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Inheritance of protection from osmotic stress

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Exposure of mother worms to mild osmotic stress induces gene expression changes in offspring that protect them from strong osmotic stress. Inheritance of protection is now shown to depend on altered insulin-like signalling in the maternal germline, which confers protection through increased expression of zygotic *gpdh-2*, a rate-limiting enzyme in glycerol biosynthesis.

Epigenetic inheritance across generations is gaining widespread attention in the research and medical communities for its potential influence on development, health, and lifespan. Epidemiological studies in humans have linked diet and environmental factors experienced by parents with the physiology of their children and even grandchildren[1]. Such studies reveal potential associations but cannot elucidate cause–effect or mechanisms. To understand how parental experiences may or may not influence future generations via epigenetics, we need to understand how parental experience is conveyed to the germline; in what form parental-experience information is stored in gametes and transmitted to embryos; how this information is delivered to target cells in offspring; and how it influences gene expression and phenotype after it is delivered to target cells. Using *Caenorhabditis elegans* as a model, Burton *et al.*, in this issue of *Nature Cell Biology*, provide a compelling example of how information about maternal environment can be transmitted to the germline to influence offspring gene expression and physiology[2]. The authors showed that *C. elegans* larvae respond to strong osmotic stress by entering a stress-resistant state of larval arrest until normal osmotic conditions return (Fig. 1a). This response permits larvae to survive, but it can cost them in time and opportunity to reproduce. However, this cost can be averted. If mother worms are exposed to mild osmotic stress, their offspring do not arrest when exposed to strong osmotic conditions but instead develop normally[2,3] (Fig. 1b). Burton *et al.* identify genes involved in this protective inheritance and provide insights into several key aspects of epigenetic inheritance along the way.

The germline is the conduit between generations. Consequently, most models of transmission of information across generations invoke packaging of information in the gametes, egg and sperm. Environmental cues could directly signal the germline or alternatively could signal somatic cells, which in turn signal the germline. Burton *et al.* provide evidence for the latter. First, the authors tackled the question of how strong osmotic stress causes larval arrest and found that the arrest response depended on changes in insulin-like signalling[4] from sensory neurons to the intestine (Fig. 1a). Their findings support a model in which strong osmotic stress inhibits release of the insulin-like peptide INS-3 from sensory neurons. This prevents activation of the insulin receptor DAF-2 in the intestine. Inhibition of DAF-2 signalling allows the FOXO transcription factor DAF-16 to enter intestinal nuclei to impact gene expression and promote entry of larvae into a stress-resistant arrested state. Next, the authors tackled the question of how exposure of mother worms to mild osmotic stress protects their offspring from strong osmotic stress (Fig. 1b). Remarkably, a similar signalling cascade is involved. While the larval response to strong osmotic stress required inhibition of DAF-2 in the intestine, the maternal response to mild osmotic stress required inhibition of DAF-2 in the germline. An additional player in the germline was shown to be the RAS–ERK pathway, which is activated by insulin-like signalling and therefore was inhibited when DAF-2 was inhibited by osmotic stress. These findings illustrate one mechanism for how environmental conditions, sensed by somatic cells, can influence germ cells.

If information about parental environment is to be transmitted to offspring, then input received by the parental germline must be packaged into the gametes for delivery to the embryo. Most research in the field of cross-generational epigenetic inheritance focuses on three major carriers of information: DNA methylation, histone modifications, and non-coding RNAs[5]. It is worth pointing out that each of these may be transmitted through the egg or sperm. There has been considerable debate over what constitutes true epigenetic inheritance, particularly when heritable changes in offspring are the result of maternal interventions[6,7]. Because early embryos inherit a stockpile of maternally loaded factors, and in most organisms at least some embryo development occurs in the uterus of the mother, it is difficult to tease apart the influences of epigenetics, maternal provisioning, and maternal physiology. For these reasons, many researchers investigating epigenetic inheritance focus on inheritance through the paternal lineage[8,9]. Notably, Burton *et al.* found that simulating mild osmotic stress through inhibition of DAF-2 signalling in father worms did not protect offspring from strong osmotic stress. A previous study also suggests that offspring protection declines when mother worms are returned to normal osmotic conditions for more than 4 hours[3]. Perhaps, mothers transmit information about osmotic conditions in a manner that does not adhere to a strict definition of epigenetic inheritance. For example, exposure to mild osmotic stress may initiate changes in maternal germline gene expression that alter maternal provisioning of transcription factors or chromatin modifiers that in offspring alter gene expression. Pinpointing the carriers of osmotic stress information would certainly shed light on the epigenetic nature of this inheritance. Canonical forms of DNA methylation do not exist in worms. Determining whether histone modifications and/or non-coding RNAs participate in maternal protection of offspring from osmotic stress, as they do in other cross-generational regulation[10,11], will be an illuminating next chapter of this story.

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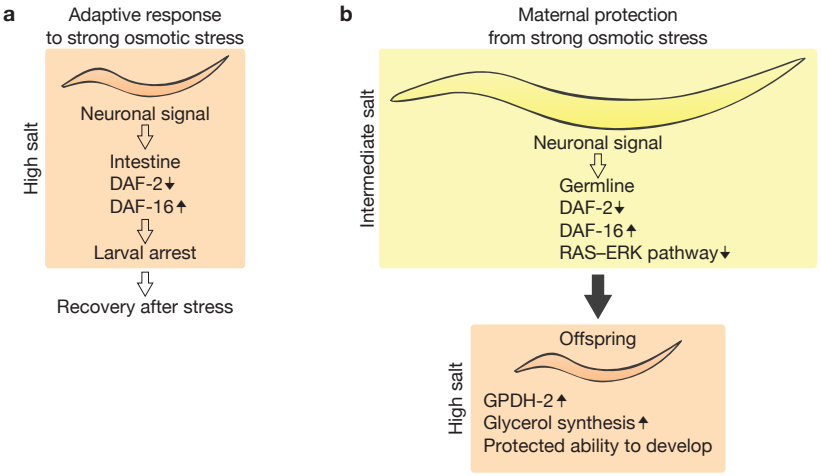

Figure 1 Adaptive and maternally inherited larval responses to osmotic stress. (**a**) High-salt conditions inhibit insulin-like signalling from sensory neurons to the larval intestine. This decreases DAF-2 receptor activation, allowing the FOXO transcription factor DAF-16 to enter intestinal nuclei and launch a gene expression programme that promotes entry into a stress-resistant state of larval arrest. (**b**) Intermediate-salt conditions inhibit insulin-like signalling from sensory neurons to the maternal germline. This decreases DAF-2 activation, resulting in DAF-16 activation and RAS–ERK pathway inhibition. This maternal signalling alters offspring gene expression, enabling larvae to develop normally in high-salt conditions.

Another important aspect of epigenetic inheritance is propagation of information from the one-cell embryo through development for delivery to the cells whose physiology is impacted by the parental exposure. Burton *et al.* elegantly dissected the transmission of osmotic stress information from neurons to intestine and germline in exposed mothers. A similar analysis in developing offspring would be equally informative. If the mechanism of transmission through cell divisions is epigenetic in nature, then it may be via propagation of appropriately marked chromatin through DNA replication and/or passage of non-coding RNAs through cell division[10,12].

An important question is how the observed effects of maternal stress are mediated in offspring. Embryos from mothers exposed to mild osmotic conditions have increased glycerol content. Glycerol is protective against several forms of stress, including osmotic stress, and probably accounts for some, if not all, of the inherited protection against strong osmotic stress. Importantly, Burton *et al.* found that protection required a functional copy of *gpdh-2*, which encodes a rate-limiting enzyme in glycerol biosynthesis, and that a functional copy of *gpdh-2* was required in the offspring not in the mother worms. These findings demonstrate that inherited protection from strong osmotic stress is mediated by changes in offspring gene expression and physiology.

While the epigenetic nature of the inheritance involved in maternal protection against osmotic stress has not been fully elucidated, Burton *et al.* provide a compelling story about how environmental information can be transmitted to the next generation. It is clear how this type of communication between generations can be advantageous. Paradoxically, it can also have a downside. It has been reported that larvae born to mothers exposed to mild osmotic stress are more sensitive to anoxia[3]. This seems to be due to a shift in sugar metabolism that increases glycerol content at the expense of glycogen stores. Increased glycerol confers resistance against osmotic stress, while increased glycogen confers resistance against anoxia[3,2]. Therefore, altering the balance between glycerol and glycogen is a gamble. The fact that exposure of mothers to mild osmotic stress conditions induces elevated glycerol production in their offspring, despite the risk, suggests that when this system evolved, parents' osmotic conditions were predictive of offspring's osmotic conditions and that increasing glycerol and lowering glycogen more often than not conferred an advantage. This trade-off may explain why this transmission is transient, requiring offspring to be produced close in time to maternal exposure, and why transmission is not from fathers. This trade-off also predicts that protection from osmotic stress is intergenerational (from parent to offspring) but is unlikely to be transgenerational (from grandparent to grand-offspring and beyond). This logic may inform us on how a system that evolved to transmit information about parental environment, including nutrient availability, may serve us when parental lifestyles are predictive of offspring lifestyles. This is a correlation that probably does not hold true for humans in many modern societies. In the modern era of dispersal of families and more reliable access to food, the conditions offspring experience may be very different from those of their ancestors.

The dramatic rise in diabetes, other insulin-related diseases, and disease-related complications[1,13] is driving efforts to understand the diverse contributors to disease incidence and progression and the phenomenon of metabolic memory. Epigenetics is already on the radar screen, as is maternal health during embryo gestation[14,15]. The analysis by Burton *et al.* is another testament to basic research in model organisms offering possible mechanistic underpinnings to links between parental diet and offspring health, and possible inroads to curbing the growing epidemic of metabolic disorders.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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