REVIEW

C. elegans dauer formation and the molecular basis of plasticity

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Because life is often unpredictable, dynamic, and complex, all animals have evolved remarkable abilities to cope with changes in their external environment and internal physiology. This regulatory plasticity leads to shifts in behavior and metabolism, as well as to changes in development, growth, and reproduction, which is thought to improve the chances of survival and reproductive success. In favorable environments, the nematode *Caenorhabditis elegans* develops rapidly to reproductive maturity, but in adverse environments, animals arrest at the dauer diapause, a long-lived stress resistant stage. A molecular and genetic analysis of dauer formation has revealed key insights into how sensory and dietary cues are coupled to conserved endocrine pathways, including insulin/IGF, TGF- β , serotonergic, and steroid hormone signal transduction, which govern the choice between reproduction and survival. These and other pathways reveal a molecular basis for metazoan plasticity in response to extrinsic and intrinsic signals.

All living things can sense change in their environment and physiologic milieu and adapt accordingly, revealing remarkable plasticity. Changes in behavior and metabolism are well-recognized forms of plasticity, which are typically rapid and geared to maintain organismal homeostasis. Sustained environmental challenge, such as nutrient limitation, stress, and shifts in photoperiod or temperature, can culminate in long lasting changes in metabolism, behavior, growth, and development, most dramatically resulting in alternate life strategies, such as hibernation, or diapause, a state of developmental arrest. Moreover, restricted dietary intake can delay reproduction and extend organismal life span in diverse species. Collectively, these patterns and their variations comprise an animal's life history. Although determined by genotype, life history traits are largely regulated and plastic, not passively dictated by resource availability. This view is supported by the discovery of myriads of

regulatory layers, including neural signaling, hormones, and signal transduction pathways that form logical circuits governing these traits.

Despite its invariant cellular development (Sulston 1988), the worm *Caenorhabditis elegans* reveals evident plasticity in its life history, which ultimately enhances its chance of survival through environmental hazards, and ensures that somatic growth and reproduction match available resources. Notably, in favorable environments, *C. elegans* will develop rapidly to reproductive maturity, but in unfavorable environments, animals will arrest at the dauer diapause, a larval stage geared for survival (Fig. 1A). A genetic analysis of *C. elegans* dauer formation has illuminated how environmental and dietary cues are coupled to evolutionarily conserved molecular pathways, including neurosensory, TGF- β , insulin/IGF, serotonergic, and steroid hormone signal transduction, which impact growth, metabolism, maturation, survival, and aging. These and related studies have led to key insights into similar processes in other metazoans, with implications for understanding disease states of cancer, diabetes, obesity, and other age-related diseases. Here, we review some of the processes, pathways, and molecules involved in the regulatory plasticity of dauer formation and other life history traits.

The dauer diapause

C. elegans dauer diapause is a dramatic form of regulatory plasticity that exemplifies the links of environment to life history traits. Although little studied in the wild, *C. elegans* is thought to feed on bacteria and other microbes as well as micronutrients found in the soil, but must often endure periods without food or extremes of temperature. In the laboratory, it is conveniently cultivated on agar plates containing *Escherichia coli*, salts, and cholesterol. In favorable laboratory environments, the worm develops rapidly from embryo through four larval stages (L1–L4) to adult in 3.5 d (20°C), called reproductive development (Fig. 1A). Hermaphrodites typically reproduce over a 3- to 5-d period and live another 2–3 wk. When hatched into environments without food, they arrest at the L1 diapause, and fail to initiate larval development (Baugh and Sternberg 2006). If exposed to overcrowded conditions with limiting food during early

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Figure 1. (A) *C. elegans* life cycle. In favorable environments, *C. elegans* undergoes reproductive development and progresses rapidly from embryo through four larval stages (L1–L4) to the adult in 3–5 d (15°C–20°C). Adults then live another 2–3 wk. In unfavorable conditions, including overcrowding, limited food, and high temperature, *C. elegans* undergoes development to a specialized third larval stage called the dauer diapause (L3d), which can live several months. Upon return to favorable environments, dauer larvae recover to reproductive adults with normal life spans. (B) Schematic of neuroendocrine cells. Integration of environmental cues (dauer pheromone, nutrients, and temperature) are transformed into endocrine signals by amphid neurons (ASI, ADF, ASG, ASJ, ASK, AWA, and AWC). Serotonergic signaling from ADF and cGMP signaling from ASJ and ASK influence production of TGF- β from ASI and the ILPs from ASI, ASJ, and other cells. Insulin/IGF-1 signaling and TGF- β signaling converge on steroid hormone signaling in the XXX cells. Not shown are the other tissues where ILP and steroid hormone production take place. SKN-1 also works in the ASI neuron to regulate DR-induced longevity.

larval life, animals will divert development to a specialized third larval stage called the dauer diapause (L3d), which can live for months (Cassada and Russell 1975). Other less well understood diapause-like stages have also been described (Ruaud and Bessereau 2006), revealing plasticity throughout the life cycle.

Dauer formation entails vast coordinate changes throughout the body, suggestive of an endocrine mechanism (Riddle and Albert 1997). Prior to the dauer molt, they feed and store fat and carbohydrate. During morphogenesis, they suppress food intake, undergo radial constriction, and remodel various tissues of the body. Once in diapause, they are nonfeeding and spend down their reserves, converting fat to glucose through the glyoxylate cycle (Riddle and Albert 1997). Aerobic respiration is suppressed in favor of glycolysis and fermentative metabolism (Vanfleteren and De Vreese 1996; Holt and Riddle 2003). While often immobile, they can move quickly when prodded, or will rear their bodies onto vertical substrates, behaviors helpful for dispersal. Sealed at all orifices, they have a thickened cuticle resistant to desiccation, with cuticular treads called alae for rapid movement. Generally, they are highly resistant to all forms of stress, including starvation, heat, and oxidative stress (Larsen 1993; Lithgow et al. 1995; Riddle and Albert 1997). Despite their apparent quiescence, several thousand genes continue to be expressed, explicitly important for survival (Wang and Kim 2003). In toto, these defenses enable them to endure literally months under adversity and prevail. When returned to favorable conditions, dauer rapidly recover to post-dauer L3/L4 stages to reproductive adults, with normal life spans. This reveals that animal longevity is plastic and under both environmental and genetic control. Similarly, in response to environmental and nutrient stress, some mammals go

through hibernation, torpor, or enter into comparable states of thrifty metabolism, delayed reproduction, and extended survival (Finch 1994).

Genetics of dauer formation

A genetic dissection of dauer diapause has revealed key molecular insights into developmental plasticity and longevity. Over 30 *Daf* loci inappropriately regulate dauer formation (Riddle et al. 1981; Albert and Riddle 1988). Constitutive mutants (*Daf-c*) always enter diapause, while defective mutants (*Daf-d*) bypass diapause, regardless of conditions. Many *Daf-c* mutants are conditional, forming dauer larvae only at moderately elevated temperatures (25°C). Prior to their molecular characterization, loci were grouped into pathways based on patterns of genetic epistasis and synergy, as well as phenotypic profile (Vowels and Thomas 1992; Thomas et al. 1993; Gottlieb and Ruvkun 1994). Identified pathways include components of sensory neuron structure and function (Shakir et al. 1993), cGMP signaling (Birnby et al. 2000) and serotonergic neurotransmission (Sze et al. 2000), which impinge on TGF- β (Ren et al. 1996) and insulin/IGF-1 signaling (IIS) (Kimura et al. 1997). Ultimately these pathways converge on steroid hormone receptor transcriptional cascades, which are instructive in the dauer decision (Antebi et al. 2000). Molecular genetic studies suggest that when hormones (serotonin, TGF- β , insulin, and steroids) are up, animals select reproductive growth. When down, they select dauer diapause. Parallel processing and molecular cross-talk ensure a robust all or none response when conditions lapse below a critical level. While screens for these major constituents are near saturation, various modulators have been identified through enhancer screens (Ohkura et al. 2003; Yabe et al.

2005; Hu et al. 2006), or by examination of dauer formation at 27°C (Ailion and Thomas 2000, 2003). Below we discuss the cellular and molecular pathways in more detail.

Sensory perception

Animal sensory systems detect and integrate a wide variety of environmental stimuli to evaluate current and predict future events. In *C. elegans*, plasticity first arises from the detection and processing of graded environmental cues that govern dauer formation—food, temperature, and pheromone—which are integrated by the nervous system to mediate developmental choice (Golden and Riddle 1982, 1984). Unidentified exudates from bacterial food sources and moderate temperatures (15°C–25°C) favor reproductive growth. Scarce food, high temperatures (27°C), and a secreted dauer pheromone (an indicator of population density) bias dauer formation. Dauer pheromone is the most potent inducer of diapause (Golden and Riddle 1982, 1984), and presumably may best predict environmental quality. Recently, its precise chemical structure has been elucidated, revealing three related species of ascarosides: one conjugated to a saturated fatty acid, the second to an unsaturated fatty acid, and the third to a ketone (Jeong et al. 2005; Butcher et al. 2007). The latter two are the most potent, working in the nanomolar range. Pheromones in other species are well known to influence sexual behavior, but are also likely to impact development and reproduction as well. For example, dominant male orangutans not only develop dramatic secondary features that announce their α status, such as facial flaps, large body size, and deep voice, but can suppress the development of subdominant males for years, presumably through release of pheromones (Harrison and Chivers 2007).

Neurons regulating diapause

C. elegans hermaphrodites harbor 302 neurons, including 60 ciliated sensory cells that respond to various modalities. Two major head sensory organs, called amphids, are critical to dauer formation. Specific amphid cells, such as ASI, ADF, and ASG regulate dauer formation (Fig. 1B); Bargmann and Horvitz 1991). Their removal in L1 by laser ablation triggers transient entry to dauer even in the presence of food. Further removal of the amphid ASJ caused constitutive arrest. By inference, these neurons provoke reproductive growth and dauer recovery. Moreover, ASJ, and to a lesser extent ASK, also promote dauer formation in the presence of dauer pheromone (Schackwitz et al. 1996). Aside from their role in chemosensation, specific amphids produce various secreted factors that not only impact dauer (see below), but also influence other traits, including fat storage, foraging, feeding, egg laying, and body size. In fact, hormones that promote reproductive development partly map to some of the neurons named above: DAF-7/TGF- β is expressed exclusively in ASI (Ren et al. 1996), DAF-28/insulin is

expressed in ASI and ASJ (Li et al. 2003), and serotonin is synthesized in ADF (Sze et al. 2000). To summarize, the amphids receive sensory input and produce hormones that govern diverse bodily functions, not unlike vertebrate endocrine axes.

G-protein-coupled receptors (GPCRs) and G-protein signaling

GPCRs sense the chemical landscape and represent the first interface between environment and the nervous system (Fig. 2). With >1000 resident GPCRs, an unidentified subset presumably detects dauer pheromone, as well as food cues relevant for dauer formation. A handful of GPCRs show dynamic changes in expression in response to dauer signals, revealing plasticity in the repertoire that likely alters perception (Peckol et al. 2001; Lanjuin and Sengupta 2002). Typically, olfactory and gustatory receptors work in conjunction with heterotrimeric G-proteins. The worm has 21 α , two β , and two γ subunits, including a handful that regulate dauer formation. Notably, mutants of *gpa-1*, *gpa-2*, *gpa-3*, *gpc-1*, and *odr-3* have reduced sensitivity to dauer pheromone, while *gpc-11* overexpression leads to greater sensitivity (Zwaal et al. 1997; Lans and Jansen 2007). These G-proteins reside in various neurons, consistent with distributed processing.

cGMP signaling

cGMP signaling is critical to neurosensory transduction in animals, and works in close association with G-proteins. Best studied in worms are *daf-11*, which encodes a transmembrane guanylyl cyclase (GCY) (Birnby et al. 2000), and *tax-2* and *tax-4*, encoding subunits of a cGMP-gated ion channel (Fig. 2; Coburn and Bargmann 1996; Komatsu et al. 1996). *daf-11*/GCY loss-of-function mutants display potent Daf-c phenotypes, as well as defects in chemosensation and olfaction (Vowels and Thomas 1994). Transmembrane GCYs convert GTP to cGMP, often in response to G-protein signaling or extracellular ligands. Accordingly, *daf-11*/GCY, but not *tax-4* mutants, are rescued by exogenous cGMP analogues (Birnby et al. 2000), consistent with the former producing cGMP and the latter responding to it. Another mutant *daf-21* (gain of function) has phenotypes and patterns of epistasis resembling *daf-11*/GCY. Intriguingly, it encodes an HSP90 homolog but its mode of action is not well understood (Birnby et al. 2000). In contrast to *daf-11*, *tax-2* and *tax-4* mutants have weak Daf-c phenotypes, as well as defects in thermotaxis. Epistasis experiments reveal that the strong Daf-c phenotypes of *daf-11*/GCY depend on functional *tax-4*, the sensory cilium components (below), as well as the presence of the ASJ neuron (Vowels and Thomas 1992; Schackwitz et al. 1996; Coburn et al. 1998). Taken together, these studies suggest that cGMP levels could be instructive, actively triggering dauer when low, and reproductive growth when high, with signaling mediated through the cilium. Accordingly, *daf-*

Figure 2. A model for the regulatory plasticity of dauer formation. Environmental cues (dauer pheromone and nutrients) are detected by GPCRs that reside in the ciliary endings of amphid neurons. These signals may be transduced via G-proteins together with the transmembrane GCY DAF-11, which converts GTP to cGMP. cGMP-gated ion channels, TAX-2/TAX-4, transduce cGMP levels into ion influx. (*Left*) For reproductive development, high cGMP levels, directly or indirectly, lead to production of TGF-β (in ASI) and ILPs in amphids and other tissues. In endocrine cells (e.g., XXX, hypodermal, intestinal cells), binding of ILP agonists to the insulin/IGF-1 receptor DAF-2 results in activation of the AGE-1/PI3K and PIP₃ production. Presence of PI3 lipids and activating kinase PDK-1, leads to activation of AKT1,2 and SGK kinases, which phosphorylate DAF-16/FOXO, resulting in cytoplasmic retention by FTT-2/14-3-3 proteins. Binding of DAF-7/TGF-β to the DAF-1/4 receptor kinases results in phosphorylation of DAF-8 and DAF-14/SMADs, and inhibition of DAF-3/SMAD and DAF-5/SNO-SKI complexes. Nuclear localization of DAF-8 and DAF-14 SMADs directly or indirectly regulates expression of hormone synthesis enzymes (e.g., DAF-9/CYP450), which produce dafachronic acids, the ligands for DAF-12/NHR. Niemann-Pick homologs NCR-1,2 deliver cholesterol and other sterols for use in hormone biosynthesis. In target tissues, liganded DAF-12 promotes reproductive and inhibits dauer programs. (*Right*) In dauer inducing conditions, low levels of cGMP diminish ILPs and TGF-β production. Down-regulated ILP and TGF-β production results in nuclear translocation of DAF-16/FOXO and DAF-3/DAF-5/SMADs to promote dauer programs and directly or indirectly inhibit expression of hormone biosynthetic genes. In target tissues, unliganded DAF-12 promotes dauer programs and through association with its corepressor DIN-1/SHARP represses reproductive programs. Note that the identified signaling pathways do not necessarily work in a strictly hierarchical fashion, can work in parallel, and have independent outputs.

11/GCY is expressed in a handful of amphids, including ASI, ASJ, and ASK, and localizes predominantly in ciliary endings (Birnbay et al. 2000).

Several lines of evidence support the notion that cGMP signaling works upstream of IIS and TGF-β pathways. First, *daf-11*/GCY *Daf-c* mutants are partially sup-

pressed by *Daf-d* mutants, *daf-5/SNO-SKI* and *daf-16/FOXO* (Vowels and Thomas 1992; Thomas et al. 1993), which mediate the transcriptional output of TGF- β and insulin signaling (below). Second, cilium structure mutants suppress the *Daf-c* phenotypes of *daf-11/GCY*, but not those of *daf-7/TGF- β* or *daf-2/insulin receptor (InR)* mutants. Third, exogenous cGMP rescues *daf-11/GCY* but not TGF- β or IIS mutants. Finally, *daf-11/GCY* mutants fail to express *daf-7/TGF- β* in ASI (Murakami et al. 2001), and *daf-28/insulin-like peptide (ILP)* in ASI and ASJ (Li et al. 2003), revealing regulatory outputs onto these pathways.

Cilium components

In all animals, ciliated sensory endings of neurons contain components of sensory signal transduction, including receptors, ion channels, and G-proteins. A large class of *Daf* mutants displays various defects in ciliary structure and biogenesis (Fig. 2; Albert et al. 1981; Perkins et al. 1986), accompanied by deficits in chemosensation (*che*, *osm*), an inability of exposed neurons to absorb fluorescent dyes (*dyf*), and often increased fat accumulation, and longevity (Starich et al. 1995; Apfeld and Kenyon 1999; Ashrafi et al. 2003; Mukhopadhyay et al. 2005). Most cilium structure mutants are *Daf-d* below 25°C, but weakly *Daf-c* above it, revealing that the chemosensory organ functions to both prevent or promote dauer formation (Ailion and Thomas 2000), and consistent with the behavior of the ASJ amphid described above. Cilium structure genes encode evolutionarily ancient proteins implicated in intraflagellar transport, including various kinesins, dyneins, and motor regulators, as well as structural components of the cilia themselves (Inglis et al. 2007), many of which are implicated in human conditions such as polycystic kidney disease and Bardet-Biedl syndrome (Barr and Sternberg 1999; Ansley et al. 2003). Among the strongest mutants, *daf-19* encodes a highly conserved RFX/Regulatory factor X transcription factor that regulates ciliogenesis in worms, flies, and mammals (Swoboda et al. 2000; Dubruille et al. 2002). Comparable to the worm, mutations in the murine RFX-3 affect ciliogenesis in pancreatic cells, and impairs insulin production and glucose tolerance (Ait-Lounis et al. 2007).

TGF- β signaling

The TGF- β pathway constitutes one of the major endocrine pathways regulating dauer formation (Fig. 2; Savage-Dunn 2005). Genetically grouped together, *daf-1*, *daf-4*, *daf-7*, *daf-8*, and *daf-14* mutants (all *Daf-c*) are all efficiently suppressed by *daf-3* and *daf-5* (both *Daf-d*) (Thomas et al. 1993). These *Daf-c* loci also show altered social feeding and foraging, increased fat deposition, and egg retention. These loci identify core components of TGF- β signaling: DAF-7 is a novel TGF- β (Ren et al. 1996), and DAF-1 and DAF-4 are type I and II serine/threonine kinase TGF- β receptors, respectively (Georgi

et al. 1990; Estevez et al. 1993). DAF-3, DAF-8, and DAF-14 are SMADs, nuclear effectors of the pathway (Patterson et al. 1997; Inoue and Thomas 2000). Finally, DAF-5 is a SNO/SKI transcription factor, which physically interacts with DAF-3/SMAD, similar to the human counterparts (da Graca et al. 2004; Tewari et al. 2004).

DAF-7/TGF- β is expressed solely in the ASI neurosensory cells (Ren et al. 1996; Schackwitz et al. 1996), while downstream receptors and transcription factors are widely expressed (Patterson et al. 1997; Gunther et al. 2000; Inoue and Thomas 2000; da Graca et al. 2004), providing striking evidence for a neuroendocrine signaling mechanism (Fig. 2). As predicted by the genetics, DAF-7/TGF- β expression specifies reproductive growth, with its production positively regulated by food, and inhibited by dauer pheromone and high temperature, showing clear coupling to environmental signals (Ren et al. 1996; Schackwitz et al. 1996). Genetic and molecular data from worms and biochemical data from other systems suggest a simple model whereby graded DAF-7/TGF- β expression from the ASI neuron couples environmental cues to shifts in metabolism and stage alternatives (da Graca et al. 2004). In favorable conditions, high levels of secreted DAF-7/TGF- β bind and activate the DAF-1/4 receptor kinases in target tissues. These receptors are thought to phosphorylate DAF-8 and DAF-14 SMADs, resulting in their nuclear activation, where they antagonize a complex of DAF-3/SMAD and DAF-5/SNO-SKI, and promote energy utilization and reproductive growth (Fig. 2). In unfavorable conditions, reduced or absent DAF-7/TGF- β signaling permits the DAF-3/DAF-5 complex to specify dauer programs, energy storage, and other traits. In addition to these core components, several other loci have been identified as modulators of the pathway (Daniels et al. 2000; Morita et al. 2001; Aoyama et al. 2004; Wang and Levy 2006).

Intriguingly, expression of DAF-4/type II receptor or DAF-5/SNO-SKI primarily in the nervous system rescues phenotypes throughout the body, suggesting that downstream secondary hormones ultimately govern the dauer decision (Inoue and Thomas 2000; da Graca et al. 2004). Consistent with an endocrine mechanism, expression profiles reveal that TGF- β signaling regulates ILPs, as well as cytochrome P450s implicated in steroid hormone production (Liu et al. 2004). Additional evidence also reveals substantial cross-talk with IIS. Notably, TGF- β *Daf-c* mutants are partly suppressed by *daf-16/FOXO* (Vowels and Thomas 1992), and cause DAF-16/FOXO to be nuclear localized (Lee et al. 2001). Moreover, DAF-3/SMAD and DAF-16/FOXO share many putative target genes and often have associated binding sites, as revealed by expression profiling (Liu et al. 2004; Shaw et al. 2007). Interestingly, vertebrate SMADs and FOXO also cooperate in cytosolic responses in epidermal, neural, and muscle development (Seoane et al. 2004; Gomis et al. 2006; Allen and Unterman 2007). Until recently, it was thought that cross-talk between TGF- β and IIS in the worm was limited to dauer formation, and that TGF- β signaling had little influence on adult longevity. However, many of the TGF- β *Daf-c* mutants are substan-

tially long lived in a manner dependent on DAF-16/FOXO, when animals are treated with FuDR to suppress death due to egg retention (Shaw et al. 2007). Thus, TGF- β signaling converges on IIS to promote states of survival, and it will be interesting to see if this holds true in other metazoans.

IIS

The IIS pathway is a pivotal regulator of many life history traits, and exemplifies regulatory plasticity. This pathway has been extensively reviewed, so we highlight only salient features here. IIS specifies alternatives of self-preservation and survival, versus rapid growth and reproduction. IIS plays a critical role in dauer formation, but is best known for its influence on life span. Notably, a modest reduction of the pathway by mutation in the insulin/IGF receptor homolog *daf-2* or the PI3-kinase *age-1* results in animals that live one- to twofold longer than wild type (Friedman and Johnson 1988; Kenyon et al. 1993). Closely coupled with longevity are associated traits of resistance to heat, oxidative stress, UV, immune infection, and other forms of stress (Lithgow and Walker 2002; Garsin et al. 2003). Remarkably, reduction of IIS in flies and mice also results in longevity and stress resistance, revealing that both the pathway and process are evolutionarily conserved (Clancy et al. 2001; Tatar et al. 2001; Holzenberger et al. 2003). In the worm, strong *daf-2*/InR mutants also constitutively enter dauer diapause, store fat, are uncoordinated, have extended reproductive periods and reduced broods (Ogg et al. 1997; Gems et al. 1998). However, these traits can be largely uncoupled from adult longevity, revealing that these do not entail obligate tradeoffs (Dillin et al. 2002).

The forkhead transcription factor DAF-16/FOXO has emerged as the key nuclear mediator of longevity and stress resistance, integrating IIS signals to promote survival (Lin et al. 1997; Ogg et al. 1997). Nearly all *daf-2*/InR phenotypes are strictly dependent on *daf-16*/FOXO, revealing that IIS antagonizes DAF-16/FOXO (Kenyon et al. 1993; Gottlieb and Ruvkun 1994). A now classic model for IIS action, based on molecular genetic work in worms and biochemical studies in mammals, links the DAF-2/InR receptor to the nucleus (Fig. 2). It is thought that in favorable environments, secreted ILP agonists bind to the receptor and cause recruitment of the IST-1/IRS adaptor protein (Wolkow et al. 2002), resulting in the activation of the AGE-1/PI3Kinase and production of PIP₃ (Morris et al. 1996). In the presence of PIP₃ lipids and the activating kinase PDK (Paradis et al. 1999), the AKT1,2 and SGK kinases phosphorylate DAF-16/FOXO (Paradis and Ruvkun 1998; Hertweck et al. 2004). This potentiates DAF-16/FOXO nuclear export (Henderson and Johnson 2001; Lee et al. 2001; Lin et al. 2001) and cytoplasmic retention by FTT-2/14-3-3 proteins (Wang et al. 2006; Li et al. 2007). Consequently, animals undergo reproductive growth and have a normal life span. In unfavorable environments, IIS is inactivated, DAF-16/FOXO enters the nucleus, where it turns on genes for stress resistance, dauer formation, and longevity. In ad-

dition, the DAF-18/PTEN phosphatase opposes the activity of AGE-1, down-regulating the pathway (Ogg and Ruvkun 1998; Gil et al. 1999; Mihaylova et al. 1999; Rouault et al. 1999).

Nuclear localization of DAF-16/FOXO is not sufficient to recapitulate its physiology, suggesting other activities are involved (Henderson and Johnson 2001; Lee et al. 2001; Lin et al. 2001). In addition to the core pathway, multiple inputs converge onto DAF-16/FOXO including several kinases such as JNK (Oh et al. 2005), MAPK (Nanji et al. 2005; Troemel et al. 2006), and STE20-like (Lehtinen et al. 2006) and AMP-dependent kinases (Apfeld et al. 2004; Greer et al. 2007). Similarly, various nuclear complexes, including heat-shock factor (Hsu et al. 2003), β -catenin (Essers et al. 2005), sirtuin protein deacetylase (Berdichevsky et al. 2006; Wang et al. 2006), SMK-1 nuclear coregulator (Wolff et al. 2006), and DAF-12 nuclear receptor (Berman and Kenyon 2006), modulate distinct aspects of DAF-16/FOXO function.

Further signaling diversity is achieved through ILPs, which number 38 in the worm (Pierce et al. 2001; Li et al. 2003). Interestingly, some function as receptor agonists (e.g., INS-7) and others as antagonists (e.g., INS-1) (Pierce et al. 2001; Murphy et al. 2003). Expressed primarily in neurons, but also in gut, muscle, and other tissues, the ILPs presumably work combinatorially to carry out multiple aspects of IIS biology. Importantly, *daf-28*/ILP is transcriptionally inhibited by dauer pheromone and low food, showing clear regulation by sensory cues (Li et al. 2003). Moreover, proteins involved in synaptic transmission such as UNC-64/syntaxin and UNC-31/CAPS (Ailion et al. 1999; Munoz and Riddle 2003), as well the conserved ASNA-1/ATPase, govern ILP release (Kao et al. 2007).

In wild-type adults, DAF-16/FOXO nuclear localization is regulated in response to environmental stress. Oxidative challenge, heat, and food deprivation send FOXO into the nucleus, giving visible molecular evidence of plasticity (Henderson and Johnson 2001; Lee et al. 2001; Lin et al. 2001). The transcriptional output of FOXO includes genes that mitigate stress and promote repair, including those involved in ROS detoxification, heat shock, innate immunity, heavy metal stress, and xenobiotic detoxification (McElwee et al. 2003; Murphy et al. 2003). Moreover, expression changes suggest increased levels of gluconeogenesis, glycolysis, and β oxidation. Targets that are repressed include genes involved in growth (e.g., TOR pathway components, Jia et al. 2004) and reproduction (e.g., vitellogenins). Interestingly, *daf-2*/InR and *daf-16*/FOXO regulate dauer formation and longevity cell-nonautonomously, principally from neurons and intestine, suggesting that downstream targets include hormones (Apfeld and Kenyon 1998; Wolkow et al. 2000; Libina et al. 2003). Accordingly, target genes include ILPs themselves, such as INS-7, as well as numerous cytochrome P450s and short chain dehydrogenases that could be involved in steroid hormone metabolism (McElwee et al. 2003; Murphy et al. 2003). Hormonal communication between tissues reflects a

high level of systemic decision-making critical to plasticity.

Neurosensory control of longevity

One of the most provocative findings is that sensory perception also influences adult life span, primarily through IIS. Many of the mutants involved in sensory signal transduction, including cilium structure mutants, *tax-4*/cGMP channel subunit, various G-proteins, and the *str-2*/GPCR extend adult life span to various extents (Apfeld and Kenyon 1999; Alcedo and Kenyon 2004; Lans and Jansen 2007). Similarly, ablation of the amphid sheath cell or specific gustatory (ASI and ASG) and olfactory (AWA and AWC) neurons modestly prolong life (Fig. 1B). Interestingly, ablation of ASK and ASJ suppresses longevity due to ASI loss, suggesting a neuronal relay that influences life span (Alcedo and Kenyon 2004). These manipulations are thought to down-regulate ILP agonists or up-regulate ILP antagonists, thereby activating transcription factor DAF-16/FOXO. Accordingly, sensory mutants result in FOXO nuclear translocation and longevity is often largely DAF-16/FOXO-dependent (Apfeld and Kenyon 1999; Lin et al. 2001). Interestingly, food derived odors can curtail the life extension due to dietary restriction in *Drosophila*, and olfactory mutants such as *or83b* are long lived (Libert et al. 2007). Moreover, insulin is released in response to the smell and sight of food in humans (Sjostrom et al. 1980). Altogether these observations suggest that perception—one of the clearest examples of neural plasticity—can deeply impact organismal metabolism, development, and life span.

Serotonin

Serotonergic transmission is an evolutionarily ancient signaling pathway that couples food and stress signals to

various parts of the body. Serotonin can work in classical synaptic transmission or at a distance as a neurohumoral modulator of peripheral tissues. Moreover, it regulates synthesis and release of a wide variety of neuropeptides, hormones, and cytokines to influence physiology and behavior related to satiety, energy expenditure, immune function, and thermoregulation (Lucki 1998; Mossner and Lesch 1998). Similarly, serotonergic signaling in *C. elegans* plays a role in adaptive behavior, physiology, development, and pathogen avoidance, coupling sensory information to IIS and TGF- β signaling pathways (Fig. 3; Sze et al. 2000; Zhang et al. 2005; Liang et al. 2006; Chase and Koelle 2007).

TPH-1 tryptophan hydroxylase is the rate-limiting enzyme for serotonin biosynthesis.

In *C. elegans*, *tph-1* mutants exhibit depressed feeding and egg retention—behaviors seen in wild type under starvation conditions (Sze et al. 2000). In addition, mutants display increased fat deposition and weak Daf-c phenotypes at all temperatures. Notably, the latter phenotypes are suppressed by both *daf-3*/SMAD and *daf-16*/FOXO, suggesting inputs onto both TGF- β and IIS pathways. Accordingly, *tph-1* mutants synergize with *daf-7*/TGF- β mutants for Daf-c phenotypes and depress *daf-7*/TGF- β expression in ASI. Moreover, *tph-1* mutants induce DAF-16 nuclear accumulation, evoke resistance to heat stress and immune challenge, and up-regulate SOD-3 expression—all in a *daf-16*/FOXO-dependent manner (Liang et al. 2006). Conceivably, serotonin impacts IIS by regulating production of ILPs, but this has not yet been shown. Consistent with reduced IIS signaling, *tph-1* mutants also exhibit an extended reproductive period, but surprisingly, demonstrate normal longevity (Sze et al. 2000; Murakami and Murakami 2007). By contrast, the activity of two different serotonin receptors, *ser-1* and *ser-4*, reduce and extend adult longevity, re-

Figure 3. Heterochronic loci and control of developmental timing. The heterochronic pathway controls temporal development specifying stage appropriate programs for each larval stage. Upon hatching, food signals lead to up-regulation of *lin-4*/miRNA, which down-regulates its targets LIN-14/NUCLEAR PROTEIN and LIN-28/RNA BINDING PROTEIN, resulting in L1-to-L2 transitions. Up-regulation of *let-7* microRNA family members (*mir-48*, *mir-84*, and *mir-241*) down-regulate *hbl-1*/HUNCHBACK to trigger the L2/L3 transitions. DAF-12/NHR integrates environmental signals from the dauer pathways (cGMP, serotonin, insulin, and TGF- β). In unfavorable environmental conditions, unliganded DAF-12 together with its corepressor DIN-1/SHARP shut down the heterochronic circuit and specify dauer development. In favorable environmental conditions, liganded DAF-12 advances the heterochronic circuit to the L3 stage, and thus promotes reproductive development and maturation.

(for details, see Fig. 2 and the text). Several gene products control late larval development by preventing expression of LIN-29/ZnF transcription factor, which is instructive for adult development. The larval-to-adult transition is triggered through expression of *let-7*/miRNA, which leads to down-regulation of LIN-41/RBCC protein and up-regulation of LIN-29/ZnF transcription factor. Not all heterochronic activities are shown.

spectively, perhaps neutralizing one another's effect (Murakami and Murakami 2007). Importantly then, serotonergic signaling converges on IIS, coupling sensory information to the stress response. Similarly, in humans, drugs that augment serotonergic signaling may improve insulin sensitivity (Lam and Heisler 2007).

TPH-1 is expressed in a handful of serotonergic neurons, including ADF. In accord with cell ablation experiments described above, TPH-1 activity in ADF regulates dauer, DAF-16 nuclear localization, and stress responses (Liang et al. 2006). TPH-1 expression in ADF itself is down-regulated in response to starvation and high temperature. Sensory transduction mutants, *ocr-2* and *osm-9*, which encode TRPV ion channel subunits, reduce TPH-1 expression, while CaM-kinase gain-of-function mutants suppress this phenotype (Zhang et al. 2004). Consistent with a unified pathway, *ocr-2*, and *osm-9*, like *tph-1*, enhance the Daf-c phenotype of *daf-7/TGF- β* mutants. This has led to a model whereby food cues result in opening of TRPV channel subunits. Ca²⁺ influx activates CaM-kinase, which in turn stimulates nuclear transcription of the *tph-1* gene. Intriguingly, TPH-1 expression itself is also regulated by IIS and TGF- β pathways: *tph-1::gfp* is down-regulated in *daf-2/InR* mutants but up-regulated in *daf-7/TGF- β* mutants, revealing substantial cross-talk or feedback among the three neuroendocrine pathways (Estevez et al. 2006).

Steroid hormone signaling

Nuclear receptors are transcription factors that often respond to lipid hormones to regulate gene transcription, and are well poised to coordinate life history traits. Typically, they contain an N-terminal DNA-binding domain (DBD), consisting of paired C4 Zn fingers, and a C-terminal ligand-binding domain (LBD), which also docks coactivator and corepressor complexes. The worm genome harbors 284 nuclear receptors, fivefold more than vertebrates, with roughly 15 conserved across taxa (Robinson-Rechavi et al. 2005). Among them, DAF-12/NHR is perhaps best understood for its various roles in dauer formation, fat metabolism, developmental timing, gonadal maturation, and longevity. DAF-12/NHR is most closely related to the vertebrate vitamin D and LXR receptors (Antebi et al. 2000; Snow and Larsen 2000), but regulates reproductive maturation analogous to the estrogen receptor. Genetic epistasis experiments reveal that it works at the end of the dauer pathways, downstream from cGMP, TGF- β , and IIS pathways (Fig. 2; Riddle et al. 1981; Vowels and Thomas 1992; Thomas et al. 1993). Null mutations, which typically reside in the DBD, are *Daf-d*, and suppress all known *Daf-c* mutants in upstream pathways. By contrast, lesions in the LBD are often *Daf-c*, suggesting that loss of hormone binding specifies diapause.

Numerous lines of evidence reveal that DAF-12 is regulated hormonally. Notably, DAF-9 is a cytochrome P450 related to steroidogenic hydroxylases that works proximal to DAF-12/NHR. *daf-9/CYP450*-null mutants are unconditionally *Daf-c*, but will slowly recover to

sterile adults that are stress resistant and long-lived (Gerisch et al. 2001; Jia et al. 2002). These phenotypes are potently suppressed by *daf-12*-null mutants, suggesting that the unliganded receptor specifies states of diapause and survival. DAF-9 is expressed in a pair of neuroendocrine cells called XXX, the epidermis, and the hermaphrodite spermatheca (Fig. 1). The XXX cells are a critical point of signal integration, where many dauer components reside (Ohkura et al. 2003; Li et al. 2004; Hu et al. 2006). However, the most visible DAF-9/CYP450 regulation is seen in the epidermis in response to food, pheromone, temperature, cholesterol, as well as TGF- β , cGMP, and insulin signaling. Interestingly, much of this regulation ultimately depends on DAF-12/NHR, suggesting feedback control (Gerisch and Antebi 2004; Mak and Ruvkun 2004). Consistent with an endocrine mechanism, DAF-9/CYP450 works cell-nonautonomously, while DAF-12/NHR is nuclear and widely expressed (Gerisch and Antebi 2004; Mak and Ruvkun 2004). Another hormone biosynthetic enzyme, DAF-36, is a Rieske-like oxygenase (Rottiers et al. 2006), whose *Drosophila* homolog has also been implicated in ecdysone production (Yoshiyama et al. 2006). DAF-36 resides predominantly in the intestine, revealing that the hormone biosynthetic pathway is distributed among tissues. A distributed biosynthetic pathway may be one way in which different tissues can register their physiologic state. Transport of sterols is likely mediated by Niemann-Pick Type C proteins, NCR-1,2, and possibly the multidrug resistance transporter, MRP-1, whose human homologs are implicated in cholesterol/steroid transport (Sym et al. 2000; Li et al. 2004; Yabe et al. 2005). Indeed, cholesterol deprivation triggers *Daf-c* phenotypes, thus linking dietary sterols directly to dauer signal transduction (Gerisch et al. 2001).

In accord with the hormone hypothesis, endogenous ligands for DAF-12/NHR have been chemically identified as bile acid-like steroids called Δ -4 and Δ -7 da-fachronic acid (DA) (Motola et al. 2006). These molecules transcriptionally activate DAF-12/NHR in the nanomolar range. A related bile acid, 25S-cholestenoic acid also serves as a low affinity ligand to DAF-12 as well as for its mammalian homolog LXR (Song and Liao 2000; Held et al. 2006). As predicted from the genetics, DA supplementation efficiently rescues the dauer and adult longevity phenotypes of *daf-9* mutants. Additionally, DA rescues *Daf-c* phenotypes of upstream IIS and TGF- β mutants, but not those of downstream *daf-12* LBD mutants. As expected for endogenous ligands, DAs are present in wild type but absent from *daf-9* mutants (Motola et al. 2006). Like its vertebrate relatives, DAF-12 assembles with coregulators in a ligand regulated fashion. Notably, DIN-1/CoR, a homolog of mammalian SHARP corepressor, forms a complex with DAF-12 to specify dauer diapause and associated traits (Ludewig et al. 2004). This complex associates in the absence of ligand but dissociates in its presence. Moreover, in the presence of DA, DAF-12 can assemble with mammalian coactivator SRC-1, although endogenous coactivators have yet to be found (Motola et al. 2006). Altogether, these studies

show that from biology to mechanism, steroid control of reproduction is evolutionarily ancient. Furthermore, they provide pioneering evidence that bile acids influence metazoan longevity (Gerisch et al. 2007).

The outline of a branched biosynthetic pathway for DAs has been deduced from the activities of biosynthetic enzymes and known sterol intermediates. Namely, DAF-9/CYP450 carries out the last steps, oxidizing the sterol sidechain to a carboxylic acid (Motola et al. 2006) a reaction that is biochemically orthologous to mammalian CYP27A1, a key enzyme in bile acid synthesis (Russell 2003). DAF-36/Rieske is involved in the first step, converting cholesterol to 7-dehydrocholesterol (Rottiers et al. 2006). Both enzymes are controlled by various upstream inputs of the dauer pathways, providing important links in the endocrine network.

Altogether, this has led to a unified model for dauer formation whereby graded signals from the environment regulate a hormone-dependent switch (Fig. 2). In favorable conditions, cues integrated by the nervous system and perhaps other tissues result in the production of TGF- β and ILPs. Activation of their respective signaling pathways stimulates synthesis of DA. When ligand bound, DAF-12/NHR and presumptive coactivators specify reproductive growth. In unfavorable conditions, failure to produce TGF- β and ILPs results in down-regulation of DA synthesis, whereby unliganded DAF-12/NHR together with corepressor DIN-1/CoR specify dauer diapause and extended survival. Despite the simplicity of this model, many of the identified pathways are unlikely to work in a strictly hierarchical manner and are likely to show feedback. Moreover, many of the mechanistic connections and cellular communication between the various signaling pathways have yet to be determined.

In other animals, regulation of reproduction by similar endocrine pathways suggests these comprise critical components of an evolutionarily ancient mechanism. In *Drosophila*, InR mutants have impaired ecdysteroid biosynthesis and are infertile (Tu et al. 2002). In mice, genetic ablation of insulin signaling in the brain reveals a role in fertility (Bruning et al. 2000; Burks et al. 2000), and IGF-1 and TGF- β signaling in the hypothalamus influence the expression and release of gonadotropes that promote maturation (Bouret et al. 2004; Daftary and Gore 2005). Moreover, TGF- β , IIS, and steroid hormone signaling converge in the ovary to orchestrate folliculogenesis (Castrillon et al. 2003; Park et al. 2005). Further study may reveal intimate connections between neural and dietary cues, and hormones to other aspects of animal life history.

Dietary restriction

Dietary restriction, a reduction of dietary intake without malnutrition, has health benefits and extends the life span of a range of animals, suggesting an evolutionarily conserved process. DR is thought to invoke a regulated mechanism that couples nutrient availability to metabolism, growth, and reproduction. Indeed, worms undergo-

ing DR utilize fat, reduce growth, and diminish reproductive output (Houthoofd and Vanfleteren 2006). Extended life span likely arises as a secondary consequence of increased protection, hormesis, or thrifty metabolism. Until recently, the molecular basis of DR-induced longevity remained obscure. The protein deacetylase SIR-2 is proposed to mediate DR in yeast, worms, flies, and mice (Lin et al. 2000; Rogina and Helfand 2004; Wang and Tissenbaum 2006; Bordone et al. 2007), but this issue remains somewhat unresolved (Kaeberlein et al. 2004; Hansen et al. 2007). IIS is an obvious candidate given the intimate connection between diet, metabolism, and longevity. Indeed, in some DR regimens a role for *daf-16*/FOXO is implicated (Greer et al. 2007), but other regimens suggest otherwise (Lakowski and Hekimi 1998; Houthoofd et al. 2003; Bishop and Guarente 2007; Panowski et al. 2007). Recently, two transcription factors, the FOXA homolog, PHA-4, and the NRF homolog SKN-1 appear to specifically mediate DR-induced longevity in worms (Bishop and Guarente 2007; Panowski et al. 2007). Intriguingly, SKN-1 does so from the ASI neurons, suggesting a hormonal mechanism coordinates the DR response. It remains to be seen whether these functions are evolutionarily conserved. Finally, genetic manipulations that down-regulate TOR kinase signaling, and protein synthesis itself, extend life span, but the relationship to DR and IIS appears complex (Vellai et al. 2003; Jia et al. 2004; Hansen et al. 2007; Pan et al. 2007; Syntichaki et al. 2007).

Body size

Body size is a phenotypically plastic trait that is genetically programmed, but also dynamically regulated. In particular, it would be beneficial to couple environmental cues, like nutrient availability, to appropriate somatic growth. In mammals, body size is principally governed by growth hormone and IGF-1 endocrine axes. In *C. elegans*, the SMA pathway (for small/male tail) regulates body size, male tail development, and immune function (Savage-Dunn 2005). It is represented by a canonical TGF- β pathway distinct from that used for dauer, although the *daf-4*/Type II receptor is common to both. The accumulated evidence suggests that body size is determined by cell volume, rather than number, and is governed by the degree of endoreplication in the epidermis (Morita et al. 2002; Lozano et al. 2006).

Like other traits, body size may be regulated by neurosensory input and diet. Expression of DBL-1/TGF- β in the nervous system is sufficient to rescue body size defects for the whole organism, implying that neural or sensory inputs could regulate growth. Accordingly, mutants in cilium structure (e.g., *che-2*, *che-3*, and *osm-6*) or neurosensory signal transduction (e.g., *tax-2*, *tax-4*, and *kin-29*) result in smaller than normal worms. Conversely, mutants of the *egl-4*/cGMP-dependent kinase result in larger animals, as well as defects in olfactory plasticity (Fujiwara et al. 2002; Lanjuin and Sengupta 2002; Hirose et al. 2003). Many of these mutations also affect dauer formation and longevity. Size differences are

not due to altered nutrient input, since animals often have normal dietary intake and broods. Wild-type animals with reduced food intake, or genetic mimetics of dietary restriction such as *eat-2* mutants, are smaller. Interestingly, DR may reduce growth in part by limiting epidermal polyploidization (Tain et al. 2008). However, dietary intake may work independently of the SMA pathway, since *eat-2 sma* double mutants are even smaller (Morck and Pilon 2006). Conceivably, at the molecular level, growth is regulated through TOR signaling, ribosomal biogenesis, or remodeling by autophagy (Morck and Pilon 2007).

Developmental timing

Temporal patterns of post-embryonic development are determined by the genome, but are highly responsive to environmental conditions and show great diversity throughout the animal kingdom. In *C. elegans*, the heterochronic loci regulate temporal patterning, specifying stage appropriate programs during each of the larval stages in a variety of tissues, including stem cell divisions of epidermal seam cells and migration programs of the gonadal distal tip cells. Mutations in the heterochronic genes transform the temporal identity of life stage programs, such that larval programs are expressed in the adult (delayed) or adult programs are expressed in the larva (precocious). Notably, most identified loci are evolutionarily conserved, including the first discovered microRNAs (*lin-4* and *let-7*), 22-nucleotide-long RNAs that down-regulate gene expression by base-pairing with the 3' untranslated region (UTR) of mRNA targets (Lee et al. 1993; Wightman et al. 1993; Pasquinelli et al. 2000; Reinhart et al. 2000; Lagos-Quintana et al. 2002). These loci have been placed into a regulatory hierarchy by performing genetic epistasis and molecular experiments; essentially the components work as switches to transition from one stage program to the next (Moss 2007). Their study has not only led to important insights into developmental timing, but also into stem cell biology, differentiation, and cancer.

An important question is whether the heterochronic circuit is hard wired, or shows regulatory plasticity. Intriguingly, plasticity is already revealed at the initiation of larval development: Only upon a food signal is *lin-4*/miRNA up-regulated, which in turn down-regulates LIN-14/nuclear protein, enabling the heterochronic circuit to proceed from the L1 to the L2 stage programs (Fig. 3; Lee et al. 1993; Wightman et al. 1993). In the absence of food, animals enter the L1 diapause, sustaining LIN-14 expression (Ambros and Moss 1994). In L2, LIN-14 and LIN-28/RNA-binding protein are further down-regulated by *lin-4* (Moss et al. 1997). In addition, members of the *let-7* microRNA family (*mir-48*, *mir-84*, and *mir-241*) specify the L2/L3 transition, in part through down-regulation of *hbl-1*/HUNCHBACK (Abbott et al. 2005; Li et al. 2005). Perhaps most dramatically, DAF-12/NHR reveals plasticity within the heterochronic circuit itself. It works at the convergence of the dauer and heterochronic pathways, coupling environmental information into the

circuit (Antebi et al. 1998). DAF-12 mutants repeat L2 programs inappropriately at the L3 stage, in epidermis and gonad. By inference, DAF-12 is required for L2/L3 transitions as well as L2/L3d (dauer) transitions. Importantly, in unfavorable environments, DAF-12 shuts down the heterochronic circuit, while in favorable environments, DAF-12 drives forward development toward sexual maturation (Fig. 3). This may be analogous to the way in which nutrient levels regulate the onset of puberty (Frisch 1987).

Late larval development and the larval-to-adult transition are tightly controlled by several loci that prevent expression of LIN-29/C₂H₂ ZnF transcription factor, which specifies terminal differentiation and adult development (Fig. 3; Rougvie and Ambros 1995). These loci include HBL-1/HUNCHBACK (Abrahante et al. 2003; Lin et al. 2003), LIN-41/RBCC (Slack et al. 2000), and DRE-1/F-box protein (Fielenbach et al. 2007). Up-regulation of *let-7*/miRNA in L4 results in down-regulation of *lin-41* and *hbl-1* allowing LIN-29 expression and the larval-to-adult transition (Reinhart et al. 2000; Slack et al. 2000; Vella et al. 2004). Interestingly, circadian rhythm homologs LIN-42/PERIOD, TIM-1/TIMELESS, and KIN-20/DOUBLETIME may also play a role in this transition (Jeon et al. 1999; Banerjee et al. 2005).

Although mammalian circadian rhythm proteins integrate environmental signals, such as daylight cycle and temperature, no such connection has been found in the worm. However, the heterochronic circuit, like the circadian circuit, resets in response to nutrients. For example, many heterochronic mutants are suppressed by transition through dauer or starvation (Liu and Ambros 1991; Euling and Ambros 1996). How this reprogramming is achieved is not understood. Intriguingly, *lin-4* and *lin-14* also impact adult longevity, working through IIS and DAF-16/FOXO (Boehm and Slack 2005). In particular, the *lin-4* mutant is short-lived, while *lin-14* mutants are long-lived in a *daf-16*/FOXO-dependent manner. It is therefore reasonable to speculate that timing circuits might retard or accelerate organismal maturation, with secondary consequences on aging.

Reproduction

Many aspects of reproduction show plasticity, and here we mention only a few. First, brood size is tightly coupled to nutrient availability, and animals with restricted dietary intake have reduced broods (Klass 1977; Lakowski and Hekimi 1998; Houthoofd and Vanfleteren 2006). Similarly, mutants in many of the pathways described above including IIS, steroid, TGF- β , and SMA, have reduced fecundity, but it is unknown whether this reflects regulation or pleiotropy. Secondly, the reproductive schedule can be extended by dietary restriction as well as by reduction in IIS and serotonergic signaling (Gems et al. 1998; Sze et al. 2000; Crawford et al. 2007). Egg laying is an important, often overlooked aspect of reproductive plasticity; wild-type animals retain eggs in response to starvation, which can lead to a process called bagging (Chen and Caswell-Chen 2004). Bagging may be

beneficial, since the progeny that hatch inside feed off the mother's carcass often make it to the dauer stage. Serotonin and TGF- β signaling influence this behavior as well (Schafer 2006). The heterochronic gene *lin-29*/ZnF regulates maturation of the serotonergic egg-laying neuron HSN (Bettinger et al. 1997; Schafer 2006), again suggesting that some plasticity could be exerted through developmental timing pathways. Finally, gonadal development itself is somehow tied to nutrients; animals starved for food or sterols will often have unreflexed gonads, not unlike certain DAF-12/NHR LBD mutants (Antebi et al. 1998; Gerisch et al. 2001).

Evolutionary theory suggests a tradeoff between growth and reproduction and somatic maintenance (Partridge et al. 2005). Given limited resources, energy channeled into one process comes at the expense of another. If so, clearly this cannot be passive since many mutants uncouple food availability, which is unlimited in the laboratory, from reproductive output. Most discussed is the tradeoff between reproduction and longevity (Partridge et al. 2005). Although many long-lived mutants diminish reproduction, some do not, notably weak *daf-2*/InR mutants (Gems et al. 1998; Tissenbaum and Ruvkun 1998). Another example is the germline longevity pathway. Ablation of the germline stem cells through laser microsurgery or mutation extends hermaphrodite life span 50%–60%, suggesting a tradeoff with reproduction (Hsin and Kenyon 1999; Arantes-Oliveira et al. 2002). However, further removal of somatic gonadal support cells results in animals that are still infertile, but yet not long lived, instead suggesting that germline and somatic gonad produce antagonistic signals that reduce or extend life span, respectively. Molecules required for germline longevity include DAF-16/FOXO, KRI-1 ankyrin repeat protein, DAF-12/NHR and hormone biosynthetic enzymes DAF-9/CYP450 and DAF-36/Rieske oxygenase, as well as dafachronic acid and the steroid pregnenolone (Hsin and Kenyon 1999; Gerisch et al. 2001, 2007; Berman and Kenyon 2006; Rottiers et al. 2006; Broue et al. 2007). Genetic analysis suggests a model where in the absence of germline derived signals, KRI-1 and dafachronic acid promote translocation of DAF-16/FOXO into the nucleus of intestinal cells, where it works in conjunction with DAF-12/NHR to extend life. Interestingly, the germline longevity pathway appears to be evolutionarily conserved, as ablation of germline stem cells in *Drosophila* also results in extension of life in a manner that implicates IIS (Flatt et al. 2008). In nature, germline longevity may represent a type of plasticity that links the state of the germline stem cells to the soma. For example, a delay in germline development could delay aging so that reproduction is coordinated throughout the organism.

Perspective

Clearly, many aspects of *C. elegans* post-embryonic development, reproductive maturation, and longevity are plastic and subject to regulation. It begins with perception of the environment through the nervous system and

dietary intake. By coupling environmental information to conserved endocrine signaling pathways, close coordination of states of survival, growth, and maturation can be achieved. Feedback and communication among tissues as well as molecular cross-talk ensure robust decision making. In addition, stochastic factors provide an important source of variation, which impacts these processes.

Despite the wealth of knowledge gleaned from the worm, many questions remain. What specific nutrient cues impact these processes and how are they sensed? How are the environmental cues integrated in the nervous system and transformed into endocrine signals? How is cross-talk achieved between the endocrine pathways? What molecular pathways mediate dietary restriction? Do nutrient sensing pathways impinge directly on timing mechanisms to retard or advance development, growth, and aging? What are the important effectors of these pathways? Although there are many unknowns, these signaling pathways have measurable molecular and physiological outputs, with the potential to yield detailed, systematic, and multidimensional understanding of the relationship between environment, genome, and physiology. It seems plausible that, in the future, systems approaches that combine empirical observations with models of these signaling networks will yield important insights into the plasticity of life history regulation. Because much of the machinery, pathways, and physiology are evolutionarily conserved, studies in these simpler organisms are bound to illuminate similar regulatory plasticity in other animals.

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