Trends in Genetics

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Passing down maternal dietary memories through lncRNAs

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Parental diet is known to influence the offspring in an intergenerational manner, and this has been implicated in species adaptation and general health. Recent studies highlight the role of maternal long noncoding RNAs (lncRNAs) in serving as one of the 'memories' of maternal diet in regulating offspring development and predisposition to metabolic disease.

Inherited parental DNA determines the physiological characteristics of the progeny. However, DNA does not rule all; environmental factors experienced by the parents can also affect the health and behavior of their offspring [1–3]. For example, when *Drosophila melanogaster* females cohabit with endoparasitoid wasps, their progenies often prefer ethanol-rich food which acts as a defense mechanism against wasp infection. This feeding behavior persisted over the subsequent five generations even in the absence of wasps, suggesting transgenerational inheritance of an environmentally influenced behavior [1,2]. Maternal dietary habits were found to affect both offspring health and disease susceptibility [3]. What is not known is 'how' – recent studies now point to maternally deposited lncRNAs as the agent mediating the intergenerational inheritance of such dietary 'memories'.

lncRNAs are typically >200 nt transcripts that do not code for proteins. They can be produced by canonical splicing of exonic sequences or derived from intronic sequences [4]. The effect of lncRNA in dietary response was seen in two studies on budding yeast, where the stable accumulation of intronic sequences upon starvation was found to enhance their survival via repression of ribosomal protein pre-mRNA splicing [5,6]. A similar phenomenon was observed in *Drosophila* where many stable intronic sequences (sis) RNAs, a type of intron-containing lncRNAs, were found to be upregulated in stage 14 oocytes of starved females. Interestingly, one such sisRNA, *sisR-2*, is maternally deposited to regulate primordial germ cell (PGC) number during starvation. Further investigation determined that *sisR-2* is involved in a homeostatic mechanism that maintains PGC number in the gonads. Upregulation of *sisR-2* reduces the activity of *bantam*, a miRNA which in turn derepresses the proapoptotic gene *hid*, increasing PGC death. Nevertheless, this is not the end of the road for offspring fertility. The reduction in *bantam* activity also leads to derepression of NHL domain protein brain tumor (*brat*) expression and a subsequent increase in cyclin B production that promotes ectopic PGC divisions [7]. Ultimately, these two pathways maintain the PGC number of *Drosophila* progenies under nutrient-scarce conditions.

In addition to *sisR-2*, another maternally deposited sisRNA, *sisR-8*, also functions to mediate intergenerational adaptation to nutritional stress in *Drosophila*. During starvation, a reduction in TOR pathway activity causes upregulation of *sisR-1* to *sisR-4* expression, leading to higher levels of apoptosis in stage 8/9 egg chambers. Even though starvation-induced oocyte loss takes place, some oocytes do survive to become fertilized and develop into embryos. These offspring that survived retain a 'memory' passed down by their starved mothers in the form of maternally deposited *RpL10Ab* and *sisR-8* transcripts which were also previously upregulated in the mothers. Both *sisR-8* and RpL10Ab inhibit *RpL10Ab* pre-mRNA splicing in the offspring, reducing RpL10Ab protein expression. As a result, the activity of the TOR pathway increases, whereas the expression of *sisR-1* to *sisR-4* is suppressed. The ultimate flip in TOR pathway activity and sisRNA levels means that the offspring are better adapted to deal with the reproductive cost of starvation by building resistance to starvation-induced oocyte loss [8]. Both *sisR-2* and *sisR-8* provide examples of how maternal starvation can regulate offspring germline cells via maternally deposited lncRNAs in oocytes (Figure 1).

Insects do not have a monopoly on intergenerational inheritance of starvation memory. A similar phenomenon was also reported in mice where the maternally imprinted lncRNA *Dio3os* was found to affect female offspring specifically. This manifests as higher levels of methylation on the imprinted *Dio3os* locus in oocytes from obese mothers, causing an overall decrease in the expression of *Dio3os* lncRNA. Because *Dio3os* lncRNA acts as an antagonist of Dio3 protein expression, this results in more Dio3 protein being produced, which in turn reduces triiodothyronine (T3) hormones available to activate brown fat (BAT) thermogenesis in the female offspring. Furthermore, the decreased BAT thermogenesis predisposes the offspring to decreased glucose tolerance, mitochondrial biogenesis, and oxygen consumption, impairing their thermoneutrality and cold adaptation [9]. Overall, this study presents an intriguing example of intergenerational inheritance of dietary response by showing how maternal obesity is able to affect oocyte imprinting which alters offspring *Dio3os* lncRNA expression, unfortunately predisposing the offspring to obesity (Figure 2).

Maternal imprinting is also seen in humans. The locus encoding the lncRNA *nc886* was also found to be maternally methylated in human oocytes, and imprinting status was associated with maternal age,

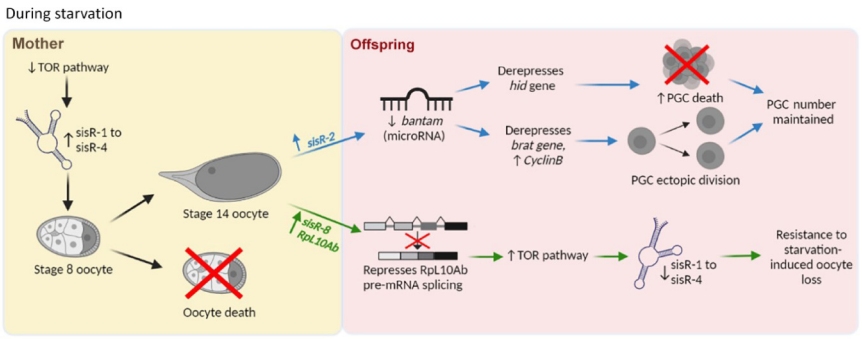


Figure 1. Upregulation of long noncoding RNAs (lncRNAs) *sisR-2* and *sisR-8* in *Drosophila melanogaster* oocytes during starvation regulates offspring germline cell development to ensure species survival. Abbreviation: PGC, primordial germ cell. Image created with BioRender.com.

calorie and nutritional intake, and alcohol consumption before conception. Women above 36 years of age were found to have increased imprinting frequency at the *nc886* locus, and this correlated with lower body mass index (BMI) in their offspring up to the age of 5 years. The same was observed for mothers on high-calorie and low-nutrition diets, as well as – surprisingly – for mothers who do not drink alcohol as opposed to those who do. Furthermore, their offspring also exhibited traits such as lower insulin levels and higher serum glucose levels during their early life (age 6–24 years). This exciting finding provides us with a strong indication of how maternal epigenetics altered by specific behavioral habits of the mother is passed down to the next generation that could result in phenotypic consequences for the offspring that persist into adulthood. In short, these studies suggest a role of the epigenetic marks at the *nc886* lncRNA locus in mediating the intergenerational transfer of maternal life exposure to ultimately affect offspring health traits [10–12] (Figure 2).

The impact of the environmental factors on the phenotype of an organism is well documented. An emerging concept is that environmentally influenced behavior in mothers can be inherited by their offspring in a way that affects their health. The studies described here highlight the importance and potential roles of maternally deposited lncRNAs as the mediators of maternal diet and subsequent progeny health. In *Drosophila*, oocyte intronic lncRNA levels change adaptively in response to the nutrient status of their mothers to ensure species survival. It is also fascinating to observe a similar phenomenon in more complex animals such as mammals where maternal obesity affects the expression levels of *Dio3os* and *nc886* lncRNAs that may ultimately influence offspring health. Although other epigenetic factors could be involved, the discovery of lncRNAs further deepens our understanding of intergenerational inheritance. A new frontier brings many new questions, one of which concerns how maternally deposited lncRNAs are stored stably for long periods of time in transcriptionally quiescent oocytes. Furthermore, to understand how maternally deposited lncRNAs culminate in intergenerational inheritance, we also need to study the molecular mechanisms by which they modulate zygote gene expression. This would ideally allow early-age intervention by diet and/or lifestyle adjustments to lessen the impact of some diseases. Better yet, a greater emphasis on proper preconception diet in potential mothers would solve many postnatal problems by ensuring greater oocyte vitality for healthier offspring.

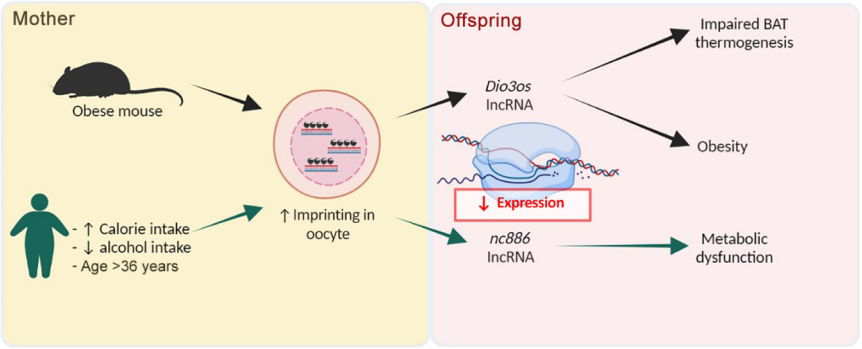


Figure 2. The effect of mouse and human maternal diet on their offspring imparted through intergenerational inheritance of the long noncoding RNAs (lncRNAs) *Dio3os* and *nc886*. Abbreviation: BAT, brown adipose tissue. Image created with BioRender.com.

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Declaration of interests

No interests are declared.

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