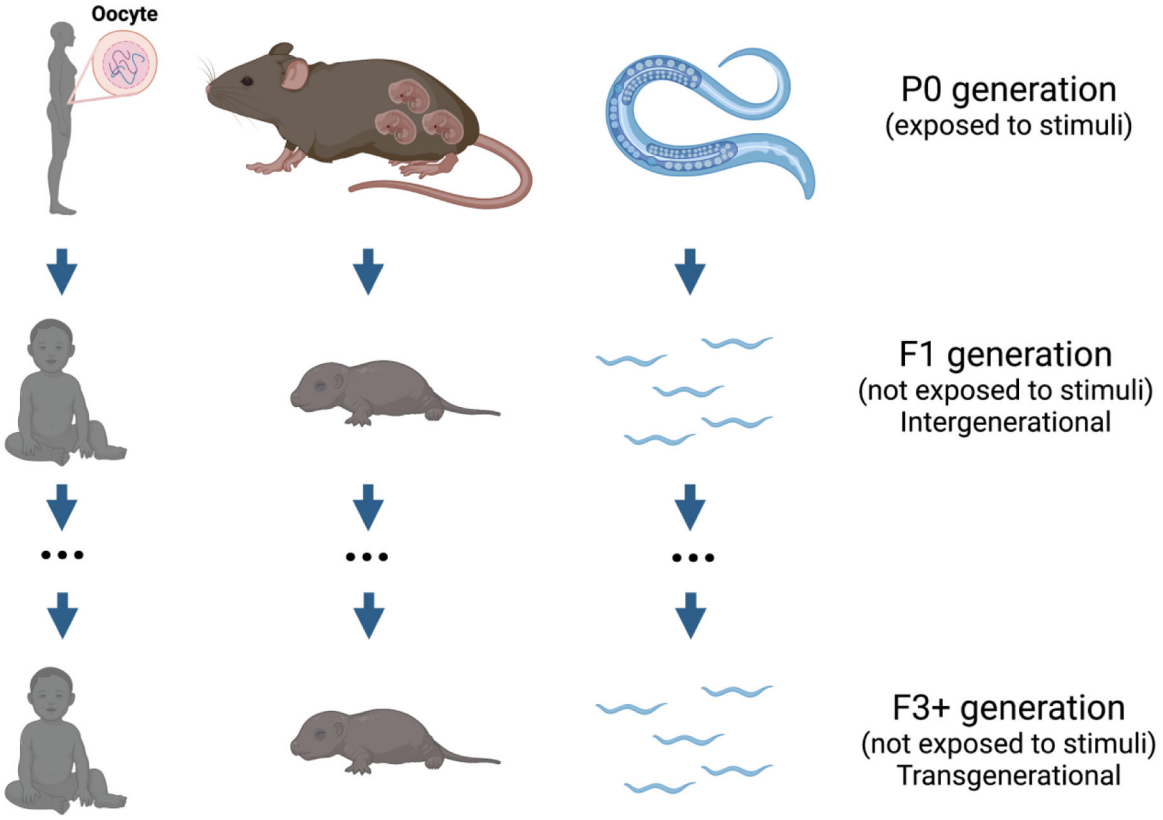

Figure 1: Distinction between inter and transgenerational phenotypes

Numerous different parental (P0) stresses can have multigenerational effects on offspring. Intergenerational effects represent any effect of parental stress on F1 progeny that either directly acts on or is communicated through P0 germ cells or developing F1 embryos *in utero*. By comparison, all effects that are initiated in the P0 generation and persist into the F3 (or later) generations are transgenerational effects. Effects that are initiated in the P0 generation and persist to the F2 generation are intergenerational if any germ cells of F1 animals have formed *in utero* when the initiating event/stress was present and transgenerational if no F1 germ cells have formed. These original distinctions between intergenerational and transgenerational effects in F2 progeny are still used as definitions in the literature irrespective of the mechanisms that mediate multigenerational effects in progeny, including cases where such effects might not be transmitted via germ cells. Figure created with BioRender.com.