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REVIEW

SPECIAL ISSUE

DEVELOPMENTAL PLASTICITY: FROM MECHANISMS TO EVOLUTIONARY PROCESSES

Developmental plasticity: a worm's eye view

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ABSTRACT

Numerous examples of different phenotypic outcomes in response to varying environmental conditions have been described across phyla, from plants to mammals. Here, we examine the impact of the environment on different developmental traits, focusing in particular on one key environmental variable, nutrient availability. We present advances in our understanding of developmental plasticity in response to food variation using the nematode *Caenorhabditis elegans*, which provides a near-isogenic context while permitting lab-controlled environments and analysis of wild isolates. We discuss how this model has allowed investigators not only to describe developmental plasticity events at the organismal level but also to zoom in on the tissues involved in translating changes in the environment into a plastic response, as well as the underlying molecular pathways, and sometimes associated changes in behaviour. Lastly, we also discuss how early life starvation experiences can be logged to later impact adult physiological traits, and how such memory could be wired.

KEY WORDS: *Caenorhabditis elegans* dauer, Developmental plasticity, Nutrient availability, Starvation, Phenotypic plasticity, Polyphenism, Transgenerational inheritance

Introduction

Development of multicellular metazoan organisms, starting from a single cell, gives rise to a large variety of cells, tissues and organs and eventually an individual with all the characteristics of the species. It entails a succession of very stereotyped stages to shape the embryo – for example, the first divisions, gastrulation and neurulation in triploblastic animals – and has been shown to be remarkably robust within each species.

However, as mentioned by the French naturalist Buffon in his *Histoire Naturelle*, 'For each species in Nature, there is a general prototype on which each individual is shaped, but which seems to be altered or perfected by circumstances' (Buffon et al., 1753).

This 270 year old description of development perfectly summarises how developmental robustness (see Glossary) co-exists with environmentally induced variations, another characteristic of living organisms. These alterations or improvements are materialised in the forms of phenotypic and developmental plasticity (see Glossary).

Developmental plasticity, the focus of this review, is the property by which a developing organism displays an array of alternative phenotypes in response to different environmental conditions, without any modification of its genotype (Beldade et al., 2011; Gibert, 2020). Indeed, plants and animals are exposed on a daily basis to a plethora of environmental factors (abiotic and biotic), including temperature, radiations, hypoxia, crowding, food availability and quality, predators and mechanical or chemical stress. Developmental plasticity is a means of coping with such environmental diversity/pressure and reflects the resulting physiological response.

It has long been known that the environment can trigger changes in living organisms during their development. In their book *Variation of Animals in Nature*, Richards and Robson (1936) gathered numerous examples of natural variations observed in response to the environment, such as temperature or season. For example, they described the correlation between the yellow colour of the wasp *Polistes foederata* and the climate. Recent studies on different wasp genera have confirmed and detailed these observations (de Souza et al., 2014; Tibbetts et al., 2018).

But what is the link between environmental factors and these phenotypic variations? How does the environment impact the expression of the genome, or even the epigenome of individuals at the molecular level? Answers to these questions have begun to emerge in the last couple of decades.

For instance, a molecular link between temperature and sex determination of reptiles has recently been made (Weber and Capel, 2021). In many reptiles, sex is determined by the temperature at which the embryo develops (Lockley and Eizaguirre, 2021; Weber and Capel, 2021). For the red-eared slider turtle, it has been shown that there is an epigenetic control of sex determination (Ge et al., 2018; Weber and Capel, 2021). Indeed, knock-down of the H3K27me3 demethylase Kdm6b in *Trachemys scripta elegans* turtles results in the development of more than 80% of females at the male-producing temperature (Ge et al., 2018). At female-producing temperatures, Kdm6b is inhibited by the phosphorylated form of the signal transducer and activator of transcription 3 (pSTAT3). This phosphorylation in turn seems to be controlled by a temperature-dependent calcium signalling pathway (Weber and Capel, 2021).

While the development of different species can be impacted to various extents by environmental variation such as the effect of temperature on reptiles, the growth of all organisms is impacted by their diet. In all phyla, the lack, reduction or type of nutrients can have a range of effects on development at the level of individuals, populations and sometimes subsequent generations.

Indeed, the diet is recognised as a significant factor influencing developmental plasticity and has garnered notable focus for its impact on human physiology (Barua and Junaid, 2015; Guo et al., 2020). Research on prenatal exposure to famine indicates that hunger during this critical period may have enduring effects on human health and lifespan. Demographic analyses reveal that babies exhibited a smaller size and lower birth weight following *in utero* exposure to the Dutch famine of 1944–1945 (Ramirez and Haas, 2022; Roseboom, 2019). It even has been suggested that this early life experience may have had longer-term effects, as later in their life and with a normal diet, these adults developed an increased risk of obesity, type 2 diabetes and cardiovascular problems (Roseboom, 2019). Six decades later, correlative analyses of epigenetic markers revealed that adult individuals exposed to starvation during the fetal

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Glossary

Canalisation
As defined by Waddington in 1942, canalisation is the ability of an organism to maintain its wild-type phenotype, regardless of minor variations in the environmental conditions or in its genetic background (Waddington, 1942). This theory at the time was supported by the fact that in nature, there is a constancy of the wild-type phenotype over the one of mutants. Robustness is often used as a synonym of canalisation (see Debat and David, 2001, for a discussion).

Developmental robustness
The ability to consistently produce a given phenotype regardless of the environmental context.

Developmental plasticity
The genotype's capacity to be transduced into diverse developmental trajectories in response to environmental conditions. Developmental plasticity is an example of phenotypic plasticity. Of note, developmental (or phenotypic) plasticity is not necessarily always beneficial.

Epigenetic mechanisms
Defined here as a change in gene expression due to DNA methylation, histone post-translational modifications, non-coding RNA (ncRNA) and RNA methylation, and independent of DNA sequence variations. These modifications can be mitotically stable.

Phenotypic plasticity
The genotype's capacity to be transduced into diverse observable traits as a function of environmental conditions. These different phenotypes can have a developmental origin or can appear during adulthood; for example, the change of fur colour for the European brown bear, which is a post-developmental adaptation to seasonal changes.

Polyphenism
A form of phenotypic plasticity where genetically identical animals present themselves in several different, discrete (referred to as non-continuous) outcomes, at the same stage of development. A good example is the outcome 'worker' or 'queen' in honeybees and other social insects.

Switch genes
Genes responsible for the adoption of an alternative developmental trajectory (i.e. a developmental switch), as opposed to genes involved in a phenotypic execution network as the Gene Regulatory Network downstream of switch genes and responsible for implementing the specific phenotypic outcome.

Transgenerational epigenetic inheritance (TEI)
Heritable epigenetic information in the absence of direct exposure of the progeny to the environmental trigger (as opposed to intergenerational inheritance, which refers to the transmission to the F1 offspring from males and F2 offspring from gravid females via a direct effect on the germ cells). The term transgenerational refers to effects seen on at least the next three generations after exposure. Intergenerational epigenetic inheritance has also been described and is not discussed here.

stage had less DNA methylation on the insulin-like growth factor II (IGF2) gene than unexposed individuals (Heijmans et al., 2008). However, when working on human populations, we should bear in mind that the influences of the cultural and societal context are very difficult to disentangle from a possible impact of environmental changes.

Another well-known example of diet-induced developmental plasticity is encountered in the honeybee (Wright et al., 2018). Although genetically identical, larvae fed with an abundance of royal jelly for their entire development will give rise to the queen, whereas larvae fed with controlled rations of royal jelly for a few days and then with pollen and honey become workers. This differential diet impacts not only the speed of development – the queen's development being faster than the workers' – but also the size, longevity and reproductive capacity. Kucharski and colleagues (2008) have shown that the DNA methyltransferase Dnmt3 is a key driver of reproductive status, as Dnmt3 silencing in newly hatched larvae phenocopies the rich royal jelly diet and gives rise to fertile queens. Among the genes that are differentially expressed upon Dnmt3 knock down are those important for lipid and hormonal regulation (Kucharski et al., 2008). So, it seems that common molecular mechanisms, such as DNA methylation in humans and honeybees, are at play to relay diet information at the developmental and molecular levels.

Many studies that focus on developmental plasticity are based on the analysis of wild populations, where a large number of individuals can be observed but not all parameters can be precisely controlled. The analysis of animal models in laboratories in stereotyped growing conditions allows us to free ourselves from the impact of multiple factors at the same time. In addition, near-isogenic animals are necessary to focus analyses on the sole effects of the environment. The nematode *Caenorhabditis elegans* is such an animal model.

The Bristol N2 strain serves as the reference wild-type strain for *C. elegans* research. It is mostly maintained through hermaphrodite self-fertilisation and is considered near-isogenic (Brenner, 1974). It is known for its robustness in terms of both cell number (959 somatic cells in the hermaphrodite) and its essentially stereotyped and invariant development (Sulston and Horvitz, 1977; Sulston et al., 1983). Therefore, it provides a powerful system for analysing the impact of environmental changes on developmental plasticity, as a slight change in its developmental robustness is often observable through phenotypic alterations. The large number of offspring at each generation, the short life cycle, the ease of culture on monoxenic (*Escherichia coli* as a food source) media, the well-known sensory nervous system and the conservation of molecular pathways are additional assets for biologists studying the impact of environmental changes on development.

In this review, we describe examples of developmental plasticity encountered in *C. elegans* and in another well-described nematode, *Pristionchus pacificus*, focusing on the impact of food availability. We describe how environmental cues are detected and by which cells; and how these cells relay the information to the target cells and by which molecular mechanisms. We also address how this developmental plasticity can be transmitted to the next generations through epigenetic modification.

Developmental plasticity in response to food deprivation

Reversible plasticity: alternative life form

In nematodes, phenotypic plasticity in response to different food sources or low nutrient availability can be observed at many levels, encompassing the whole organism or specific organs. At the whole-organism level, several traits such as developmental speed, alternative life forms or behaviour have been shown to exhibit developmental plasticity. For instance, *C. elegans* nematodes have been observed to grow at different rates in the wild, and this has been correlated to their diet (Samuel et al., 2016). These varying growth rates can be reproduced in the laboratory by feeding the worms specific bacteria (e.g. *Comamonas aquatica* bacteria enhances the growth rate of *C. elegans* compared with the commonly used *E. coli* OP50) or by using a minimal 'axenic' medium (MacNeil et al., 2013; Rashid et al., 2021; Samuel et al., 2016; Shtonda and Avery, 2006; Vanfleteren, 1974). An impact of the environment on life traits such as growth speed suggests that *C. elegans* has a mechanism that couples nutrient usage and/or sensing to animal growth.

One of the most striking and well-known examples of developmental plasticity illustrating this coupling in *C. elegans* is provided by its ability to enter alternative developmental trajectories depending on the environmental conditions. When the worm

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encounters adverse conditions, such as a lack of food, it can reversibly arrest its development. These arrests, or 'diapauses', can occur at all developmental larval stages or as reproductive quiescence in the adult (Angelo and Van Gilst, 2009; Baugh and Hu, 2020; Schindler et al., 2014), and two of them have been extensively characterised: the larval 1 (L1) arrest, which occurs shortly after hatching in the absence of food (Baugh, 2013) and the dauer diapause, which corresponds to an alternative larval 3 (L3) stage and can occur if the worm experiences overcrowding, high temperature or lack of nutrients during the first larval stages (Fig. 1) (Hu, 2007). The dauer diapause is the longest lived of all arrested forms in *C. elegans*, allowing survival for several months (Hu, 2007; Klass and Hirsh, 1976).

Several significant changes are associated with arrest into a dauer state that allow it to endure adverse conditions; dauers exhibit specific morphology and behaviour including a thinner body, a specific cuticle composition and structure, closed mouth and orifices, enlarged lipid droplets and altered metabolism, and a quiescent behaviour (Cassada and Russell, 1975; Hu, 2007). When more favourable environmental conditions are encountered, dauers are able to quickly adjust their metabolism and resume developmental growth.

This model, endowed with a solid genetic toolbox, has not only enabled the detailed description of this developmental plasticity event and the conditions that can trigger it but also allowed the genetic cascades and the cellular networks involved to be deciphered.

Which pathways are involved in transmitting and interpreting information on food availability? Several studies have focused on elucidating the regulatory mechanisms controlling reversible developmental plasticity, starting with understanding the switch to entry into dauer. A number of screens have identified genes that regulate dauer formation, and yielded many Daf-c (dauer formation-constitutive) and Daf-d (dauer formation-defective) mutants (Hu, 2007). Cloning of these mutants has identified two main neuroendocrine pathways that control the growth versus dauer decision in response to environmental cues: the daf-2/IIS insulin/IGF-1 signalling pathway and the daf-7/TGF-β pathways, the components and activities of which have been amply described elsewhere (for reviews, see Fielenbach and Antebi, 2008; Hu, 2007; Table 1). These pathways converge on a nuclear receptor DAF-12-dependent transcriptional cascade required for the dauer state (Fielenbach and Antebi, 2008). In addition, long-term survival of dauer larvae – or germline integrity and arrest during starvation-induced L1, dauer or reproductive adult diapause – requires proper metabolic resource allocation through the downstream activity of the AMP-activated protein kinase (AMPK; Table 1) (Rashid et al., 2021).

Neuronal mechanisms: interpreting the environment

Several cues can trigger dauer polyphenism (see Glossary), including food unavailability or pheromones: how are the environmental variations sensed and what cells relay them? *Caenorhabditis elegans* hermaphrodites have a total of 302 neurons, each uniquely identifiable based on distinctive properties such as morphology, connectivity and position. The detailed characterisation of numerous neurons responsible for detecting sensory cues related to food has been instrumental in enhancing our understanding of how individuals perceive and interpret their environment. The switch to a dauer form is preceded by entry into an alternative L2 stage, called L2d. This binary decision to go into an alternative trajectory versus staying the course of normal development involves a neuronal signal. Several head neurons, which together form the amphid sensilium (Altun and Hall, 2003),

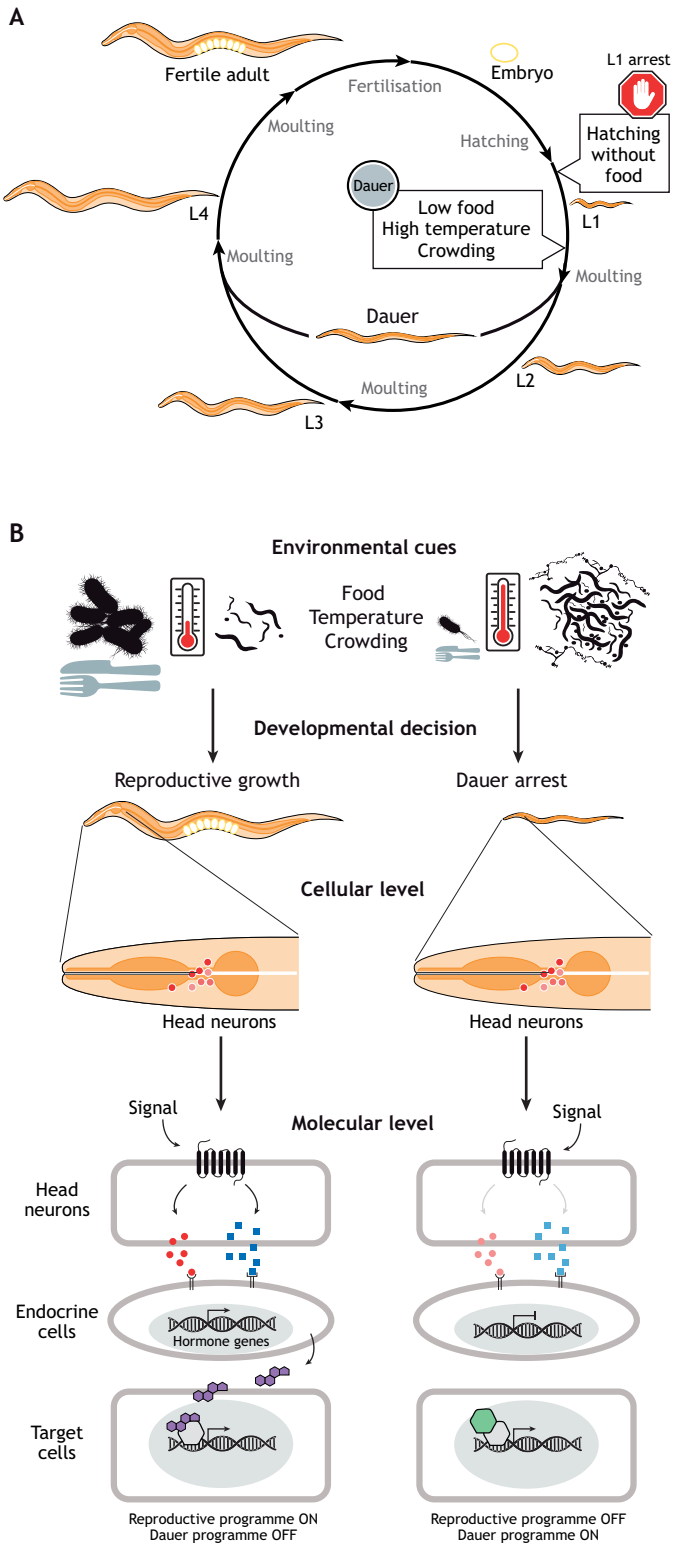

Fig. 1. *Caenorhabditis elegans* life cycle and a striking developmental plasticity instance: the switch to a dauer stage. (A) During the *C. elegans* life cycle, developmental plasticity can be observed in response to the environment at different developmental stages. For instance, when the embryo hatches, the absence of nutrients induces entry into a diapause, the 'L1 arrest'. In addition, the response to stressful conditions at the end of the L1 stage, such as low food, high temperature or crowding, induces entry into an alternative developmental trajectory called dauer. (B) This 'environmental cues/developmental response' model provides the ability to test the impact of each environmental stress on the phenotype in order to highlight the cells and the molecular networks involved.

Table 1. Conservation of the molecular players between worms and humans

Process	Gene symbol	Product/function	Human orthologue/protein function
Adult reproductive diapause	*hlh-30*	bHLH transcription factor	TFEB
Dauer formation	*crh-1*	Transcription factor (cAMP response element-binding)	ATF1, CREB1
	daf-2	Insulin receptor	IGF1R, INSR and INSRR
	daf-7	Transforming growth factor	TGF-β, GDF11
	srbc-64, srbc-66	G-protein-coupled receptors for ascarosides	-
	srg-36, srg-37	G-protein-coupled receptors for ascarosides	-
Foraging behaviour	*glb-5*	Neuroglobin/O_2-sensing	Neuroglobin
Pristionchus pacificus mouth morphs	*eud-1*^{PPA}	*N*-Acetylgalactosamine-6-sulfatase	GALNS
	lsy-12^{PPA}	MYST histone acetyltransferase complex	-
	nag-1^{PPA}, *nag-2*^{PPA}	α-*N*-acetylglucosaminidase	NAGLU
	nhr-1^{PPA}	Nuclear hormone receptor	Hepatocyte nuclear factor 4-alpha
	nhr-40^{PPA}	Nuclear hormone receptor	NR2A3
	sult-1^{PPA}	Sulfotransferase	SULT1B1, SULT2A1, SULT2B1
	mbd-2^{PPA}	Methyl binding protein	MBD2
Transgenerational epigenetic inheritance	*hrde-1*	RNA endonuclease	Protein argonaute-4
	rde-4	Double-stranded RNA binding	PRKRA and TARBP2
Vulva formation	*lin-39*	Homeobox transcription factor	HOXA5

PPA, *Pristionchus pacificus*; IGF1R, insulin like growth factor 1 receptor; INSR, insulin receptor; INSRR, insulin receptor related receptor.

have been shown to promote (e.g. the ASK and ADL neurons) or suppress (e.g. the ASI, ASG, ADF and ASJ neurons) entry into dauer, opening a window on how developmental plasticity is wired.

For instance, in the presence of antagonist signals such as abundant food plus higher levels of pheromones such as ascaroside #5 (or asc#5), a cascade comprising the asc#5 GPCR receptors SRG-36, SRG-37 and (to a lesser extent) SRBC-64 and SRBC-66, and the downstream transcription factor CRH-1/CREB1 controls the expression of DAF-7/TGF-β in the ASI head neuron pair. When expressed, DAF-7/TGF-β then acts cell-autonomously in ASI to block entry into L2d (Park et al., 2021; Ren et al., 1996; Schackwitz et al., 1996). Similarly, laser ablation of the head sensory neurons ASG, ADF and ASJ showed that these neurons promote reproductive growth (Bargmann and Horvitz, 1991), in large part by producing insulin peptides (Li et al., 2003). Thus, external variations in nutrients are integrated in sensory neurons and transduced by secretory signalling pathways directly to other tissues in the worm. In contrast, the head sensory neurons ASK and ADL have been shown to promote dauer formation through both laser ablation and chemical inhibition by selective expression of the ectopic histamine-gated chloride channel HisCl1 (Bargmann and Horvitz, 1991; Chai et al., 2022; Kim et al., 2009; Schackwitz et al., 1996). These sensory neurons detect external variation in pheromones and trigger an increase in their intracellular calcium; genetic analyses further suggest that glutamate acts downstream of these two neurons to affect target interneuron activity, revealing neuronal circuits also at play (Chai et al., 2022). Indeed, some of the target interneurons of these sensory neurons, such as AIA, have also been shown to elicit entry into diapause, by integrating sensory neuron cues and propagating them through neuropeptide signalling (Chai et al., 2022), altogether forming a complex dauer-controlling neuronal network. Thus, neuronal sensing balances pro- and anti-dauer entry information that is transmitted both cell autonomously (e.g. DAF-7 in the ASI neuron) and non-autonomously (through insulin, neuropeptides, not unlike the vertebrate endocrine axis) to impact downstream neurons as well as non-neuronal tissues.

Behaviour plasticity

Changes in the environment can also induce behavioural changes. For instance, in presence of food, *C. elegans* hermaphrodites tend to move slowly and stay near the food source (Flavell et al., 2020; Fujiwara et al., 2002). By contrast, foraging strategies are observed when food is lacking. First, the animal intensively explores its nearest environment where food was last experienced, a local search-for-food behaviour. As time goes by, this local search behaviour is replaced by more global strategies to explore distant areas. Such local-to-global foraging strategies have been observed across phyla, from insects to mammals. What and how is this starvation-induced behavioural plasticity, from quiescence to foraging, triggered? A neuronal circuit has been shown to control these decisions, which are influenced not only by food itself but also by food odours, pheromones and past experience (Gray et al., 2005). This circuit, which includes chemosensory neurons in parallel with mechanosensory neurons, responds to multi-sensorial cues through glutamate/G-protein coupled glutamate receptor signalling. This combination of sensory neurons converges on interneurons controlling the reorientation of foraging modes (López-Cruz et al., 2019).

Recently, in an example of adaptive developmental plasticity, early life developmental starvation has been associated with more cautious foraging strategies in the adult, where exploration is reduced. Interestingly, such a change in adult foraging behaviour was only observed in adult worms having experienced passage through the dauer diapause. Passage through other types of diapause, such as the L1 diapause, or only experiencing starvation during development without entering the dauer state did not impact adult foraging behaviour. The reduction in time spent in exploration correlated with increasing time spent in the dauer state (Gray et al., 2005). Altered foraging abilities of animals that have experienced starvation do not appear to be due to a deficient sensory response to food or locomotion ability. Rather, these adult animals appear blocked in a local search mode, unable to switch to global search exploration mode. Some evidence points to changes in activity patterns of a neuronal motor circuit regulating stimulus-evoked

reversal probability (Pradhan et al., 2019). In addition, the genetic background of the animals influenced whether adults would exhibit foraging behaviour plasticity. Indeed, the foraging behaviour of wild isolates, exhibiting wild (ancestral) variants of the neuroglobin *glb-5* gene known to be involved in oxygen sensation, was impacted by early life starvation and dauer entry, whereas a domestication-acquired polymorphism in *glb-5* led to a loss of foraging plasticity in the common laboratory *C. elegans* strain (Pradhan et al., 2019). Interestingly, plasticity loss in a (stable) lab environment could suggest that the domestication-acquired polymorphism in *glb-5* contributes to fitness benefits in lab conditions (Pradhan et al., 2019). Another study indeed suggested that the increased fitness associated with the *glb-5* domestication allele requires an O_2-sensing neuronal circuit which impacts fat mobilisation among others (Zhao et al., 2018). In addition, these studies highlight a memory of life experiences that may be retained to impact animal fitness later in life. Below, we will explore in more detail how this form of memory might be encoded at the molecular level.

Developmental plasticity of organs

Besides alterations at the whole-organism level, the development of specific organs can exhibit variability in response to nutrients levels. Here, we will focus on two well-characterised examples of developmental plasticity, with different consequences for the animal: acquisition of new abilities versus a variable developmental scheme but invariant properties of the organ.

Pristionchus teeth

The type or abundance of nutrients can also impact the development of defined organs. Mouth development in the nematode *Pristionchus pacificus* represents a striking example of irreversible polyphenism. Two different feeding structures can be found in this species that are dictated by their life history.

In this dimorphic species, genetically identical animals can develop either a narrow buccal cavity with only one dorsal tooth, a morph called stenomatous (or St), or a large buccal cavity with two hooked teeth, a morph called eurystomatous (or Eu) (Bento et al., 2010). The Eu mouth, which confers a greater ability to kill prey, allows *P. pacificus* animals to feed on other nematodes in addition to feeding on bacteria, while the St-mouthed worms feed on bacteria only (Kiontke and Fitch, 2010; Serobyan et al., 2014).

The decision to make an Eu or St mouth is taken during larval development (Serobyan et al., 2013). Several environmental factors can influence this decision, such as pheromones, diet, sex, crowding or liquid versus solid culture medium (Bento et al., 2010; Bose et al., 2012; Serobyan et al., 2013; Werner et al., 2017). Consequently, while a ∼2:1 St:Eu ratio is found in the wild-type PS312 population (Bento et al., 2010), changing environmental conditions impact on this ratio.

Recent studies have suggested that a cost is associated with this particular phenotype (Dardiry et al., 2023; Serobyan et al., 2014). Different natural isolates with a bias towards one mouth morph or the other were tested on diverse food conditions. These studies showed that a bacterial diet is a better food resource for both mouth-form animals; and indeed, when offered both types of food, *P. pacificus* worms exhibit a preference toward a bacteria meal. They further showed that, when grown on bacteria, St-mouthed animals had a faster developmental speed than Eu-mouthed animals, while exhibiting similar fecundity rates, suggesting higher fitness. However, Eu nematodes exhibit better fitness on a prey diet (as quantified by examining longevity, offspring survival and fecundity), or when transferred from a prey diet to a bacteria diet. Finally, when induced by diet in a St-biased strain, the Eu morph is associated with reduced developmental speed and fecundity (Dardiry et al., 2023; Serobyan et al., 2014). Thus, a cost seems to be associated with the ability to generate an additional mouth form, and fitness advantages associated with a given mouth form are modulated by context and experience. In addition, the percentage of Eu morphs under laboratory conditions (grown on bacteria) fluctuates between 70% and 90% (Ragsdale et al., 2013). Especially in light of the St-mouthed animals' ability to grow faster, such stochastic variation may represent a bet-hedging strategy whereby the presence of a low percentage of the St morph in the population may allow rapid adaptation to a changing environment (growth conditions) for a given generation.

How is this developmental plasticity generated? Genetic screens have suggested that a genetic switch controls this polyphenism decision: indeed, several monomorphic loss-of-function mutants have been identified that lead to the whole population being either all Eu or all St mouthed (Kieninger et al., 2016). Consistent with the notion of a switch, in such mutants, it is the proportion of St versus Eu animals in a population that is affected while the mouth of these mutants is properly formed. In addition, gain-of-function experiments for these loci lead to the opposite phenotype, showing that they are necessary and sufficient to induce a binary switch towards a given mouth form.

Over the years, a network controlling the decision has been identified (Fig. 2), with two chromatin remodellers, the MBD-2 methyl binding protein and the LSY-12 histone acetyltransferase, positively regulating the levels of the extracellular aryl-sulfatase EUD-1 (Serobyan et al., 2016). EUD-1 activity is both necessary and sufficient for the development of an Eu mouth form. Indeed, *eud-1* loss-of-function mutants exhibit St mouths while all animals overexpressing *eud-1* have an Eu mouth (Ragsdale et al., 2013). The NHR-40 nuclear hormone receptor, identified in a suppressor screen of *eud-1*, also exhibits switch properties. While the original allele isolated was a gain-of-function mutation, *nhr-40* appears to act downstream of EUD-1 and *nhr-40* loss-of-function mutants similarly exhibit St mouths only (Kieninger et al., 2016; Sieriebriennikov et al., 2020). In addition, the

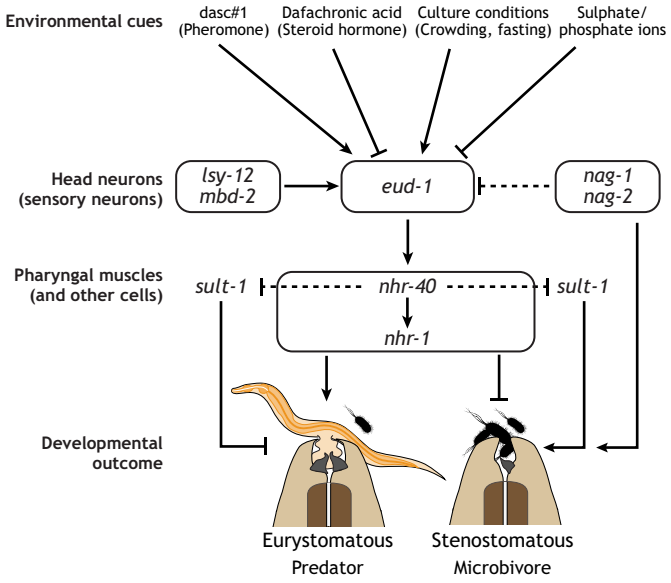

Fig. 2. Gene regulatory network involved in the control of mouth form in *Pristionchus pacificus*. See text for further description.

N-acetylgalactosaminidases NAG-1 and NAG-2 promote the St morph (Sieriebriennikov et al., 2018), as does the sulfotransferase SULT-1, which also exhibits switch properties and is partially epistatic over *eud-1* (Namdeo et al., 2018). SULT-1 appears to act downstream of *nhr-40* as its expression level is negatively regulated by *nhr-40* (Namdeo et al., 2018).

In which cells is the switch decision made? As the switch decision is influenced by environmental factors that can be sensed, including the pheromones dacs#1 or small molecules such as sulphate and phosphate ions which inhibit EUD-1 (Bose et al., 2012; Ragsdale et al., 2013), it is perhaps not surprising that some of the switch factors were observed in head neurons. Indeed, *eud-1* was found to be expressed and act in particular in the anterior sensory neurons know as amphids that make the head sensilla, consistent with a role in sensory transduction (Namdeo et al., 2018; Ragsdale et al., 2013). By contrast, the switch nuclear hormone receptor *nhr-40*, its downstream effector *nhr-1* and the sulfotransferase *sult-1* are all co-expressed in pharyngeal muscle cells, suggesting that these switch genes (see Glossary) have different targets and mechanisms of action (Namdeo et al., 2018; Sieriebriennikov et al., 2020).

Finally, besides the developmental plasticity event per se, it is interesting to note that it is associated with behavioural plasticity: a complex feeding behaviour is associated with the Eu morph in particular, which involves serotonin (Ishita et al., 2021; Okumura et al., 2017; Wilecki et al., 2015) and small peptides mediating self-recognition and preventing cannibalism (Lightfoot et al., 2019).

Caenorhabditis elegans vulva

The *C. elegans* egg-laying organ, the vulva, is patterned via the interaction and successive action of several signalling pathways and surrounding cells. Much work has focused on unravelling how this organ is formed and, as a consequence, the cellular mechanisms and molecular pathways involved are well understood. Before organogenesis proper occurs, precursor cells that will contribute to vulva formation are specified and patterned (Fig. 3). During early larval development, six cells of the ventral epidermis, named P.3p to P8.p and collectively called the ventral precursor cells (VPCs), are first made competent to adopt a vulval fate (a feat involving the activity of the hox gene *lin-39* and the Wnt signalling pathway). These six VPCs are aligned in an antero-posterior manner with P6.p roughly positioned mid-body of the worm. Later in the L3 larval stage, three of them, the P5.p to P7.p cells, are selected to form the vulva via an EGF/ras signal originating from one cell of the somatic gonad, the anchor cell positioned just above, and Notch intersignalling, with centring on P6.p. The combined action of these two pathways robustly leads to the adoption of a vulval primary fate by P6.p, and a vulval secondary fate by P5.p and P7.p. The remaining three VPCs consistently adopt a tertiary non-vulval fate, with P4.p and P8.p undergoing one round of division and P3.p either dividing once or remaining undivided before fusing with the underlying hypodermal syncytium (Fig. 3) (Sternberg, 2005).

This invariant patterning is found in all *Caenorhabditis* species examined, underscoring its robustness (Félix, 2007). However, slight patterning changes that do not preclude the formation of a functional vulva can be observed when environmental conditions are changed. Vulval patterning outcome is in fact essentially invariant: in wild-type animals, the P3.p cell can either divide before fusing with the underlying hypodermis (~45% of animals), like P4.p, or directly fuse with the hypodermis (~55% of animals) (Besnard et al., 2020; Delattre and Félix, 2001). In addition, around 1% of wild-type individuals exhibit a direct fusion of the P4.p or P8.p cells to the hypodermis, without any prior cell division (Delattre and Félix, 2001). In an instance of non-adaptive (passive) developmental plasticity, the proportion of dividing P4.p and P8.p cells can increase in response to high temperature (Grimbert and Braendle, 2014). An impact of nutrient levels remains to be reported in this case.

Furthermore, environmentally induced variation in both the number of vulval cells induced and the centring of the vulval patterning has been reported: for instance, when wild-type worms have experienced early starvation, a larger proportion of them have a

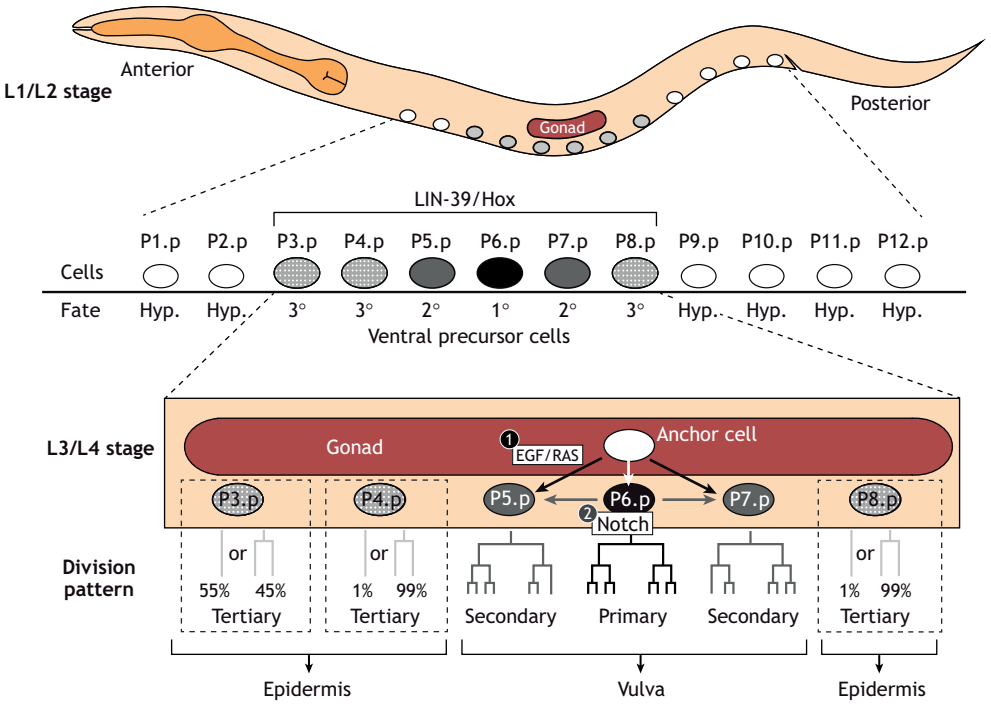

Fig. 3. Vulval development in *C. elegans*. Six ventral cells, P3.p to P8.p, acquire the competence to adopt a vulval fate through the action of LIN-39/Hox. Patterning of these ventral precursor cells (VPCs) via the EGF and Notch pathways results in P6.p adopting a vulval primary (1°) fate, and P5.p and P7.p adopting a vulval secondary (2°) fate. The other three VPCs will fuse with the underlying hypodermis, after undergoing, or not, a cell division with variable penetrance [i.e. a tertiary (3°) non-vulval state]. See text for further description.

vulva centred on P5.p instead of P6.p (Braendle and Félix, 2008); as all six VPCs are competent to make the vulva, the final outcome (the vulva) remains identical to that of unchallenged worms, albeit with a slightly changed positioning.

Similarly, low penetrance hyper-induction of VPCs (induction of more than three Pn.p cells) is observed in response to starvation. The extent of such starvation-induced non-adaptive developmental plasticity depends on the genetic background tested (Grimbert et al., 2018). Indeed, mutant backgrounds for several players in VPC patterning, which lack a vulva, have been found to be rescued by starvation, a process that involves TOR but is independent of the IIS pathway (Braendle and Félix, 2008; Ferguson and Horvitz, 1985; Grimbert et al., 2018).

Thus, this system appears to be sensitive to environmental perturbations, resulting in slight developmental changes apparently through altering the levels of the existing molecular networks, while the overall developmental trajectory and outcome remain unchanged.

Long-term consequences of varied early life conditions

Traits in individuals

As we have seen above, examples of both irreversible and reversible developmental plasticity can be observed in response to specific environmental cues. In the latter case, when the environmental context returns to a previous state, can animals resume or return unaffected to their previous developmental trajectory as well? Or do they retain some kind of memory of this life experience? *Caenorhabditis elegans* provides us with a model to address these questions. Indeed, entry into dauer can be followed by the resumption of reproductive growth when the environment is once again favourable.

Worms that have experienced a starvation period in their early life, and have been able to resume growth, reach adulthood and reproduce. Post-dauer adult animals are morphologically identical to control adults that did not experience a dauer stage. However, they exhibit a decreased brood size, a phenomenon called reproductive plasticity (Ow et al., 2018), while showing a longer lifespan (Ow et al., 2021). Interestingly, reproductive plasticity depends on the initial trigger of the dauer stage as adult animals that have experienced a crowding-induced dauer stage exhibit, in contrast, a longer mean lifespan and a larger brood size compared with adult animals that bypassed the dauer stage (Hall et al., 2010).

Reproductive plasticity involves an active response. The decreased brood size following a starvation-induced dauer stage is correlated with a change in expression of a large cohort of genes. These differentially expressed genes may represent a specific life-history transcriptional programme which is dependent on the exchange of signals between the soma and the germline (Ow et al., 2018, 2021). Interestingly, the genes appear to cluster on specific portions of some chromosomes, an aspect conserved in the *Caenorhabditis briggsae* nematode, further arguing for an active response (Ow et al., 2018). Decreased brood size is also correlated with a delay in germline proliferation at the stage where sperm is normally produced, suggesting that sperm count may underlie it (Ow et al., 2018). A neuronal network might be involved in linking the perception of the absence of food to reproductive plasticity, as at least two neurons, the olfactory neuron AWB and the AIY interneuron, have been shown to translate food-related olfactory cues to the rate of reproductive mechanisms during adult diapause (Jeong and Paik, 2017; Sowa et al., 2015). Reproductive plasticity is observed in both hermaphrodite-based and male-oriented reproduction. Importantly, this early life experience memory is also observed in *C. elegans* wild isolates, as well as in the closely related nematode species *C. briggsae*, suggesting that such memory does not represent an adaptative trait due to decades of laboratory culture (Ow et al., 2021). Thus, some long-term consequences of early life history have been revealed.

What are the mechanisms underlying memory of life experiences? Again, the ability of *C. elegans* worms to enter and exit the dauer phase provides a model to pursue these questions. The stress-specific transcriptome of adults that have experienced a crowding-induced or starvation-induced dauer stage during their development has highlighted transcriptomic changes. Post-dauer adult worms that have experienced a lack of food during their early development present a set of around 1600 genes that are significantly upregulated or downregulated compared with control worms, with an enrichment in somatic gene expression (Ow et al., 2018), while post-dauer adults that have experienced a pheromone-induced dauer stage present an altered expression for 2000 genes with upregulated expression of genes involved in reproduction (Hall et al., 2010). Interestingly, pheromone-induced dauers show a different – or even opposite, for a subset of genes – transcriptional signature during their adult reproductive life compared with starvation-induced dauers (Ow et al., 2018). Therefore, different dauer-inducing stresses are associated with specific and distinct transcriptional memories in adulthood. These transcriptional profiles seem to be under the control of genome-wide chromatin state (Hall et al., 2010) as well as RNAi pathways (Hall et al., 2013). Consistent with these studies, new work has found that fasting induces a large-scale spatial reorganisation of chromatin in the worm, and that these changes are reversible (Al-Refaie et al., 2023). Together, these studies suggest that life experiences may leave transcriptional and chromatin vestiges that could account for altered traits in post-stress life.

In addition, studies examining the mechanisms underlying life-experience memory in individuals that underwent an L1 diapause suggest that small non-coding RNAs (sncRNAs) could also play a key role. The transmission of sncRNAs following complete food deprivation during the L1 stage has been explored more deeply by Rechavi and colleagues (2014). They observed that experiencing starvation-induced L1 diapause results in the misregulation of sncRNAs later during adulthood, after food has been restored and growth has resumed. These sncRNA fall into the 22G and 26G small RNA family (22 and 26 nucleotides long, respectively, with a 5′ guanine). Some of them are antisense to genes important for nutrient reservoir activity. Many genes targeted by these sncRNAs were found to be downregulated in the adult P0, in agreement with a role for these sncRNAs in gene silencing (Rechavi et al., 2014).

Transgenerational impacts

For a long time, it has been assumed that acquired traits could not be transmitted to the next generations. This notion was illustrated by the famous theory of August Weismann. The theory was based on his observation that germ cells are segregated away from the soma early during development. He assumed that a theoretical barrier is then established between these germ cells (and the hereditary determinants contained in their nucleus in the form of a germ plasm) and the soma. Therefore, any action on the somatic cells would not be transmitted to the next generation (Nilsson et al., 2020).

However, mounting evidence shows that environmentally induced acquired traits can be transmitted over generations, via epigenetic mechanisms (see Glossary), in a large variety of organisms from plants to humans (Nilsson et al., 2018). Such transmission to the progeny was suggested to provide information about future – and possibly changing – living conditions and enables offspring to adapt

more quickly to their environment. However, many studies have shown a negative impact of these environmental changes on parental and descendant fitness (Morgan, 2019). For instance, an increased neonatal adiposity and poorer health during adult life have been observed in the grandchildren of women who had been exposed to the 1944–1945 Dutch famine (Painter et al., 2008). This may be related to the fact that the descendants have not themselves been exposed to the same adverse conditions.

To study long-lasting transgenerational epigenetic inheritance (TEI; see Glossary), *C. elegans* has proved again to be an excellent model. Many generations can be analysed over a short period of time, in very controlled growing conditions, and the lab strains are essentially near-isogenic owing to self-fertilisation.

TEI of life experiences has been established in *C. elegans* in very diverse conditions such as bacterial infections, hypoxia, heat and starvation (for review, see Baugh and Day, 2020). In the context of long-term dauer-inducing diet restriction, for example, well-fed third generation (F3) progeny of post-dauer individuals (P0 for initial generation) display increased starvation resistance during the first larval stage (L1), and longer lifespan in adults, compared with well-fed F3 progeny from well-fed P0 (Webster et al., 2018).

The molecular mechanisms underlying such transgenerational memory remain poorly understood and have been the focus of recent studies. One key process that has been uncovered is gene silencing via sncRNAs. In addition to their role in setting up a memory of early life starvation in the same individuals after resumed growth, sncRNAs can be inherited transgenerationally in the worm (Seth et al., 2013). When examining the misregulated sncRNAs of (P0) adults that had experienced a starvation-induced L1 diapause, a large proportion of these sncRNAs (40% of the 22G-RNAs and 69% of the 26G-RNAs) were found to also be misregulated in the F3 generation that had never experienced starvation. Thus, the small RNA pools in the F3 worms reflect the changes that occurred following the L1 starvation in the P0 ancestor. This TEI was shown to be dependent on the germline-expressed argonaute HRDE-1 and the dsRNA-binding protein RDE-4, a specific component in the DICER endo-siRNA pathway (Rechavi et al., 2014).

Starvation during L1 results in adult animals having an extended lifespan (Jobson et al., 2015; Rechavi et al., 2014). Interestingly, F3 derived from initial L1-starved P0 animals also present an extended lifespan, showing once again that there is a transgenerational memory of past conditions (Rechavi et al., 2014), although a direct link between sncRNAs and lifespan was not clearly established by the authors.

More recently, some differentially expressed genes known to be downstream targets of the IIS insulin pathway have been identified using a complex starvation paradigm where the L1s of five successive generations were starved to maximise exposure to stress (Vogt and Hobert, 2023). Misregulation of these genes has been observed in the 7th and 8th generations, i.e. two and three generations after the last starvation, respectively. So early life starvation leads to an increased activity of IIS in the subsequent generations grown in the presence of food. This was correlated with a switch to more exploratory behaviour, typical of worms experiencing food shortage, in the fed animals of these 7th and 8th generations. The authors postulate that there is a dynamic interplay between changes in metabolism and the biogenesis of epigenetic factors that could in turn contribute to metabolic and behavioural programming across generations. Indeed, they found a misregulation of genes important for the biogenesis and function of sncRNAs known to be involved in TEI, in adult animals that experienced starvation during L1. However, they were not able to identify the misregulation of these genes in subsequent fed generations (Vogt and Hobert, 2023), leaving open the question of how this increased IIS activity is transgenerationally inherited.

In parallel sncRNAs, histone modifications have also been shown to play an important role in long-lasting epigenetic memory (Demoinet et al., 2017; Kishimoto et al., 2017; Klosin et al., 2017; Rechavi and Lev, 2017). Acute starvation of AMPK (aak-1/2) L1 mutants leads to a reduced brood size over multiple generations associated with an increase in H3K4me3 levels (Demoinet et al., 2017). This suggests that AMPK plays a critical role in blocking histone modifications during adverse conditions (Demoinet et al., 2017). In other stress contexts, histone modifications have been shown to play an important role in long-lasting epigenetic memory (Kishimoto et al., 2017; Klosin et al., 2017; Rechavi and Lev, 2017). Inheritance can be paternally or maternally transmitted and is associated with altered trimethylation of histone H3 lysine 9 (H3K9me3) (Klosin et al., 2017) or requires H3K4me3 modifiers (Kishimoto et al., 2017). Although not directly linked to developmental plasticity, these studies tend to demonstrate that TEI is tightly associated with histone modification. However, a clear link between sncRNAs and histone modification needs to be established (Rechavi and Lev, 2017).

Conclusions and perspectives

Developmental plasticity gives rise to different outcomes in response to environmental changes, without the acquisition of new genomic mutations. This has been postulated to occur in unstable environments and may be particularly important for most organisms when food availability is considered. Developmental plasticity can also stem from a variety of conditions such as infection, climate change, liquid versus solid environment or the presence of pheromones. Responses can be viewed as ‘active developmental plasticity’, i.e. integrated phenotypic changes that reflect changes in the developmental plan through the modification of developmental pathways and gene regulatory networks. For example, caloric restriction has been shown to trigger a robust programme though actively regulated programmes from worms to rodents (Ly et al., 2019; Roth and Polotsky, 2012). Another thoroughly documented instance of active developmental plasticity involves *Daphnia*, which develop a protective helmet structure in response to predators (Agrawal et al., 1999). Responses can be either discontinuous or graded, and are often regarded as adaptive. In contrast, ‘passive plasticity’ is generally used to describe higher or lower functioning of the original pathways, as a consequence of the environment. For instance, a decreased intracranial volume has been observed in the brain of individuals exposed *in utero* to the Dutch famine (Hulshoff Pol et al., 2000), and has been postulated to be a consequence of an impoverished (low-protein, low-vitamin) diet.

Caenorhabditis elegans has provided a powerful model to address the impact of the environment on the development of the organism or of specific structures, as well as on its behaviour, allowing studies bridging from the population and macroscopic level to cellular circuits and the molecular pathways involved. A few assests stand out, such as the possibility of following and testing many generations in a short period of time, owing to its very short life cycle. Several generations of large, yet synchronised populations can be subjected to the same tightly controlled environments without any concerns about psycho-societal parameters. This has proved important as studies of the consequences of the Dutch famine on descendants of pregnant mothers have suggested a differential impact on the next generation depending on the developmental stage

of the fetuses experiencing it (Hanson and Gluckman, 2014). In fact, in addition to the concepts derived from human epidemiological studies on relatively small cohorts, the use of a tractable genetic system such as the worm allows us to go beyond correlations between dietary restriction and health, up to causation. Of note, the large majority of *C. elegans* research has focused on the hermaphrodite, leaving male-specific responses to starvation a largely unchartered territory to be explored. Several questions remain unanswered and we expect *C. elegans* to further contribute valuable insights.

Are plasticity and robustness mutually exclusive? Changes resulting from plasticity, which can be reversible or not, may provide populations with flexibility, allowing a better match of phenotypes to environments. However, even when developmental plasticity is observed, the alternative outcome is often invariant. For instance, nutrient availability can give rise to a consistent discontinuous phenotypic change. This is the case when developing *C. elegans* choose to enter the dauer diapause – as opposed to reproductive growth – in response to starvation. Both this alternative and the original developmental trajectories, while being different, are very robustly executed, and no intermediate, aborted or alternative outcome is observed. This suggests that there are mechanisms ensuring a robust response to an environmental stress. Possible molecular mechanisms underlying robustness have been described in the context of cellular plasticity in *C. elegans* (Zuryn et al., 2014). It remains to be shown whether similar mechanisms support the robustness of developmental trajectories during phenotypic plasticity. Current and future research will further decipher whether and how such robustness allows for the evolution of its underlying mechanisms.

Another exciting area of research is to tease apart the possible costs and advantages associated with alternative developmental trajectories (e.g. Billard et al., 2020). For example, a study that compared the impacts of various stresses on four *Caenorhabditis* species revealed that exposure to the same pathogenic bacteria induced an adaptive intergenerational effect in *C. elegans* but had deleterious intergenerational effects in *C. briggsae* (Burton et al., 2021). A complex picture is thus emerging as related species can exhibit opposite impacts. In addition, for a given species, different conditions, or the order of transition between conditions, dramatically change the associated cost and fitness, as seen with the *Pristionchus* mouth morphs: a context-dependent evaluation of these costs will be warranted to assess the impact of different or changing environments.

Future research will probably deepen our understanding of what impacts the reversibility of the process and a safe exit of the alternative state. For instance, recent findings suggest that the coupling of food perception to actual ingestion is crucial to allow exit from dauer (Kaplan et al., 2018). Such reversible acclimation is also observed in other animals (Ligon et al., 2012).

Finally, several studies reported the importance of small RNAs not only for transgenerational adaptive responses, but also in immediate responses to starvation (Bharadwaj and Hall, 2017; Kadekar and Roy, 2019; Kasuga et al., 2013), sometimes signalling from one tissue to another (Posner et al., 2019). Other epigenetic determinants such as DNA methylation and histone modification, have been implicated in TEI, e.g. the *Daphnia* protective helmet structure in response to predators. This trait endures in subsequent generations without exposure to the original predator cues (Agrawal et al., 1999), suggesting a transgenerational inheritance through an epigenetic mechanism (Harris, 2012). This epigenetic contribution to TEI appears to be a conserved mechanism, as mounting evidence suggests that epigenetic changes, e.g. mediated by sncRNAs or histone modifications, also occur in mammals in response to the environment and could be passed from one generation to the next. However, an associated causality or adaptive roles remain to be thoroughly demonstrated (Skvortsova et al., 2018). How small RNAs are partitioned and packaged in individuals to mediate either immediate response and long-term transgenerational effects remains to be elucidated.

Common themes underlying developmental plasticity in many organisms are emerging. Recognising and deciphering these common principles should enhance our broader understanding of how organisms adjust or adapt to diverse environmental conditions, offering potential implications for areas such as evolutionary biology, developmental biology and human health.

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