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Evolutionary Biology: Patchy Food May Maintain a Foraging Polymorphism

Two naturally-occurring alleles in the nematode *Caenorhabditis elegans* that differ by a single amino acid and cause striking differences in foraging behavior are probably maintained by selection in patchy environments.

Karin Kiontke

One major question of evolutionary biology is how genetic diversity is maintained in natural populations. Darwin figured that natural selection could not only explain how new adaptive variants replace old, less-adaptive variants, but also how different variants can coexist if, for example, the variants allowed different resources to be used. Finches with bigger beaks could crack bigger seeds, reducing competition with smaller-beaked ones. Darwin thought this 'divergence of character' could explain speciation. Since Darwin, mathematical models which describe how evolution could shape genetic variation have multiplied. Density- and frequency-dependent selection, heterozygote advantage, resource partitioning and environmental heterogeneity have all been suggested as mechanism that maintain variation [1]. But it is rare to find a system that is amenable to controlled experimental studies and in which the genetic basis of natural variation is known — especially one affecting a clearly adaptive behavior such as foraging.

Two examples of such variation have been described in two of our best-known model organisms: the solitary *versus* gregarious polymorphism in the nematode *Caenorhabditis elegans*; and the sitter *versus* rover polymorphism in the fruit fly *Drosophila melanogaster*. Both of these polymorphisms influence how the animals forage for food, occur in nature and depend on allelic differences in a single gene. How these polymorphisms are maintained has puzzled researchers for years. In this issue of *Current Biology*, Gloria-Soria and Azevedo [2] report new data suggesting that the foraging polymorphism in *C. elegans* is maintained by a trade-off between dispersal propensity and competitive ability in a fragmented environment.

Natural isolates of *C. elegans* differ in their behavior on food, which in the laboratory is a lawn of *Escherichia coli* in a Petri dish. Animals from the standard laboratory strain N2 forage alone and over the entire surface of the food patch — 'solitary' behavior. Animals from other strains forage at the thick border of the bacterial lawn and do so in groups — 'gregarious' behavior [3]. This behavioral difference depends on a single amino acid difference in the G-protein-coupled receptor NPR-1 [4]. Along with the solitary *versus* gregarious feeding behavior, the *npr-1* polymorphism influences a host of other phenotypes: gregarious animals move faster on food and tend to bury into the agar of their plate [3]; they are better at avoiding hyperoxia [5]; and they adapt faster to elevated ethanol concentrations [6] than solitary worms.

Gloria-Soria and Azevedo [2] have discovered that this polymorphism also influences short-distance dispersal in a fragmented food environment, adding an important piece to the puzzle of how this polymorphism evolved. When placed in the middle

of a plate with 12 food patches in three concentric rings, worms with the solitary *npr-1* allele stayed in the food closest to the middle, whereas most worms with the gregarious allele ventured to the outer food patches. This difference in dispersal propensity is also seen in experiments with single worms, which are more likely to leave a food patch when they carry the gregarious allele. The authors also found that solitary and gregarious worms can partition a continuous food resource. They showed this in a clever experiment with GFP-labeled *E. coli* which allowed them to visualize the effect of worm grazing on the bacterial lawn. As expected, fluorescence of the food is reduced predominately at the border of the lawn when gregarious worms feed on the bacteria; but the fluorescence declines throughout the lawn when a solitary strain is tested. When the two strains were mixed at various proportions, this difference in foraging sites was maintained.

The foraging polymorphism in *D. melanogaster* resembles the *npr-1* polymorphism of *C. elegans* in several aspects: 'rover' larvae with a for^R allele move more when feeding and thus leave longer foraging trails on a yeast-covered Petri dish than 'sitter' larvae carrying the for^s allele [7]. Also, in a patchy food environment, rover larvae move significantly more from food patch to food patch than sitters [8]. As with the *C. elegans* foraging behavior polymorphism, these differences are only apparent when food is present. The foraging polymorphism in *D. melanogaster* is caused by variation in a single gene which encodes a cGMP-dependent protein kinase [9].

Natural populations of *D. melanogaster* comprise 70% sitters and 30% rovers (references in [7]). A recent study [10] concluded that this polymorphism is maintained by negative frequency-dependent selection, although allele frequency is also influenced by density-dependent selection during the larval stage [11]. Under laboratory conditions with low food abundance, each morph has a higher fitness when it is rare. When food is abundant, the sitter morph shows higher fitness. Heterozygote advantage did not appear to play a role [10].

To date, we know much less about natural polymorphisms in *C. elegans*. Only two alleles of *npr-1* were found among 17 *C. elegans* isolates from across the globe [4]. Thus, the existence of these two alleles must predate the global expansion of the *C. elegans* range and should therefore be old. Evidence that both alleles occur together in the same population is still scant, but on two occasions, gregarious and solitary worms were found in the same sample or in the same location at different times (references in [2]). Experiments with a GFP-marked solitary strain and a gregarious wild isolate found no evidence that either density- or frequency-dependent selection maintains this polymorphism in *C. elegans* [12].

Although solitary and gregarious worms can partition a continuous food source, this is not sufficient to allow coexistence. In competition experiments with a continuous food source, worms with the solitary allele of *npr-1* had higher fitness than worms with the gregarious allele in the same genetic background [2]. But when the food environment was fragmented — with several food patches present — the two strains performed equally well. Thus, both alleles should be able to coexist in nature provided their habitat is patchy, unlike the uniform bacterial lawn on a laboratory Petri dish.

Until recently, very little was know about the natural habitat of *C. elegans*. In the last few years, we have learned that *C. elegans* prefers bacteria-rich habitats such as compost or garden soil. Even in compost samples, however, most *C. elegans* individuals were found as dauer larvae [13], an alternative third juvenile stage which is resistant to many stresses, arrests its development and does not feed [14]. Under which natural conditions *C. elegans* reproduces remained uncertain. Lately, populations with feeding larvae and adults of *C. elegans* and other *Caenorhabditis* species were repeatedly isolated from rotting fruit ([15] and M. Alion, M-A. Felix and M. Rockman, personal communication). It is increasingly clear that *C. elegans* shares its habitat with fruit flies and is not a soil nematode but a fruit-worm. It is thus likely that the natural habitat of *C. elegans* is temporary, rapidly changing and patchily distributed like those of *D. melanogaster* and of many nematode species related to *C. elegans* [16–18].

Conditions are unlikely to be uniform across a food resource, and the conditions under which the gregarious and solitary morphs can coexist should be common. These recent advances in understanding *C. elegans* ecology should greatly help us to understand the biological relevance and evolution of the foraging polymorphism in this species. For instance, it is now possible to sample sufficiently large reproducing populations of *C. elegans* to assess the frequency of the two alleles in each population. It should also be possible to follow the colonization of a food resource under more natural conditions, and to study the role of short-distance dispersal. Adaptation to high ethanol concentrations, also influenced by *npr-1,* gains a different importance in a habitat full of yeasts like a rotting apple or peach. Finally, it is quite possible that the similarities between the foraging polymorphisms in *C. elegans* and *D. melanogaster* are not mere coincidences but evolved as a reaction to similar habitat properties.

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Protein Quality Control: On IPODs and Other JUNQ

The accumulation of misfolded cytosolic or aggregation-prone proteins leads to cellular stress. To protect the cell, damaged or aggregated proteins are actively sequestered in two newly discovered quality control compartments, JUNQ and IPOD, which are highly conserved in evolution.

Katrin Bagola and Thomas Sommer

Quality control systems monitor the correct folding, assembly and functionality of cellular proteins. Proteins that are singled out by these systems generally exhibit altered functions and tend to form aggregates. Cells have developed different strategies to cope with defective proteins: if possible, chaperones refold aberrant proteins to restore their native conformation [1], but, if these unwanted proteins cannot be repaired, they are rapidly destroyed by the ubiquitin–proteasome pathway [2,3]. Defects in the breakdown of aberrant polypeptides may result in their aggregation. Formation of aggregates is tightly linked to several neurodegenerative disorders collectively termed 'protein folding diseases'. Current studies, however, suggest that the cellular toxicity is associated with non-native soluble protein oligomers and that the formation of large aggregates is instead cytoprotective [4].

In a recent study aimed at gaining a better understanding of the mechanisms that lead to the formation of protein aggregates, Kaganovich *et al.* [5] found that an increased incidence of misfolded proteins led to their accumulation in two distinct subcellular compartments in both yeast and mammalian cells. Kaganovich *et al.* expressed aggregation-prone proteins as well as substrates that were unable to mature properly due to different defects: in the case of Ubc9^{ts} misfolding is triggered by a thermal shift, whereas the actin E364K mutant fails to fold as a result of the point mutation. Another substrate tested was the von Hippel-Lindau protein VHL, which is expressed in the absence of partner proteins. Under stress conditions, immunofluorescence analysis revealed the formation of two distinct inclusions. Firstly, a juxtanuclear inclusion was formed as a consequence of protein overexpression or proteasome inhibition. Additional stress, like elevated temperature, then led to the development of a second, large perivacuolar inclusion at the cell periphery. Most interestingly, all disease-related amyloidogenic proteins Kaganovich *et al.* [5] tested (Rnq1, Ure2, and the disease-related Huntingtin mutant HttQ103, which contains an extended polyglutamine stretch) form an aggregate that exclusively colocalized with a perivacuolar peripheral compartment, without showing any colocalization with the juxtanuclear inclusion. In contrast to misfolded cytosolic proteins, aggregation of amyloidogenic proteins in the perivacuolar compartment occurred even in unstressed cells. These findings indicate that different classes of defective proteins are sequestered in distinct inclusions. Given that both newly discovered compartments can be found in yeast and mammalian cells, these inclusions thus seem to be evolutionarily conserved.

The ensuing analysis of the protein diffusion kinetics between the two quality control compartments and the cytoplasm revealed that the juxtanuclear inclusion largely harbors misfolded but soluble proteins that can exchange with the cytoplasmic pool. Therefore, this compartment is called 'juxtanuclear quality control' or JUNQ. In contrast, results for the perivacuolar peripheral compartment led to the suggestion that this inclusion contains mostly non-diffusing and probably aggregated substrates, which leads to its designation as 'insoluble protein deposit' or IPOD.

Interestingly, the two compartments have similarities regarding their development and function. The formation of both JUNQ and IPOD was found to depend on the formation of microtubules. Benomyl, a drug that depolymerizes microtubules, led to substrate accumulation in small puncta throughout the cytosol. This implies that both JUNQ and IPOD are formed by an active mechanism that requires the cellular transport machinery. The proposed function of both compartments as quality control compartments implies that molecular chaperones contribute to the formation of JUNQ and IPOD and in the partitioning of substrate proteins to these compartments. Indeed, the cytosolic chaperone Hsp104, which interacts with misfolded or aggregated proteins, colocalizes with both compartments where it may assist in solubilizing aggregated proteins to allow either their degradation or refolding [6]. It should be noted, however, that several *in vitro* studies demonstrated that Hsp104 can fulfill its function only in cooperation with Hsp70 [7–9]. Thus, it remains to be shown whether