Maternal Inheritance: Longevity Programs Nourish Progeny via Yolk

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Epigenetic effects can be mediated by changes in chromatin state that are transmitted from parent to child via gametes, but support is gathering for maternal yolk, which is deposited into ooctyes, as an extranuclear epigenetic factor that can contribute to phenotypic plasticity across generations in *Caenorhabditis elegans*.

The possibility that environmental factors, such as diet or stress, might induce an organism to modify its gametes to generate progeny with improved fitness was initially proposed by Jean-Baptiste Lamarck [1]. Such views were arguably heretical before the dawn of the 21st century, but factors such as curiosity, serendipity and the description of a variety of ways to modify metazoan gene expression in a manner that is both heritable and reversible have created significant interest in the topic of epigenetic inheritance.

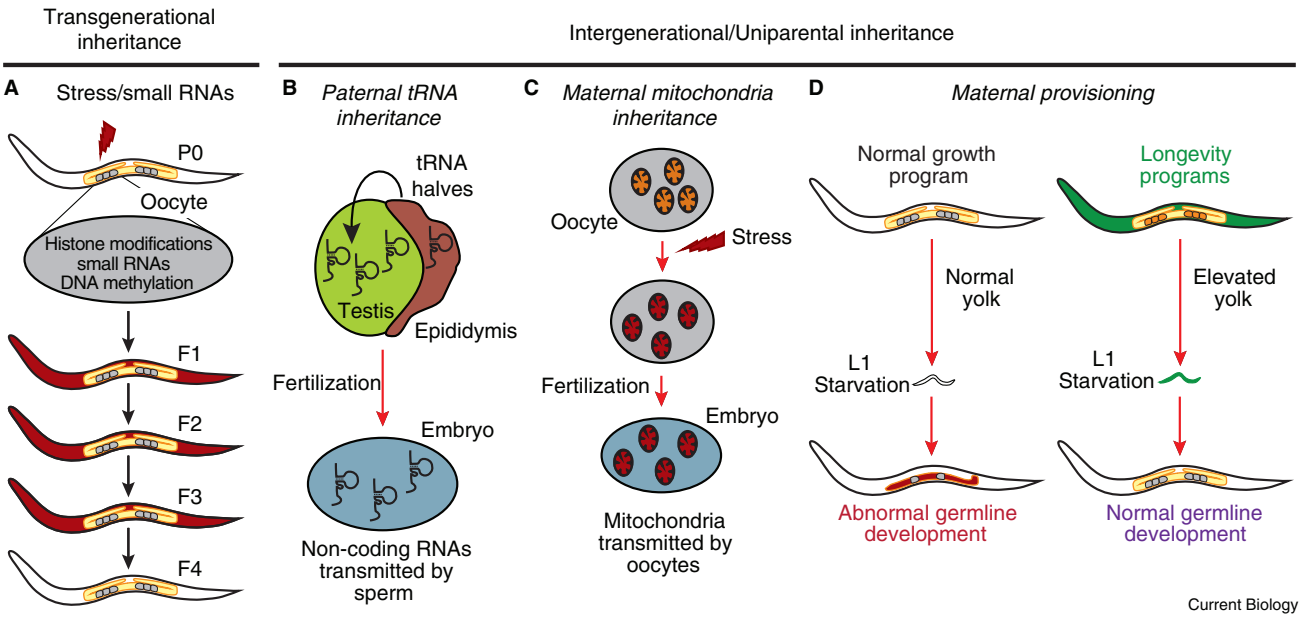

Figure 1. Mechanisms of epigenetic inheritance.
(A) Transgenerational inheritance in response to stress or exogenous small RNAs can induce transient multigenerational phenotypes (red). For uniparental inheritance, cytoplasmic epigenetic factors include (B) tRNA halves in sperm and (C) mitochondria of oocytes. (D) Jordan *et al.* show that longevity programs modify yolk abundance in oocytes to license normal development of starved L1 larvae.

Transgenerational epigenetic inheritance refers to phenotypes that are transmitted by female gametes for at least three generations (F1, F2 and F3), or by male gametes for at least two generations (F1 and F2). This excludes the possibility that environmental stresses that trigger epigenetic inheritance in F0 animals might directly affect F0 sperm, F0 oocytes or even F1 fetal oocytes *in utero* [2]. Maternal or paternal effects that persist across a single generation are considered a specialized form of epigenetic inheritance that is relatively simple to study, termed uniparental or intergenerational inheritance [3,4]. Maternal provisioning is a form of uniparental inheritance that is dictated by factors that are transmitted to zygotes via oocytes. Altered levels of genomic silencing are now recognized as a major molecular driver of epigenetic inheritance [5]. In a recent issue of *Current Biology*, Jordan *et al.* discuss a novel mechanism for non-genetic inheritance in *Caenorhabditis elegans* where the abundance of maternally provisioned yolk contributes to the developmental success of progeny (Figure 1) [6].

Epigenetics refers to a heritable change that occurs in the absence of genomic DNA mutations. Studies of gene silencing have revealed roles for histone modifications, sometimes directed by small RNAs, as well as DNA methylation as factors that can control transcription at specific genomic loci, which, when established in gametes, can be transmitted to offspring [4] (Figure 1A). Other factors that might alter phenotypes via epigenetic inheritance include metabolites, proteins, lipids or RNAs. For example, paternal diet can influence the abundance of somatically derived fragments of specific tRNAs, termed tRNA halves, that are secreted from the mouse epididymis in vesicles and deposited into developing spermatozoa where they impart a form of epigenetic inheritance that is distinct from modification of DNA or chromatin [7] (Figure 1B). Given their size relative to sperm, oocytes could harbor significant non-nuclear 'maternal epigenetic factors' such as mitochondria that could alter phenotypic plasticity in offspring [2] (Figure 1C).

The paper by Jordan *et al.* demonstrates that induction of independent pro-longevity pathways (e.g., dietary restriction or reduced insulin/IGF-1 signaling) in mothers but not fathers alters the developmental success of progeny that are confronted with stressful conditions [6]. *C. elegans* embryos hatch to become first stage larvae (L1) that will arrest development in the absence of food and can survive for weeks while searching for a food source. Extended periods of starvation-induced L1 arrest followed by reintroduction of food results in abnormal germline development. The authors discovered that activation of longevity and stress response pathways in somatic cells of mothers generates offspring that are better equipped to recover from L1 arrest and develop normally. Moreover, the molecular regulators of longevity that were active in mothers were utilized by their progeny to promote developmental fidelity [6].

To gain mechanistic insight into how modified longevity programs can be transmitted across generations, the authors investigated whether yolk, which was recently implicated in maternal inheritance [8], played a role. Yolk is synthesized in the adult maternal intestine and is composed of vitellogenin lipoproteins and large quantities of lipids. Delivery of these particles to oocytes, a process called vitellogenesis, provides embryos with the nutrients they need to develop until hatching, when the animals

normally obtain food from their environment. Starvation-induced arrest of L1 larvae demands that yolk provide additional resources for survival that are normally used to propel development. Consequently, mutants defective in vitellogenesis have been previously shown to survive for shorter periods of time in L1 arrest [9]. At the same time, reduced yolk production promotes somatic longevity of mothers, possibly by altering intestinal autophagy pathways and/or by activating pro-longevity transcription factors [10–14]. The authors used a variety of approaches to show that deposition of yolk into maternal oocytes may protect starved L1 animals from developmental defects (Figure 1D) [6].

Jordan *et al.* expand upon existing models of the relationship between yolk, development and longevity by describing a sophisticated mechanism by which an organism can improve viability across generations during challenging survival conditions. In this scenario, longevity signaling networks interface with vitellogenesis pathways in the mother to promote developmental fidelity in starved progeny. One maternal longevity pathway that promotes germline development in starved progeny is activated in response to mutation of the insulin/IGF-1 receptor *daf-2*, which reduces insulin/IGF-1 signaling [6]. Although reductions in DAF-2 signaling have previously been reported to down-regulate maternal vitellogenin gene expression [12,15,16], yolk deposition in *daf-2* mutants could ultimately be elevated due to a dramatic reduction in ovulation rate [17], which would increase the amount of time that oocytes spend receiving yolk deposits. Jordan *et al.* suggest that vitellogenesis could serve as an elegant epigenetic strategy to relay information across generations [6], and future work may resolve how longevity pathways alter vitellogenin expression and yolk uptake to nourish the next generation.

If increased yolk provisioning promotes resistance of L1 larvae to starvation, then this has several ramifications for the field of transgenerational inheritance. Yolk has the potential to deliver a suite of bioactive lipids to progeny that could be the epigenetic cargo that reprograms insulin receptor expression or that modifies the activity of pro-longevity transcription factors in the subsequent generation [14]. Alternatively small RNAs can be transported and delivered to recipient cells by high-density lipoproteins in mammalian plasma [18,19], so yolk-associated small RNAs could act in the nuclei or cytoplasm during development to modify gene expression or mRNA stability/translation. Thus, if the transgenerational inheritance described by Jordan *et al.* is due to small RNA-dependent transcriptional regulation in progeny, then this outcome would mirror known consequences of nuclear epigenetic inheritance [3].

In mammals, pronuclear transfer experiments can be performed to explicitly test if an epigenetic effect is caused by oocyte cytoplasm, but such experiments are not possible for *C. elegans* embryos that are encased in rigid eggshells. If cytoplasmic yolk is not solely responsible for improved development of starved L1 larvae, then it is possible that other oocyte constituents such as hormones, steroids, amino acids, vitamins or even altered chromatin states in oocyte nuclei might be responsible. Precedent for the *daf-2* insulin/IGF receptor locus being under epigenetic control exists in metazoans, as parent-of-origin-mediated gene silencing affects mouse development via the insulin/IGF2 gene on chromosome 7 as well as the insulin/IGF2 receptor gene on chromosome 17, both of which are located within imprinted loci that are expressed from the allele that comes from sperm or oocytes, respectively [20]. If this were the case in *C. elegans*, then the *daf-2* locus might be silenced in sperm, such that crosses of wild-type males with *daf-2* mutants might result in skewed or monoallelic expression of the maternal (mutant) *daf-2* allele in progeny. This might be consistent with the observation that *daf-2* mRNA levels are reduced in progeny of long-lived mothers [6], although additional genomic loci might contribute to recovery of starved L1 larvae.

In summary, the study by Jordan *et al.* indicates that longevity pathways modify oocytes in a manner that confers resistance to starvation-induced developmental defects in their progeny, possibly via a novel epigenetic mechanism that depends on the quality or quantity of yolk in oocytes. This feed-forward uniparental circuit offers an unexpected twist to the special relationship between mother and child.

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