Transgenerational Epigenetic Inheritance: From Phenomena to Molecular Mechanisms

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Abstract

Inherited information not encoded in the DNA sequence can regulate a variety of complex phenotypes. However, how this epigenetic information escapes the typical epigenetic erasure that occurs upon fertilization and how it regulates behavior is still unclear. Here we review recent examples of brain related transgenerational epigenetic inheritance and delineate potential molecular mechanisms that could regulate how non-genetic information could be transmitted.

Introduction:

Since the discovery that genomic DNA transmitted heritable information 75 years ago [1], the vast majority of traits have been found to follow Mendelian inheritance. However, since Alexander Brink first reported transgenerational epigenetic inheritance in maize in 1956, the number of examples of non-Mendelian inheritance continues to grow [2]. Non-genetic information has been shown to regulate an increasing number of complex phenotypes, including physical appearance [3,4], energy metabolism [5], behavioral state [6], and longevity [7–9]. Misregulation of epigenetic inheritance causes imprinting disorders in humans [10], and non-genetic information has also been implicated in inherited responses to environmental change [11,12]. For example, human epidemiological data suggest that poor diet of parents and even grandparents increases susceptibility to obesity [13]. Extending beyond the phenomenology to understand the molecular basis of epigenetic inheritance has become the goal of a growing field of research. Identifying the mechanistic basis by which epigenetic information from a parent can be transmitted across generations in model organisms could define basic mechanisms of transgenerational inheritance relevant to human health. In this review, we highlight some recent examples of transgenerational epigenetic

inheritance induced by behavioral and environmental manipulations, focusing on brain related phenotypes, and discuss the potential molecular mechanisms that could underlie the transmission of non-genetic information between generations.

Behavioral and Environmental Changes That Alter Inheritance

Non-Mendelian inheritance, termed transgenerational epigenetic inheritance, has been reported in a wide range of both prokaryotes and eukaryotes. These phenomena may have evolved to allow organisms to adapt to extreme environmental conditions and transmit information critical for survival under adverse conditions to their progeny without mutating the genome. By avoiding mutation, stressed organisms may be able to return to a basal state once conditions improve. Stimuli shown to trigger transgenerational inheritance may be environmental, such as changes in temperature [14–17], oxygen availability [18], amount of sunlight [19], osmotic stress [20], odorants [6,21], radiation [22], and diet [23–26], or behavioral, such as predation [27], exercise [28], and trauma [29–32]. These factors are thought to signal through the somatic tissues of the body to the germline, or directly to the germline, to alter the epigenome and induce effects in subsequent generations (Fig 1). As these phenomena are just beginning to be described, the critical steps involved in sensing, signaling, and epigenetic alteration and maintenance are still largely unknown.

In what follows we describe some examples of phenotypes in multiple species that have been attributed to epigenetic inheritance and review the evidence.

Traumatic Stress—In humans and other species, traumatic experiences in the parental generation have been shown to alter the biological phenotypes of offspring, even in the absence of the initial stressor. Predators induce the crustacean *Daphnia magna* to mature more rapidly and increase reproduction, changes that persist for two additional generations even in the absence of predators. However, how this epigenetic state is induced or inherited is still unclear [27]. Correlative studies suggest that stress induces heritable consequences in humans. The offspring of stressed fathers are more susceptible to stress themselves [31]. Similarly, male and female offspring of stressed adult mice display depression and anxiety behaviors that correlate with altered plasma corticosterone and gene expression [32]. The children of parents who experienced post-traumatic stress disorder (PTSD) or were Holocaust survivors have elevated cortisol and DNA methylation alterations. In particular the chaperone gene *FKBP5* has decreased DNA cytosine methylation in the children of Holocaust survivors [29]. Cortisol was reduced in mothers and their babies who were diagnosed with PTSD in response to September 11 [30]. It is still unclear whether these epigenetic differences in progeny are reactions to a still stressed parent rather or transmission of stress-induced epigenetic changes from stressed parent to offspring.

Parental Care—Maternal behavior can also shape the development of offspring in subsequent generations. Several studies have suggested that the offspring of mothers who do not provide appropriate care in the postpartum period are also deficient in nurturing their newborns. Women who grew up in institutional settings without parental care behave less sensitively and more aggressively towards their own children [33]. Female rats frequently lick and groom their offspring during the first week postpartum [34,35]. Offspring reared by

mothers who do not do this have elevated stress hormone levels and hypothalamic-pituitary-adrenal activity [36] and are less likely to lick and groom their own offspring [37]. Another rodent model of impaired maternal care used mice heterozygous for a mutation of *Peg3*, which show increased neophobia and decreased exploratory behavior. *Peg3* is an imprinted gene expressed exclusively from the paternal allele [38]. When *Peg3* heterozygous females are crossed with wildtype males, the wild-type daughters and granddaughters do not retrieve their pups normally, even though the granddaughters were raised by wild-type mothers. These results have been interpreted as examples of non-genetic inheritance of maternal behavior. An alternate explanation could be that early memories of maternal behavior cause alterations in the newborn brain that affect later behavior in the adult animal that can be passed on to future generations. Yet, there are some indications that epigenetic changes may be at work. A high frequency of pup licking and grooming in mice has been correlated with decreased DNA cytosine methylation of the *ERalpha1b* promoter in female offspring [39]. However, whether DNA methylation regulates maternal grooming and is transgenerationally transmitted has not been examined. Chronic and unpredictable maternal separation in the early life of mice newborns (postnatal day 1 to 14) can trigger depression in mature animals [31,40]. The F1, F2 and F3 generations of these maternally deprived animals have decreased exploratory behavior, independently of their genotype and persist even with cross-fostering. This behavioral phenotype correlates with DNA cytosine hypermethylation in *MeCP2* and hypomethylation in *CRFR2* in the germline of F1 and F2 males. All of these studies taken together suggest that deficient maternal care of neonatal animals causes lasting psychological damage in multiple subsequent generations. However, whether this is due to transgenerational epigenetic inheritance or the consequences of learned behavior is not clear.

Exercise—Environmental enrichment (EE) by a combination of physical exercise and cognitive training of mice has been shown to lead to elevated hippocampal synaptic plasticity and enhanced learning and memory in the F1 offspring. This enhanced learning was correlated with increased miR212/132 expression in the sperm and hippocampus of the mice [28]. Sperm RNA from EE or control fathers was injected into fertilized oocytes and the progenies long term potentiation (LTP) and cognition were examined. Excitingly, mice from EE father sperm displayed elevated LTP and a modest cognitive advantage. The elevated LTP was reverted by treatment with miR212/132 inhibitors but the cognitive advantage was not affected. Together these results suggest the tantalizing possibility that EE can induce heritable effects that are partially regulated by sperm RNA. More experiments will be needed to tease out what molecules are regulating the heritable cognitive advantage of EE.

Olfaction—Odorants have also been proposed to induce epigenetic changes in the offspring. The benzaldehyde and citronellol odorants are attractants for *C. elegans* and contact with them leads to increased reproduction by parents exposed during the larval L1 stage. Increased fecundity was transmitted to unexposed F1, but not F2, generation worms [21]. Surprisingly, repeated generational priming, over five successive generations, with odorant exposure as larvae led to a stronger chemotaxis to these odorants than naïve descendants that persisted for at least 40 generations [21]. How this non-genetic cue is transmitted and whether these descendants would ever revert to the ancestral naïve state or

have undergone a permanent genetic change remains to be determined. Similarly, when parental mice are exposed to acetophenone in conjunction with fear conditioning, their naïve unexposed F1 and F2 generation descendants show elevated fear learning. A hint at a possible link to epigenetic transmission is the observation that both conditioned parents and naïve F1 generation mice have hypomethylated cytosines at the olfactory gene *Olfr151* [6]. More experiments are required to validate whether odorants can induce transgenerational epigenetic inheritance and to delineate the molecular mechanisms by which these cues could be inherited.

These examples provide intriguing hints that transgenerational epigenetic inheritance could be a broadly conserved phenomena regulating many different brain related processes. However, it is clear that more experiments must be performed to distinguish between learned behaviors and *bona fide* epigenetic inheritance.

Molecular Mechanisms

Definitive evidence for epigenetic inheritance and transmission of complex phenotypes will require a molecular understanding of the epigenetic changes that underlie these phenotypes and how they are transmitted and maintained for multiple generations. In principle, any molecular change in the zygote other than alterations in DNA sequence could carry non-genetic information. These include chemical modifications of DNA and chromatin proteins and possibly modifications of non-coding RNA, non-chromatin proteins or microbiota [42–44] (Figure 2). Here we briefly describe examples of each of these modes of non-genetic inheritance in diverse species. Comprehensive reviews of what is known about epigenetic mechanisms responsible for inheritance of transcriptional memory are available [13,45–47].

DNA methylation—Because of the semi-conservative nature of DNA replication, DNA modifications can be inherited through cell division [54,64] and therefore provide an ideal carrier of non-genetic information across generations. In eukaryotes, DNA methylation of the 5 carbon position of cytosine (5mC) [48], which is catalyzed by the Dnmt enzymes [49], is the predominant form of DNA modification. 5mC is a stable but dynamic [54–56] transcriptionally repressive epigenetic mark that regulates development [57,58], differentiation [59,60], aging [61] and disease [62,63]. The factors that mediate the initial deposition, maintenance, and removal of DNA methylation are well characterized. Unmodified DNA can be de-novo methylated by the DNA methyltransferase enzymes, Dnmt3a and Dnmt3b [65,66] and established methylation patterns can be maintained during DNA replication by Dnmt1 [49,67,68]. Recruitment of these methylases to DNA is mediated by additional factors such as DNMT3L (de-novo) [69,70] and UHRF1 (maintenance) [71,72]. DNA methylation can be removed actively by Ten–eleven translocation (TET) family demethylases, TET1, TET2 and TET3 [73–75], or passively by successive rounds of replication [76].

There are several notable examples of DNA methylation patterns that can be inherited across generations, including imprinting of gene promoters and mobile DNA elements (e.g. transposons). Although 5mC moieties are globally removed during fertilization of the zygote and in primordial germ cells (PGCs) [77], a small subset of cytosines are resistant to post-

fertilization demethylation and exhibit a form of intergenerational inheritance, termed imprinting. For each imprinted gene, persistently methylated cytosines occur specifically in either the maternal or paternal DNA. Errors in the establishment or maintenance of imprinting in the parental germ line can lead to imprinting diseases, such as Prader–Willi syndrome and Angelman syndrome [78]. While it is still unclear how imprinted cytosines escape demethylation, identifying the mechanisms and molecules that facilitate this process may provide insight into how non-genetic information can be transmitted across generations. Another persistent form of epigenetic inheritance regulated by DNA methylation suppresses activation of retrotransposons, such as Intracisternal A particles (IAPs), in the mouse genome [80]. Like imprinted genes, IAPs are mostly methylated and silenced in the germline and resist the wave of DNA demethylation during fertilization [81,82]. One of the best characterized examples of epigenetic inheritance in mammals is the agouti viable yellow (A^{vy}) locus in mice that determines coat color. A^{vy} harbors an IAP sequence upstream of the agouti coding sequence. A^{vy} expression varies among littermates depending on the DNA methylation state of IAP in the locus. The spectrum of agouti phenotypes in the offspring depends on the mother's coat color. Maternal dietary supplementation with methyl donors shifts the coat color of the pups, suggesting a connection between germ line methylation and epigenetic memory in the progeny [3,83–85]. Other examples of inheritance and transposon silencing involving DNA methylation have been studied in plants [47,86], making this one of the most well studied mechanisms of transmission of non-genetic information.

Accumulating correlative epidemiological evidence suggests that environmental signals can be encoded in DNA methylation patterns that are subsequently passed on through generations. For example, prenatal exposure to famine during the Dutch Hunger Winter was associated with lower cytosine methylation on the imprinted insulin-like growth factor 2 (*IGF2*) gene [87] and decreased cytosine methylation in the *FKBP5* (FK506 Binding Protein 5) gene was correlated with stress levels in the offspring of Holocaust survivors [29]. More direct evidence of transgenerational inheritance of changes in 5mC is provided by experimental manipulation in other organisms. In mice, for example, nutritional deprivation in utero reduces 5mC in sperm of adult progeny and leads to metabolic perturbations [88].

Because the molecular mechanisms for deposition and maintenance of 5mC on DNA are understood, 5mC has often been proposed as a mechanism underlying transgenerational inheritance. However direct molecular evidence connecting environmental cues and stresses to DNA methylation and its effect on progeny phenotypes is scarce. Additional experimental evidence that 5mC is responsible for transgenerational phenotypes is needed to be certain that DNA methylation is an important carrier of epigenetic information between generations. Interestingly, rare DNA methylation events, such as methylation on the 6 nitrogen position of adenine (6mA), which is frequent in prokaryotes, have been described in eukaryotes [50–52] and could also play a role in epigenetic inheritance [51,53]. However, assaying this DNA mark has been hampered by possible bacterial contamination of eukaryotic samples and thus its contribution to epigenetic inheritance remains to be determined once more sensitive tools have been developed.

Proteins—Several proteins are transmitted from parents to children in the zygote to facilitate early growth and cell divisions [89–95]. One of the most well studied non-genetic proteins which can be transmitted are the self-replicating prions [96–98]. Prions are thought to have evolved to infer beneficial phenotypes in response to adverse environmental conditions [99–105] without permanently altering the DNA sequence. However, prions were originally characterized as the cause of several heritable neurodegenerative diseases including; Creutzfeldt–Jakob disease (CJD), kuru, scrapie and bovine spongiform encephalopathy, in humans, sheep and cows, respectively [98,106–110]. Work in *Saccharomyces cerevisiae* [111–113], has deciphered how altered proteins can self-perpetuate in the absence of altered nucleic acid. The capacity of prions to respond to environmental cues and subsequently be non-genetically transmitted is exemplified by [URE3] and [PSI+]. In response to poor environmental conditions, yeast will convert Ure2p to [URE3] and Sup35 to [PSI+] [114] which are cytoplasmically inherited as non-mitochondrial, non-Mendelian dominant traits [109,115–117]. Prions have the capacity to adopt multiple conformations, at least one of which can self-template over long biological timescales. Prion forming proteins have a "native" non-prion conformation, occasionally these fold into a prion conformation that then replicates itself by templating the conformational conversion of other molecules of the same protein. These changes in conformation alter the functions of the proteins involved, resulting in phenotypes specific to each determinant protein [101,112,118–127]. At the molecular level, virtually all known prions produce new traits by forming highly stable cross-beta-sheet amyloid fibers [119,128–132]. Propagation of these traits, and the amyloids that confer them, relies on the severing of prion templates into smaller "seeds" by the protein-remodeling factor Hsp104 [118,120,133]. These seeds are passed from mother cells to their daughters, serving as "replicons" to template future rounds of assembly [118,120]. Thus, inhibiting Hsp104 eliminates the prion state and its heritable capacity [134–137]. It will be important, in future studies, to determine whether these non-histone proteins can carry non-genetic information in multicellular organisms.

Histone Methylation—One specialized class of proteins which are poised to carry non-genetic information across generations are histones. Histones are the basic proteins that DNA is wrapped around in order to package and organize chromatin into the structural units termed nucleosomes [138,139]. Histone tails are heavily modified by a variety of post-translational modifications (PTMs) including phosphorylation, acetylation, ubiquitinylation, methylation, ADP-ribosyation and SUMO-laytion [140]. These reversible modifications integrate environmental cues to contribute to control of gene expression by influencing chromatin compaction and/or signaling to transcription factor complexes [141]. To date, there are several potential mechanisms by which histone PTMs can be maintained through cell division and then across generations to mark critical regions of the genome. Nucleosomes can be removed at the replication fork and immediately reapplied to alternating daughter strands [142–148], the histones themselves can be replicated in a semi-conservative manner [144,149], histones could be added to specific newly synthesized DNA from a pool of pre-modified histones, long ncRNA could be used to reapply chromatin modifications in specific genomic locations [150,151], RNAi machinery can play a role in maintaining epigenetic memory [152–154], histone modifying enzymes are present at the

replication fork and can modify the newly incorporated histones [155,156]. Several or all of these different modes of inheritance might contribute to the epigenetic memory of histone modifications, and different combinations could be revealed in different systems or in response to different initiating signals. While the specific mechanism for the inheritance of histone modifications is still being worked out, there is already a rich literature out there demonstrating the correlation between histone modifications and transgenerational epigenetic inheritance which we will briefly summarize here.

In several species, including yeast, *C. elegans, Drosophila*, and plants, histone methylation, predominantly the canonically repressive modifications H3K9me3 and H3K27me3, has been shown to communicate with and help to reinforce RNAi-mediated silencing across generations [157,158]. Fission yeast have been used to demonstrate that H3K9me-dependent heterochromatin can be retained across generations in the absence of DNA methylation [159]. In yeast, H3K9me-dependent heterochromatin maintains silencing of centromeric RNAs and transposons. siRNAs are produced from noncoding centromeric RNAs (ncRNAs) and loaded onto the RNA-induced initiator of transcriptional silencing (RITS) complex [160]. RITS is then directed to nascent noncoding centromeric RNAs [161]. The RITS complex promotes H3K9 methylation, spreading and maintenance by recruiting the H3K9 methyltransferase Clr4/Suv39 [162]. Once this repressive state is set, the heterochromatic state can be inherited in the absence of RNAi [159,163,164]. In *C. elegans* exposure to high temperature leads to reduced H3K9 modifications at a silenced transgene locus. Genetic analysis indicates SET-25 as mediating this effect [15]. MET-2-dependent H3K9 methylation suppresses transgenerational small RNA inheritance suggesting that H3K9me3 might be required for specific instances of siRNA-dependent inheritance [165]. The H3K27 trimethyltransferase PRC2 is maternally supplied to progeny and is required for active propagation of H3K27me3 during early embryogenesis in several organisms [166]. Both H3K9 and H3K27 are affected by paternal diet [167]. The sperm chromatin of both zebrafish and mammals contains the repressive mark H3K27me3 and the active marks H3K4me2 and H3K4me3, raising the possibility of inherited transmission of these marks [168]. Furthermore, it was shown in *C. elegans* that X-chromosome inactivation can be intergenerationally transmitted from both oocytes and sperm to the embryos [166]. Fertility depends on continued X-chromosome repression in the germ line, which requires inheriting a repressed X chromosome. H3K27-methylated histones can transmit a short-term memory of repression in embryos and maternally supplied PRC2 mediates through H3K27 histone methylation the long-term memory of repression during development. In worms lacking PRC2, a paternal repressed X chromosome via H3K9 methylation provides an alternative mode of transmitting X repression to progeny [166].

There is also evidence for the inheritance of active histone modifications. H3K4me1/2/3 generally, although not always [44], characterize transcriptionally permissive or active chromatin [169,170]. Mutations in proteins of the Trithorax H3K4 trimethyltransferase complex, WDR-5, ASH-2 and SET-2 cause a ~20–30% extension of *C. elegans* lifespan [171], which is transmitted for three generations to genetically wildtype descendants [7]. Removal of the H3K4me3 demethylase RBR-2 abolished the transmission of extended lifespan in WDR-5-deficient worms, suggesting that this transgenerational effect depends on histone methylation. Knock out of the H3K4 methyltransferase Set1, or complex subunit

Ash2 in *Dictyostelium* eliminated the inheritance of active transcriptional states [172], suggesting that H3K4me3 might play a conserved role in regulating epigenetic memory. Similarly, knockout of the H3K4me1/2 demethylase *spr-5* (the homologue of LSD1) in *C. elegans*, causes a transgenerationally progressive decline in fertility and a transgenerational extension of lifespan [173,174] which can be repressed by removal of an H3K4 methyltransfserase as well as H3K9me3 regulating enzymes [174–176]. In mammals, overexpression of human LSD1 in mouse sperm resulted in deregulation of gene expression in embryos and the effects were heritable across generations [177]. H3K36me1/2/3 methylation is also generally associated with actively expressed genes [178]. In *C. elegans*, embryos inherit H3K36me3-marked chromosomes from both the oocyte and sperm and receive a maternal load of MES-4 and MET-1 that are H3K36 methyltrasnferases. In this model, MET-1 is suggested to mediate transcription-coupled H3K36me3 in the parental germline while MES-4 seems to transmit the H3K36me3 mark across generations and through early embryo cell divisions by maintaining inherited patterns of H3K36me3 [179].

RNA—A substantial quantity of non-coding RNA is both maternally [180–184] and paternally [185–187] transmitted. Non-coding RNAs play key roles in regulating gene expression [181,188,189], genome stability [190–192], development [193–195], differentiation [196–198] and defense against foreign genetic elements [199–201]. Non-coding RNAs include long non-coding RNAs >200nts and short non -coding RNAs <30nts. Short non-coding RNAs are subdivided to additional classes; miRNAs (miRNAs), siRNAs (small-interfering RNAs), piRNAs (PIWI-interacting RNAs), tRNAs (transfer RNAs), tDRs or tsRNAs (tRNA-derived small RNAs) and snoRNAs (small nucleolar RNAs) [202]). The best characterized heritable RNAs are the RNA interference (RNAi) mechanism. This system has been elegantly mapped out in yeast [43,152,203], *C. elegans* [204–209], and *D. melanogaster* [191,210–212] and is reviewed elsewhere [213–216]. A small subset of RNAi's have been shown to be heritable, although it is still unclear as to how these RNAi's are selected or transmitted. In *C. elegans*, RNAi's are amplified by RNA-depedendent RNA polymerases [217–221] which can be transmitted across generations [199,207,222–224]. The heritable maintenance of silencing is dependent on the nuclear RNAi pathways [207,208,217,223,225–229]. Hints of how RNAi's can selectively be transmitted across generations have been proposed due to forward genetic screens which have identified specific Argonauts [205,208,230–232] and a conserved RNA helicase, ZNFX-1, that is involved with formation of phase-separated granules bordering the nucleus [232,233]. It is possible that RNAi's are potentially marked and physically separated into granules for transmission across generation. piRNAs have been identified in *C. elegans* [158,207,223], *D. melanogaster* [184,191,234,235], zebrafish [192] and mammals [236–240] to maintain genome stability by silencing transposon elements. In *C. elegans* [158,207,223] and *D. melanogaster* [184,241,242] this function has been shown to be inherited across generations. The transmission of dsRNA-initiated silencing between cells requires the conserved transmembrane protein SID-1 (systemic RNAi defective). SID-1 function in both the parent and progeny is required for the efficient transmission of dsRNA-initiated silencing from parent to progeny [243–248]. Interestingly, an uncharacterized mechanism keeps the inheritance of small RNAs restricted to 3–5 generations. A molecular characterization of how this transgenerational clock is regulated is required for a deeper understanding of how

non-genetic information is transmitted through small RNAs. In addition to the RNAi machinery, work initially in yeast [225–228,249] and subsequently in *C. elegans* [165,166,207,229,250–253] has shown that histone methylation at H3K9 and H3K27 can communicate to help reinforce the RNAi maintenance machinery.

In mammals, less is known of the molecular mechanisms that regulate RNA inheritance, however, several studies have correlated heritable distinct RNA species which are present in sperm and oocytes and can be carried into the zygote upon fertilization. How these specific RNAs are marked for generational retention is still unclear. Recent work suggests that modifications to RNAs might be involved in marking a subset of RNAs to regulate heritability of metabolic phenotypes. The tRNA methyltransferase, DNMT2, partly through its enzymatic activity, participates in transmission of paternally acquired metabolic disorders in mice. Deletion of mouse, Dnmt2, prevented the elevation of RNA modifications (m5C, m2G) in sperm small RNA fractions that are induced by a high-fat diet. Offspring produced from oocytes injected with RNA from Dnmt2 KO sperm showed reduced phenotypes associated with high-fat-diet-induced metabolic disorders [254]. Intergenerational transmission of small RNAs in mammals with effects on progeny phenotypes involve miRNAs [187,255,256] and tRFs [23,186,254]. Interestingly, tRFs have mostly been linked to the transmission of metabolic phenotypes [23,185,186,254,257–262].

In plants paramutation involves RNA-mediated heritable chromatin changes and several genes in the RNAi pathways have been implicated [263]. In paramutation, one allele can stably alter the expression of a homologous allele *in trans*. The first reported example of transgenerational gene silencing by paramutation was in maize [2,264]. Individual alleles at three different color gene loci gave rise to epialleles with reduced pigmentation. These epialleles led to a heritable non-Mendelian silencing of the wildtype alleles in heterozygotes which can be transmitted stably over many generations in the absence of the original allele [265]. Together these examples illustrate how ncRNA can transmit specific non-genetic information across generations, and in certain instances communicate with DNA and histone methylation to reinforce and perpetuate non-genetic information.

Microbiota—In addition to heritable cues transmitted in the cell itself, foreign microorgansisms in the form of microbiota – which may include bacteria, viruses, and fungi – are putative carriers of non-genetic information across generations. The vast majority of the human microbiota is present in the gut which harbors an estimated 10^{13} microbes [266]. Early work in the 19th century from Pasteur and Metchnikoff examined the microbiota-gut interactions [267,268], however, advanced sequencing technologies of the past decade have spurred a renaissance of microbiota research and how these microorganisms respond to changing environment and are transmitted within families and across generations [269]. Host-microbe interactions have been studied in a variety of model organisms, including hydra [270,271], *C. elegans* [272], squid [273,274], fly [275,276], zebrafish [277], mice [278] and humans [279], to regulate numerous pathological states, mainly metabolic related to diseases such as inflammatory bowel disease, Colitis, obesity and diabetes [280] but also neurological related disorders and depression [281–285]. In addition, the microbiota affects a wide spectrum of host physiological traits, including development [286–288], fitness behaviors [289–291], immunity [292,293], nutrition [294,295], and longevity [296,297].

Mammalian microbiotas are acquired both vertically from mother to offspring [298–301] and horizontally among non-relatives through social interactions and shared environments [301–304]. Several studies have reported the importance of the fetal environment in the womb, and of postnatal colonization of the gut by commensal bacteria [305–309]. The microbiota population of the infant that is influenced by the maternal gut [305,310,311] is influenced by mode of delivery [300] as well as breastfeeding [312–317]. Microbiota are also regulated by diet [318–322], and are therefore well situated to transmit non-genetic cues across generations. Once transmitted, microbiota communicate with host cells through ligands and receptors to activate insulin signaling [286] and the TOR pathway [287]. In addition, microbial produced metabolites also seem to activate host cell signaling pathways [323–325] and modulate enzymatic activities and pathways involved in histone modifications [326–328] chromatin remodeling [329] and DNA methylation [330–332] which can reinforce non-genetic information. Many of these metabolites such as folate, choline and butyrate are involved in one carbon metabolism and the production of methyl donors for cellular methylation reactions [284,333]. Other microbial metabolites are donors of acetyl groups involved in the formation of acetyl-CoA that participates in epigenomic acetylation reactions [334]. These metabolites and signal molecules could therefore be transmitted from the ancestral microbiota to lead to long-term indirect effects via epigenetic mechanisms mentioned above. However, evidence for the effect of microbiota on epigenetic mechanisms leading to heritable phenotypes is correlative and therefore is a ripe field for future studies to probe mechanistically how microbiota could regulate transgenerational epigenetic inheritance. However, the evidence that connects microbiota-gut interactions to this complex relationship is still lacking. Some interesting results have recently been demonstrated in the *Drosophila* microbiota-gut system. Removal of commensal Acetobacter species from F1 embryos did not alter F1 larvae development, but caused F2 delay. Reintroduction of isolated Acetobacter species prevented the inheritance of the delay and this prevention is partly mediated by vitamin B2 (Riboflavin) which is produced by these bacteria [335]. The presence of gut bacteria affects gut transcriptome with both up-regulated and down-regulated genes, the majority of these are associated with immune responses, tissue homeostasis, gut physiology, and metabolism [336]. Furthermore, the involvement of microbiota in transgenerational inheritance of environmental exposures was tested by looking at transcriptional profiles of progeny of flies reared in the cold versus normal temperatures. 116 genes were found to be differentially regulated in a microbiome dependent manner, 45 were up-regulated, are expressed in various tissues and are involved in cuticle development, chitin metabolism and response to oxidative stress. Most of the 71 genes that were down-regulated in response to the cold temperature were mainly highly expressed in various parts of the fly's gut and are involved in cilium movement and multicellular organism reproduction [337]. In recent years there has been a growing body of evidence supporting the pivotal role of the microbiota population and diet on neurodevelopment and behavior of the offspring [338–340]. The establishment of the neonatal gut microbiota coincides with major processes of neurodevelopment. Neurogenesis, the development and maturation of the microglia, formation of the blood-brain barrier and myelination are all influenced by the presence of microbiota as shown in studies utilizing germ free mice and perinatal administration of antibiotics and probiotics. Furthermore, similar studies have shown that the offspring exhibit hypoactivity, anxiety-like behavior and

reduced social behavior. These studies are comprehensively reviewed in Gil, et. al. [338] In addition, immune activation during fetus development has potential implications on offspring physiology, neuropathology and behavior, as well as the microbiome [341,342]. Autism spectrum disorder, Schizophrenia and depression have been linked to the gut microbiota, but still require deeper study [338]. The maternal microbiome and the microbiome transmitted to the offspring, their metabolites, and other microbial products seem therefore to be important in driving healthy neurodevelopment, and when perturbed are sufficient to induce behavioral deficits in offspring.

Each of these modes of epigenetic inheritance do not function in isolation and, as we mention above, will oftentimes communicate and reinforce other non-genetic cues. Deciphering which specific molecules are transmitted across generations to regulate complex traits remains one of the outstanding questions of the field. Now that epigenetic inheritance has been demonstrated to be so pervasive, future studies focusing on the transmitted molecules and the conservation of molecular mechanisms will be essential.

The importance of rigor

It is clear that transgenerational epigenetic inheritance is an exciting and dynamic field which illustrates the communication between many layers of biological regulation. However, it is also exceptionally prone to errors and misinterpretations. Some prominent examples include the extremes of Lamarckism, Lyshenckoism, and Lamarckian eugenics [343]. In these instances, theories rather than experiments were allowed to drive the scientific progress. One prominent example stems from work done in Ivan Pavlov's lab, where a student had initially demonstrated that mice became successively trained across generations at responding to a bell to expect to be fed. Upon further tests it was demonstrated that the student had become a more efficient mice trainer rather than the mice inheriting the memory of the bell from their parents [344]. This example highlights the need for rigorous controls within these experiments and the identification of the appropriate molecular mechanisms through traditional necessity and sufficiency experiments. As epigenetics is modulatory in its very nature, resulting transgenerational phenotypes are often subtle and therefore can be swayed by investigator bias. It is therefore important to incorporate rigorous controls and blind experiments to ensure that the results are robust. Ultimately, the identification of the underlying molecular mechanisms will facilitate more traditional necessity and sufficiency experiments which will help to transition transgenerational epigenetic inheritance more decisively from phenomena to believable biology.

Summary:

Here we have summarized some of the exciting recent findings in the brain in the burgeoning field of Transgenerational Epigenetic Inheritance. We have laid out some of the potential molecular mechanisms that could underlie how non-genetic information can be transmitted across generations and discussed some of the controversies inherent in studying traits which by their very nature are modulatory and exist at the interface between genetics and environment. It is becoming increasingly clear that none of these epigenetic cues functions in isolation, and that by their very nature epigenetic cues communicate with each

other to help reinforce epigenetic signatures. The complex nature of transgenerational epigenetic inheritance makes it a complex trait to tackle. However, as the sequencing age has come into its own, and the ease with which non-model organisms can be adapted and manipulated, we will no longer be restricted to studying canonical model organisms. Thus, this field can expand to take advantage of the incredible diversity throughout the eukaryotic kingdom to decipher how these complex traits can be regulated.

Transgenerational Epigenetic Inheritance has been subject to many false starts. While the early extremes of Lamarck and Lyshencko have not held up to the test of time, it is becoming increasingly apparent that some non-Mendellian Inheritance is contributing to our diversity. Transgenerational Epigenetic Inheritance's very nature is susceptible to subtle changes in the environment and therefore finding robust, reproducible paradigms of epigenetic inheritance is critical for pushing the field forward. Now that we have entered the molecular age, pushing beyond the correlative observations, where some transgenerational phenomena are associated with epigenetic changes towards direct manipulation of the epigenome to test whether epigenetic manipulations are not only necessary but also sufficient, independent of the initiating stimuli, to regulate transgenerational epigenetic phenotypes will be critical to push this field forward. The recent advent of tools to direct epigenetic modifications to specific loci, such as the fusion of a nuclease null Cas9 to chromatin modifying enzymes to target epigenetic regulators to specific loci [345], will be critical for determining the sufficiency of epigenetic changes to regulating transgenerational epigenetic inheritance phenotypes and probing whether these tantalizing preliminary results will stand the test of time.

Acknowledgements

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Highlights

- Examples of transgenerational epigenetic inheritance of brain related phenotypes

- Overview of putative molecular carriers of non-genetic information are described

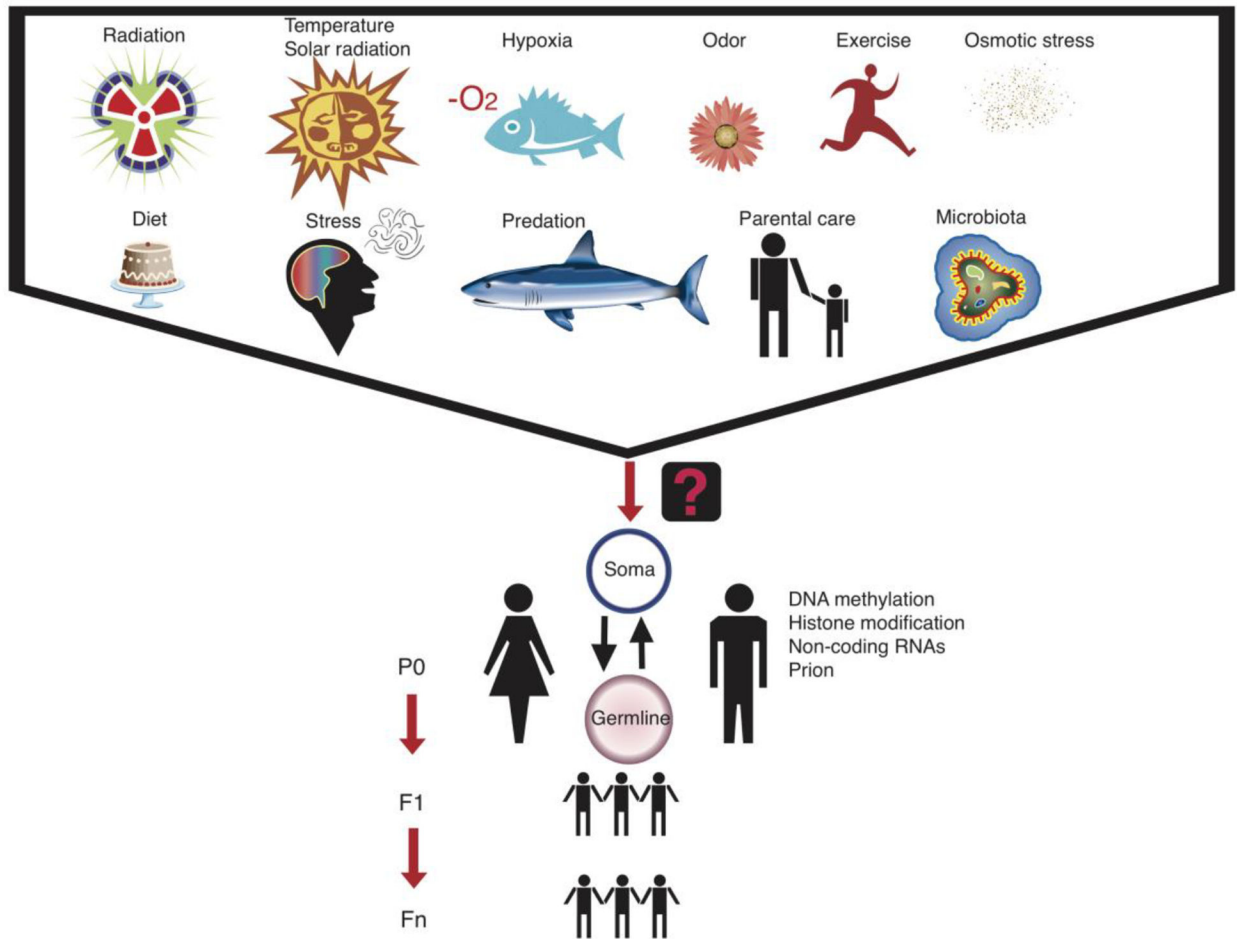- Highlight of potential pitfalls and next steps of the field

Figure 1.
Several behavior and environmental cues have been proposed to induce phenotypic changes in the parental generation that can be transmitted to subsequent generations through the germline in a non-genetic manner.
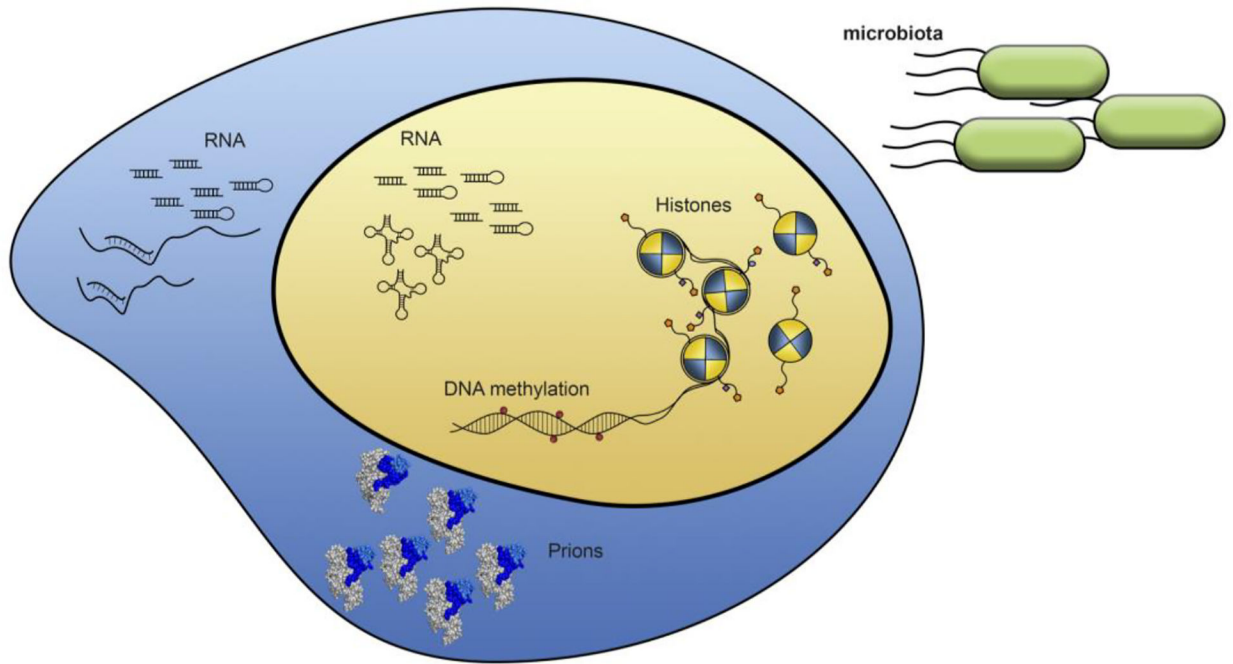
Figure 2. Putative carriers of non-genetic information.
Different mechanisms that may transmit non-genetic information are depicted here; DNA methylation, non-coding RNAs, histone post translational modifications, prions and microbiota.