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Viewpoint

Molecular insights into the transgenerational inheritance of stress memory

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ABSTRACT

There is accumulating evidence to show that environmental stressors can regulate a variety of phenotypes in descendants through germline-mediated epigenetic inheritance. Studies of model organisms exposed to environmental cues (e.g., diet, heat stress, toxins) indicate that altered DNA methylations, histone modifications, or non-coding RNAs in the germ cells are responsible for the transgenerational effects. In addition, it has also become evident that maternal provision could provide a mechanism for the transgenerational inheritance of stress adaptations that result from ancestral environmental cues. However, how the signal of environmentally-induced stress response transmits from the soma to the germline, which may influence offspring fitness, remains largely elusive. Small RNAs could serve as signaling molecules that transmit between tissues and even across generations. Furthermore, a recent study revealed that neuronal mitochondrial perturbations induce a transgenerational induction of the mitochondrial unfolded protein response mediated by a Wnt-dependent increase in mitochondrial DNA levels. Here, we review recent work on the molecular mechanism by which parental experience can affect future generations and the importance of soma-to-germline signaling for transgenerational inheritance.

Introduction

It has become increasingly recognized that parental environmental experiences and physiological stresses can influence the traits and fitness of descendants in various organisms (Greer et al., 2011; Rechavi et al., 2014; Jobson et al., 2015; Chen et al., 2016; Kishimoto et al., 2017; Perez et al., 2017; Webster et al., 2018; Nono et al., 2020; Jawaid et al., 2021). These transgenerational effects provide a basis to understand how the transgenerational phenotypic adaptations acquired during a lifetime in response to various environmental challenges can be passed on to offspring. As influenced by Darwin's theory of natural selection and the Weismann barrier theory, the traditional view of inheritance is mainly focused on the transmission of DNA across generations via gametes. The central tenet of the Weismann barrier that the 'immortal' germ cells are separated from the somatic cells, which prevents the transmission of heritable information from soma to germline, is facing challenges at present.

Transgenerational epigenetic inheritance has been reported for a variety of traits across multiple species—the color of flowers in plants, fur color in mice, and longevity in *Caenorhabditis elegans* are all known to be epigenetically inherited (Robert and Randy, 2003; Cropley et al., 2006; Greer et al., 2010, 2011; Radford et al., 2014; Siklenka et al., 2015; Zhao et al., 2019). Epigenetic alterations such as DNA methylations, histone modifications, and small non-coding RNAs in the germline that mediate transgenerational effects have been described (Skvortsova et al., 2018; Perez and Lehner, 2019; Duempelmann et al., 2020). However, the mechanism by which the germline perceives the acquired phenotypic information and passes it to descendants remains largely unknown. In this review, we aim to summarize current knowledge about the transgenerational inheritance of environmentally induced stress responses and highlight the mechanisms by which transgenerational cues are transmitted from somatic cells to the germline.

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Environmentally-induced transgenerational inheritance

Animals face many adverse situations in the wild, including pathogens, fluctuating food availability, temperature shifts, olfactory imprinting, and toxins, among others. The capacity to detect, respond, and adapt to various stressors in the environment through defensive mechanisms that protect the entire organism from being attacked is crucial. However, there has long been debate on how much transgenerational inheritance of stress responses actually occurs. In many experimental systems, as well as in human epidemiological studies, some stress-induced responses were shown to persist for several generations (Fig. 1). The transgenerational effects might facilitate the genetic assimilation of stress-induced effects, ensuring the evolutionary persistence of stress response strategies and turning individual adaptability into an evolutionary adaptation (Badyaev, 2005).

Food supply

Evidence from human epidemiological surveys and different animal models has demonstrated that food supply affects the health and longevity of their descendants. In humans, the Dutch famine birth cohort study has provided convincing evidence that exposure to famine during early gestation is associated with increased risk of diseases, including coronary artery disease, elevated cholesterol, altered blood clotting, and increased obesity (Painter et al., 2008; Senaldi and Smith-Raska, 2020). In mammals, paternal exposure to a high-fat diet (HFD) in mice that causes paternal obesity diminishes the reproductive health of both male and female F_1 and F_2 offspring (Fullston et al., 2012), and increases their risk of developing diet-induced obesity and metabolic syndrome (Huypens, 2016). Both low-protein and high-fat diets affect the levels of small RNAs in mature sperm and cause metabolic disorders in offspring in mice (Chen et al., 2016; Sharma et al., 2016; Zhang et al., 2018b).

In *C. elegans*, starvation during the developmental stage not only leads to dramatic changes in gene expression in the parents but also leads to lifespan extension, heat resistance, and starvation resistance in their progeny (Maxwell et al., 2012; Rechavi et al., 2014; Jobson et al., 2015; Kishimoto et al., 2017). These transgenerational effects of longevity and stress resistance last more than three generations, and depend on the nuclear RNAi Argonaute HRDE-1 and the endogenous small RNA pathway protein RDE-4 (Rechavi et al., 2014). In addition, exposure to high glucose levels in the parental generation leads to resistance to protein-damaging stress in their descendent progeny with trade-offs of decreased lifespan and fertility in *C. elegans* (Tauffenberger and Parker, 2014). In *D. melanogaster*, male flies exposed to a poor food diet during the developmental stage produced offspring with shortened developmental times and larger size compared to males raised on a standard diet (Valtonen et al., 2012).

Heat stress

Environmental temperatures are constantly changing as a result of global climate change and are crucial for biochemical reactions and significantly affect animal physiology. Mild heat stress can induce stress resistance and cause lifespan extension in different organisms (Hercus et al., 2003; Seong et al., 2011; Kumsta et al., 2017). For example, *C. elegans* is usually grown at a temperature of 20°C, and when it is grown at 25°C, it is thought to be mildly stressed, resulting in changes in stress-responsive gene expression. Research has shown that the high temperature (25°C) triggers a transgene de-silencing phenotype that can persist for 14 generations after the growth temperature is back to 20°C (Klosin et al., 2017). Decreased H3K9me3 levels are required for the transgenerational transgene de-silencing phenotype that is induced by heat stress (Klosin et al., 2017). Moreover, lifespan extension induced by hormetic heat stress response (35°C for 1 h) in *C. elegans* can also be transmitted to the progeny for five generations, and epigenetic modifications are required for the transgenerational survival advantages (Wan et al., 2021).

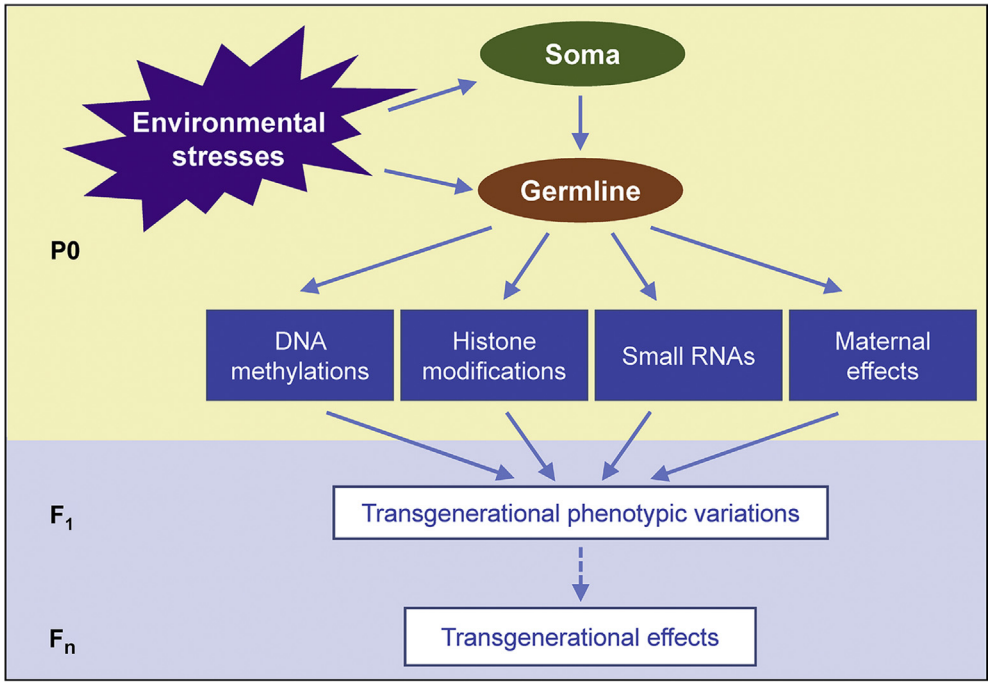

Fig. 1. Environmental stresses can influence the phenotypes of offspring. Exposure to various environmental stresses can induce phenotypic changes in the parental generation that can then be transmitted to subsequent generations through the germline.

Olfactory imprinting and fear memory

The olfactory system is a critical sensor for environmental cues, and it plays an essential role in inducing various physiological responses to stresses, as well as behavior changes, such as attraction, fear, and social behaviors (Sakano, 2020). Sometimes these responses induced in early life during a critical period could permanently alter behavior in individual animals, which has been called olfactory imprinting. For example, *C. elegans* exposed to the chemical benzaldehyde during the first 24 h after hatching showed significantly increased chemotaxis toward benzaldehyde as adults, and this olfactory imprinting depends on the expression of *sra-11* in the AIY interneurons (Schuster et al., 2016). When worms were exposed to the benzaldehyde imprinting paradigm for four generations, this olfactory imprinting could be passed on for at least 40 generations (Remy, 2010).

The transgenerational inheritance of olfactory imprinting is also observed in mammals. Parental fear conditioning by acetophenone exposure leads to an increase in the size of the olfactory bulb and an altered response to acetophenone in the F_1 and F_2 offspring. Interestingly, the behavioral sensitivity to odor is accompanied by increased activity of the olfactory receptor (*Olfr151*) and the hypomethylation of the *Olfr151* gene in the parental sperm (Dias and Ressler, 2014).

Bacterial pathogens and avoidance behavior

Viruses, bacteria, fungi, and parasites can all cause infection in their hosts. The immune response limits the negative impact of infection on host fitness. Multiple studies provide evidence that at least 20 species, including insects, crustaceans, and mollusks, have been shown to transmit a protective immune response to their progeny following infection (Tetreau et al., 2019).

Exposure to a bacterial pathogen (*Pseudomonas aeruginosa,* PA14) induces avoidance behavior after the induction of innate immune responses in *C. elegans* (Zhang et al., 2005), and this avoidance behavior can be inherited transgenerationally, which serves to protect the progeny from PA14 pathogen exposure (Kaletsky et al., 2020; Moore et al., 2019, 2021). PRG-1/Piwi-dependent piRNA pathways in the germline are required for the transgenerational inheritance of avoidance behavior (Moore et al., 2019). Worms use the RNAi pathway to obtain and read the small RNAs (sRNAs) from bacteria, which then induces avoidance behavior that can be passed on for four generations (Kaletsky et al., 2020). In addition, parental exposure of *C. elegans* to the soil bacteria *Pseudomonas vranovensis* promotes resistance to infection in progeny via increasing the expression of the cysteine synthases (*cysl-1* and *cysl-2*) and the hypoxia-inducible factor (*rhy-1*) (Burton et al., 2020). In addition, an immune transcriptional response in parents experiencing microsporidia and viral infection, as well as heavy metal stress, also induces an inherited immune response in the offspring (Willis et al., 2021).

Light

Plant's life-history traits can be influenced by the maternal light environment. In the American bellflower, *Campanulastrum americanum*, individuals grow either in the forest understory (no direct sunlight) or in tree-fall light gaps (full sunlight for part of each day). Offspring grown in their maternal light environment (forest understory or tree-fall light gaps) had greater fitness than siblings moved to another light environment (Galloway and Etterson, 2007). As seeds are typically dispersed over short distances, these transgenerational effects provide an adaptation by which sedentary organisms can better cope with heterogeneous environments. Moreover, both temperature and drought have been shown to promote epigenetic transgenerational effects in both flowering and growth characteristics (Norouzitallab et al., 2014; Quadrana and Colot, 2016). In the common toadflax, *Linaria vulgaris*, floral symmetry is changed from bilateral to radial due to silencing of the *Lcyc* gene, which is controlled by increased levels of DNA methylation (5-methyl cytosine) in the promoter region rather than by changes in the DNA sequence, and these transgenerational effects can be transmitted for more than 100 generations and persist for many decades (Cubas et al., 1999).

Mitochondria stress

Mitochondrial proteotoxic stress activates a specific transcriptional response known as the mitochondrial unfolded protein response (UPR^{mt}) (Martinus et al., 1996). Activation of UPR^{mt} induces the expression of mitochondrial chaperone genes, as well as genes involved in the innate immune response, which alleviates mitochondrial proteostasis stress and also defend against bacterial infection in *C. elegans* (Haynes et al., 2007; Nargund et al., 2012, 2015; Liu et al., 2014; Berendzen et al., 2016). Exposure of worms to antimycin A, the electron transport chain inhibitor that is derived from a species of bacteria *Streptomyces*, can strongly induce the UPR^{mt}-mediated increase in transgenerational resistance against antimycin A (Ma et al., 2019). The transgenerational mitochondrial stress adaptation persists for four generations and requires epigenetic modifications mediated by the H3K4me3 methyltransferase SET-2 and the N6-methyldeoxyadenine methyltransferase DAMT-1 (Ma et al., 2019).

Maternal effects

Maternal effects often provide a mechanism for adaptive transgenerational phenotypic variations that result from environmental experiences, in which cytoplasmic factors in the egg (e.g., mitochondria, yolk amount, hormones, and mRNAs) may influence offspring phenotype and fitness. Alteration in maternally supplied organelles, particularly mitochondria, may also underlie transgenerational phenotypic adaptation. Conplastic mice (created by transferring the mitochondrial genome of one strain into another strain by repeatedly backcrossing to males) exhibited a range of problems such as defects in behavior, susceptibility to autoimmune disorders, metabolic syndrome, and changes in longevity. It was suggested that these physiological changes are orchestrated by the complex network of mitochondrial stress response pathways, including the UPR^{mt} and ROS signaling (Latorre-Pellicer et al., 2016). These results indicate that mtDNA variations may cause mtDNA/nDNA mismatching, thus affecting the fitness of the progeny maternally. In addition, maternal obesity causes altered mitochondrial dynamics in the oocytes, reduced levels of mtDNA/nDNA, impaired peripheral insulin signaling, and altered metabolism in their progeny, suggesting maternal reprogramming of metabolic state may affect offspring health through aberrant oocytes (Igosheva et al., 2010; Wu et al., 2015).

Oocyte quality is decreasing with maternal aging (Ma et al., 2020). In *C. elegans,* maternal age affects progeny growth and starvation resistance due to differences in vitellogenin provisioning to the oocytes (Perez et al., 2017). Reduced Insulin/IGF signaling increases vitellogenin provisioning maternally, protecting the progeny from starvation-induced abnormalities (Jordan et al., 2019). Maternal dietary restriction results in fewer but larger eggs, which helps the offspring to survive better under starvation stress (Harvey and Orbidans, 2011; Hibshman et al., 2016).

Soma-to-germline communication

The germ cells are usually affected by environmental stresses directly in most transgenerational inheritance studies; examples of

these stresses are maternal provision, dietary alterations, temperature, and light. Nevertheless, it is the somatic cells that sense and respond to environmental cues first in some cases, and these cells then transmit the stress signals to the germ cells and subsequently induce the transgenerational effects. These examples profoundly challenge the Weismann barrier theory, suggesting that soma-to-germline communication could serve as a way for the 'immortal' germ cells to inherit the information that the 'disposable' somatic cells. The evidence supporting the involvement of soma-to-germline information transfer for transgenerational inheritance has been emerging in recent years; however, the molecule mechanism by which the message is transmitted remains poorly understood. Most of the studies focused on the small RNAs (sRNAs) that can cross cell boundaries, serving as candidates for transmitting the information from soma to the germline. Interestingly, a recent study extends the current understanding of soma-to-germline information transfer. The researchers found that neuronal mitochondrial stress can be passed down across multiple generations through the mitokine Wnt signaling in *C. elegans*.

Transmissible small RNAs

Small non-coding RNAs (sncRNAs), particularly transfer RNA-derived small RNAs (tsRNAs), rRNA-derived small RNAs (rsRNAs), piRNAs (PIWI-interacting RNAs), siRNAs (small-interfering RNAs), and microRNAs (miRNAs), are possible mediators of the transmission of environmental information through sperm cells (Houri-Zeevi and Rechavi, 2017; Zhang et al., 2018b; Nätt et al., 2019; Sharma, 2019; Wahba et al., 2021). Numerous studies have provided strong evidence showing that paternal environmental conditions, such as altered diet or stress, influence small RNA levels in sperm (Gapp et al., 2014; Grandjean et al., 2015; Rodgers et al., 2015; Chen et al., 2016; Cropley et al., 2016; de Castro Barbosa et al., 2016; Schuster et al., 2016; Sharma et al., 2016; Rompala et al., 2018). Moreover, several waves of microRNAs and tRNA fragments are shipped to sperm during post testicular maturation from the epididymal epithelial cells (Conine et al., 2018). Increasing evidence now suggests that soma-to-germline transport of RNAs in various model organisms influences the health of offspring.

Studies in model organisms suggest that RNAs produced in somatic cells that are modulated by paternal environmental conditions could be transferred into developing germ cells and regulate genomic integrity during gametogenesis (Sharma, 2019). For example, sncRNA and long non-coding RNAs (lncRNA) can transmit heritable information from fathers subjected to chronic stress or trauma, which ultimately reprograms gene expression in the hypothalamus and induces stress-related phenotypes in their offspring (Rodgers et al., 2013, 2015). Deletion of a mouse tRNA methyltransferase DNMT2, which mediates RNA modifications, abolished the increased levels of tsRNAs and rsRNAs in the sperm and restored the high-fat-diet-induced metabolic disorders to offspring (Zhang et al., 2018b). Moreover, microinjection of sperm tsRNAs extracted from HFD (high-fat diet) males into normal zygotes has been shown to sufficiently modify the phenotypes of the offspring, including metabolic dysfunction in the case of the paternal high-fat diet (Chen et al., 2016; Sarker et al., 2019). Remarkably, the increase in sperm tsRNAs is not mediated by intrinsic pathways; rather they are acquired via the transfer of extracellular vesicles from the epididymis, offering a hint of soma-to-germline information transmission (Sharma et al., 2016). Thus, environmental or physiological influences that alter the contents of small RNAs in the somatic tissue of paternal animals may affect the RNAs in the germ cells and further alter the phenotypes of their offspring.

Recent studies in *C. elegans* have demonstrated that the impact of numerous environmental cues can be inherited for several generations and provide a molecular explanation for the mechanisms of soma-to-germline transfer of small RNAs that direct transgenerational inheritance. Small RNAs in neurons can influence gene expression in the germline and trigger transgenerational changes in the offspring's transcriptome and chemotaxis behavior (Devanapally et al., 2015; Posner et al., 2019).

Pathogen avoidance is an innate trait used by worms to avoid pathogenic microbes and survive in nature. *C. elegans* learns the identity of the pathogenic *Pseudomonas aeruginosa* strain PA14 via bacterial small RNAs, and that avoidance behavior triggered by bacterial infection can be transferred to the progeny in a piRNA-dependent manner for multiple generations (Moore et al., 2019; Kaletsky et al., 2020). Furthermore, the Murphy lab has shown that *Cer1* retrotransposon virus-like particles (VLPs) induce PA14 avoidance behavior in naive animals. *Cer1* retrotransposon VLPs enable the memory of learned pathogen avoidance not only between generations, but also between individuals (Moore et al., 2021).

'mitokine' signaling

Recent work stemming from a serendipitous observation in *C. elegans* showed that neuronal mitochondrial stresses induce the mitochondrial UPR^{mt} that can be transmitted to offspring for more than 50 generations even after the original neuronal stress signal was removed. The transgenerational UPR^{mt} enables the descendants to live longer and confers increased stress tolerance with the trade-offs of delayed development and reduced fertility (Zhang et al., 2021) (Fig. 2).

The activation of the UPR^{mt} requires the transcription factor ATFS-1 and several epigenetic factors (Benedetti et al., 2006; Nargund et al., 2012, 2015; Merkwirth et al., 2016; Tian et al., 2016; Zhu et al., 2020). Moreover, neuronal mitochondrial stress can communicate the stress signaling with peripheral tissues via the 'mitokine' signaling, which enables a global UPR^{mt} response that can ultimately protect an organism from local mitochondrial challenges (Durieux et al., 2011; Berendzen et al., 2016; Shao et al., 2016). Wnt/EGL-20 is one of the identified 'mitokine' signals that coordinates the mitochondrial stress response between the nervous system and the intestine (Zhang et al., 2018a).

In this study, the mitokine Wnt signaling that mediates the neuron-to-intestine cell-non-autonomous UPR^{mt} is also essential for the communication of stress signal originating from neurons to the germline, thus triggering the transcriptional up-regulation of the mitochondrial DNA polymerase gene *polg-1* in a Wnt-dependent manner. The maternal inheritance of elevated mtDNA levels disturbs the balance between mitochondrial proteins encoded by mtDNA and nuclear DNA in each generation, resulting in mitochondrial proteostasis stress and induction of the UPR^{mt} (Zhang et al., 2021). This study revealed that memory of neuronal mitochondrial stress could be passed on to descendants via the maternal inheritance of elevated mtDNA levels.

Perspectives

Numerous examples of transgenerational effects in organisms as diverse as nematode worms and humans have been described, suggesting that parental state can affect their descendants (Rechavi et al., 2014; Jobson et al., 2015; Chen et al., 2016; Perez et al., 2017; Skvortsova et al., 2018; Webster et al., 2018; Perez and Lehner, 2019; Baugh and Day, 2020). It is of significant scientific interest to determine what environmental and physiological conditions can impact descendants. If the germline senses the environmental stress directly, the parental experiences may be transmitted to their progeny. This can then function to forecast upcoming challenges and increase the overall population adaptation to stress. It will be

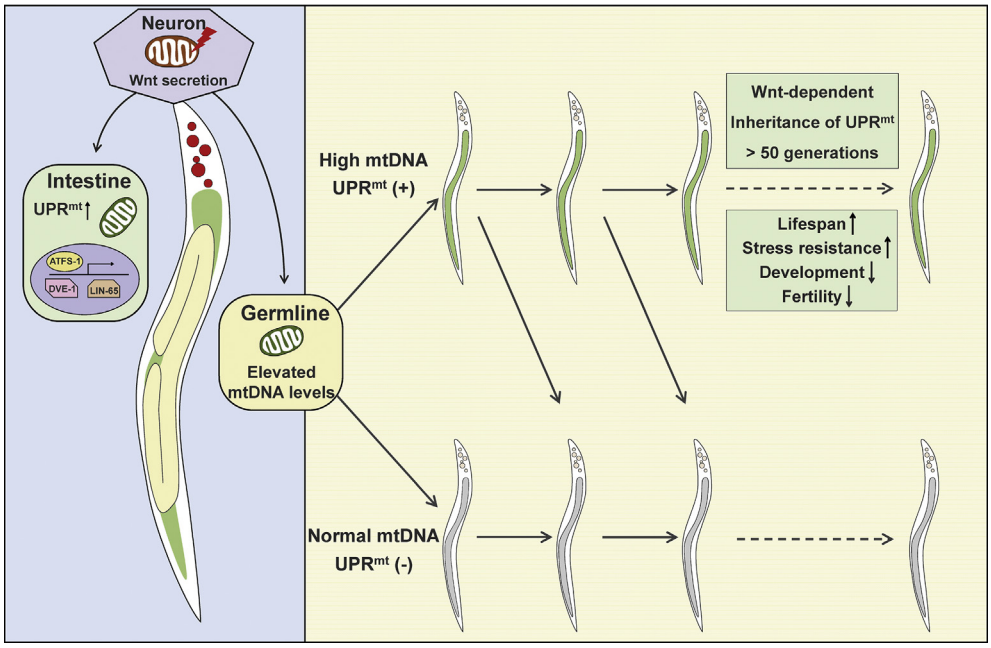

Fig. 2. Transgenerational inheritance of increased mtDNA levels and the UPR^{mt}. Neuronal mitochondrial stress induces the activation of neuronal Wnt signaling that not only induces the UPR^{mt} in the intestine, but also leads to increased mtDNA levels in the germline. The increased mtDNA level can be transmitted to the progeny with a certain penetrance for many generations (>50) and causes the transgenerational UPR^{mt} even after the original stress signal has ceased. The transgenerational effects confer increased lifespan and enhanced stress tolerance to offspring with trade-offs of delayed development and reduced fertility.

interesting to further explore how the specific epigenetic alterations avoid reprogramming in the germline and are maintained in their progeny. Furthermore, do germ cells carry information about the general quality of life, or do they transmit more specific information about various environmental exposures?

Recent studies revealed that parental environmental information could be transmitted to offspring from soma to the germline via small RNAs (Rodgers et al., 2013, 2015; Gapp et al., 2014; Devanapally et al., 2015; Chen et al., 2016; Sharma et al., 2016; Rompala et al., 2018; Moore et al., 2019; Nätt et al., 2019; Posner et al., 2019; Sarker et al., 2019; Wahba et al., 2021). Future studies should focus on elucidating the mechanism by which the environmental cues influence the small RNAs in germ cells and explore their impact on offspring health. In addition, the development of unconventional RNA-based sequencing technologies will provide further information to dissect the detailed mechanisms of how noncoding small RNAs are involved in transgenerational inheritance (Stark et al., 2019; Zu et al., 2020; Shi et al., 2021). Furthermore, the 'mitokine' Wnt signaling that responds to neuronal mitochondrial stress and alters the mtDNA content in the germline extends our current understanding of soma-to-germline communication. Are there other soma-to-germline signaling pathways besides small RNAs and the cell-non-autonomous UPR^{mt} that could serve as signals generated from somatic tissues and be transmitted to the germline to mediate transgenerational effects? Despite the interest that has been generated in this area, the knowledge of underlying mechanisms of transgenerational inheritance of environmental stress responses in mammals remains limited. Much work needs to be established to explore the physiological relevance of transgenerational inheritance in natural contexts.

Conflict of interest

The authors declared that they have no conflicts of interest to this work.

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