How Flower-mediated cell comparison and the immune pathways are connected remains to be determined. It has also been proposed that cell competition could have a tumor suppressor role [14], but there is no evidence of increased tumorigenesis in *azot* mutants.

Cell competition has so far been attributed to increased or decreased ability to proliferate. During adulthood, however, proliferation is very limited, even more so in the nervous system. What determines the competitive power of a cell in this context? The observation of two mechanistically different waves of apoptosis following brain lesion raises the possibility that these two phenomena eliminate different types of damaged neurons. The first wave of apoptosis disposes of physically damaged neurons and could correspond to a Wallerian-like degenerative process. The second wave could remove functionally damaged neurons, i.e. neurons that have lost their presynaptic or postsynaptic partners and are therefore functionally unnecessary in a circuit. Alternatively, the second wave of apoptosis could be disposing of old neurons that are outcompeted by newer ones for the uptake of neurotrophic factors, in a process recapitulating neuronal development [15,16]. Interestingly, during fly retina development, Flower-mediated fitness comparison is used to cull out photoreceptor neurons from incomplete ommatidia that are not functionally useful [17].

With the identification of Flower and Azot, as well as other cell competition effectors such as members of the Toll and immune deficiency pathways, a more complete and complex picture of cell competition is emerging. However, we are still far from fully understanding several fundamental questions regarding this phenomenon. The flower code seems to be the tag that allows comparison of fitness between cells within a tissue, while Azot is the downstream effector of this code. But how is the absolute fitness of a cell sensed? How is this information transmitted to the Flower code? The more we learn about cell competition, the more questions arise. The conservation of cell competition processes in animals as diverse as flies and mice illustrates its evolutionary and medical significance.

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Evolutionary Genetics: You Are What You Evolve to Eat

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The evolution of host specialization can potentially limit future evolutionary opportunities. A new study now shows how *Drosophila sechellia*, specialized on the toxic *Morinda* fruit, has evolved new nutritional needs influencing its reproduction.

A critical decision every female makes is where to rear her offspring. For any potential environment she must assess: what is the risk of harm? Are resources suitable? Is competition intense? In insects, this decision often involves

Figure 1. Tasty and nutritious, if you happen to be *Drosophila sechellia*.
A *Drosophila sechellia* male on the fruit of its host plant *Morinda citrifolia* (noni), which is toxic to other closely related *Drosophila* species. (Photo: Corbin Jones and Betty Wanjiru.)

identifying appropriate host plants for oviposition. Many plant-eating insects are highly specialized and selective as to which host plants they use. These specializations allow insects to take advantage of underutilized plant resources and enemy-free spaces, and may even drive speciation. Evolving new specializations presents new challenges: finding the new host, coping with its secondary compounds, and remediating any of its nutritional deficiencies. A new paper by Lavista-Llanos, Hansson and colleagues [1] sheds light on how insects mechanistically and evolutionarily overcome these challenges.

The authors focus on *Drosophila sechellia*, a sister species of *D. melanogaster* and *D. simulans*. Unlike the catholic tastes of its evolutionary cousins, *D. sechellia* primarily uses the fruit of *Morinda citrifolia* as its host on its native Seychelles Islands (Figure 1) [2]. This fruit, a.k.a. 'noni', is noxious to most other *Drosophila*, including *D. melanogaster* [3]. Ripe noni fruit contain high levels of hexanoic and octanoic acid, which are toxic and repulsive to most fruit flies. *D. sechellia*, in contrast, has evolved to tolerate these compounds and exhibits strong behavioral preference for noni [2,4,5].

The remarkable life history of *D. sechellia* has made it a model for understanding how insects evolve new host specializations. Early work characterized *D. sechellia*'s life history and adaptation to noni [2,4,6–8]. Recent work, largely from Bill Hansson's group, has focused on dissecting the neurological and physiological basis of *D. sechellia*'s adaptation to noni [9].

The new paper by Lavista-Llanos *et al.* [1] heads in a new direction: they investigate how the nutritional spectrum of the host plant influences egg production in *D. sechellia*. They confirmed earlier work showing that *D. sechellia* greatly increases its rate of egg production when given noni compared to standard *Drosophila* medium or other fruit [8,10]. This is consistent with an earlier suggestion that egg production was related to the availability and quality of hosts and that specialists often produce larger, but fewer eggs [11]. This idea makes sense when specialists benefit from investing more in a single egg placed on an optimal host versus generalists depositing many smaller eggs across a variety of sub-optimal hosts. As expected, *D. sechellia* has fewer ovarioles and its eggs are larger than those of its generalist sister species [12,13].

As with many animals, provisioning eggs in *Drosophila* uses considerable resources [14]. Not surprisingly *Drosophila* egg development within the ovariole is tightly controlled just prior to the up-regulation of yolk formation. For undernourished *D. melanogaster*, nurse cells, which provide the egg resources, undergo programmed cell death and reabsorption instead of proceeding through normal egg development and yolk formation [15]. In *D. sechellia*, Lavista-Llanos *et al.* [1] show that this developmental checkpoint is associated with low egg production by *D. sechellia* reared on standard *Drosophila* medium [1]. This observation suggests that the standard diet is nutritionally deficient for *D. sechellia* despite normal feeding by *D. sechellia* and this diet having sufficient protein and other nutrients for its sister species.

Given the abundance of octanoic and hexanoic acid in noni and their roles in oviposition-site preference, these fatty acids seemed like obvious candidates. However, supplementing with octanoic acid did not influence egg production nor alter patterns of nurse cell apoptosis. Instead, Lavista-Llanos *et al.* [1] found clues from genetic studies in *D. melanogaster* where reduction in dopamine signaling resulted in females with smaller ovaries and reduced egg production [16]. Prior work also suggested that dopamine regulators were differentially expressed between *D. sechellia* and *D. simulans* [17]. Following these clues, the authors asked if arrest of egg development resulted from an evolutionary change in the dopamine requirements of *D. sechellia*. While adding dopamine had no effect, adding its precursor, L-DOPA, caused a ~40% increase in egg production, a decrease in apoptosis, and an increase of yolk formation in developing eggs [1].

Thus, *D. sechellia* appears unable to get adequate levels of L-DOPA except on noni, which in turn would suggest that noni should have high levels of L-DOPA. Indeed, substantial L-DOPA is present in noni fruit, and chemical depletion of L-DOPA in noni dramatically reduces *D. sechellia* egg production, while increasing nurse cell apoptosis. Furthermore, the low L-DOPA levels in *D. sechellia* raised on the 'standard' diet could be rescued with dietary supplementation. Thus, *D. sechellia* appears to have evolved — in contrast to its sister species — a nutritional requirement for high levels of exogenous L-DOPA.

So, what is the genetic basis for this change in nutritional requirements? Dopamine is derived from L-DOPA, which itself is derived from tyrosine. As supplemental dopamine had no effect while additional L-DOPA did, Lavista-Llanos *et al.* [1] reasoned the evolutionary change must lie in the production of L-DOPA from tyrosine. They examined variation in the gene *pale*, encoding tyrosine hydroxylase, and one of *pale*'s negative regulators, *catsup*. Along with several other substitutions, they identified a 45 bp in-frame deletion (relative to *D. melanogaster*) in *catsup* that removes 15 amino acids, and showed that *catsup* (but not *pale*) expression was reduced in *D. sechellia*. This suggested that these genetic changes might mediate the need for L-DOPA in *D. sechellia*.

To test the effect of *catsup* the authors utilized a clever (and lucky) genetic proxy. One sequenced *D. melanogaster* strain (DGRP-357) has a similar, but not identical, deletion in the *catsup* gene. Using DGRP-357 as an analog for the

D. sechellia mutation being 'introduced' into a *D. melanogaster* strain, they showed reduced egg production and higher apoptosis in DGRP-357 compared to other strains. Much like *D. sechellia*, the phenotype of the DGRP-357 *catsup* allele could be alleviated by addition of L-DOPA.

The authors relate two other traits to dopamine activity: egg size and tolerance to noni. When raised on noni (or food supplemented with L-DOPA or dopamine), females of *D. sechellia* increase their relatively large egg size (already 45% greater volume than *D. melanogaster*) to more than 200% of the egg volume of *D. melanogaster*, while flies on L-DOPA-depleted noni did not increase egg size. Lavista-Llanos *et al.* [1] speculate that these larger eggs could be more tolerant of noni. L-DOPA-induced larger eggs indeed improved survival on noni, but large embryos reared on standard media survived even better than those on their native substrate, suggesting the effect was due to improved maternal health rather than egg size *per se*. Turning to adults, *D. melanogaster* resistance to the neurotoxic effects of noni was improved by dopamine — but *not* L-DOPA — supplementation. Not surprisingly, DGRP-357, with its *D. sechellia*-like *catsup* allele, was not different in survival from other *D. melanogaster* strains. This result is consistent with new work showing that the genomic region near *catsup* does not harbor major resistance genes [18]. These results suggest that dopamine and L-DOPA, while not necessarily tied to *D. sechellia*'s tolerance of noni, play key roles in determining the maternal health of this noni specialist.

The experiments of Lavista-Llanos *et al.* [1] suggest that *D. sechellia*'s dependency on the L-DOPA found in its preferred host plant affects egg size and production. Genetic data in *D. melanogaster* are consistent with the *D. sechellia* allele of *catsup* having a reduced ability to produce endogenous L-DOPA. Like any interesting study, this one raises as many questions as it answers. Given that L-DOPA is a precursor for dopamine, either L-DOPA or another, as yet unknown product of L-DOPA may be required for the increase in egg size and production. However, the physiological basis for this is unclear. Is L-DOPA from noni functioning as a micronutrient in *D. sechellia*, directly supporting metabolism? Alternatively, is it more like insulin, acting as a mediator of nutritional signals. Indeed the mutation in the *catsup* gene is unlikely sufficient to entirely explain the effects observed for a number of reasons. While *D. sechellia* shows a relative reduction of L-DOPA specifically, *catsup* mutants in *D. melanogaster* show a reduction in tyrosine but an increase in both L-DOPA and dopamine [16]. This suggests that there are additional mutations in the gene or other components of the biosynthetic pathway. Furthermore, the genetic changes associated with ovariole number (as opposed to egg number) are separable from the role of *catsup* [6,19].

What also remains unanswered is how the dependence on L-DOPA relates to *D. sechellia* becoming a specialist on noni, despite this fruit's toxicity to *D. sechellia*'s ancestor and other *Drosophila* species. Lavista-Llanos *et al.* [1] propose that the 45 bp deletion in the *catsup* gene was segregating in the ancestral population, and then fixed (perhaps due to a population bottleneck). Individuals from this population feeding on (less toxic) over-ripe noni had increased egg production. Subsequently they evolved increased tolerance to the toxic compounds, increased egg size, and sensory specialization leading to host preferences. While a thought-provoking model, the deleterious effects on fecundity documented by the authors strongly suggest fixation of a *D. sechellia*-like *catsup* allele is improbable in a population not already exploiting ripe noni. We prefer an alternative scenario akin to how humans evolved a dietary requirement for vitamin C [20]: the fixation of the deletion in *catsup* and the L-DOPA nutritional requirement evolved after the association between *D. sechellia* and noni arose. That is, L-DOPA was present at sufficiently high concentrations in noni that the mutation in *catsup* was effectively neutral.

Regardless of how the L-DOPA requirement of *D. sechellia* evolved, the work by Lavista-Llanos *et al.* [1] suggests that evolving a novel specialization may pose a genetic risk as the accumulation of nutritional dependencies may prevent it from exploiting other or future resources. In other words, a mother's evolutionary choice may limit her daughter's options.

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Thyroid Hormones: A Triple-Edged Sword for Life History Transitions

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Thyroid hormones have long been known for their metabolic role in humans and for triggering amphibian metamorphosis. More recently they have been uncovered as an important effector mechanism in seasonality. A recent study of salmon smoltification relates these various biological roles.

Hormones are key regulators of vertebrate development and physiology, allowing coordinated changes to occur in various tissues and helping the organism to cope with environmental variations. Of the numerous types of hormones known in vertebrates, thyroid hormones (THs) are among the most puzzling [1]. First, they are the only known biological iodinated compounds, with thyroxine (also known as T4) containing two coupled tyrosine residues that are iodinated with four iodine atoms. Second, THs are known to control very different processes in different species: in many amphibians and teleost fish they trigger metamorphosis defined as a spectacular post-embryonic life history transition in which a larvae (e.g., the anuran tadpole) is transformed into a juvenile (e.g., the froglet) [2]. However, in mammals, including humans, these hormones play a very different role, regulating many homeostatic processes such as basal metabolism, thermogenesis and heartbeat [3]. Overall, THs increase energy expenditure as exemplified by an increase of oxygen consumption observed after TH treatment. The importance of this pathway in human is well illustrated by the numerous diseases that affect the thyroid axis. Indeed up to 10% of the population in industrialized countries suffer from clear or subclinical thyroid disorders. More recently a third role of THs has emerged as major effectors of seasonality, the process by which species adapt their physiology and reproduction to the annual change in photoperiod [4]. This variety of disparate roles is striking and their relationship has remained mysterious for a long time. However, in a recent issue of *Current Biology*, Lorgen *et al.* [5], studying smoltification in salmon, provide the first example in which the three edges of TH action can be related. They suggest that THs are key coordinators of post-embryonic development, allowing its coupling with external conditions and the adjustment of the internal physiology of the organism.

Smoltification is a post-embryonic life history transition that is specific to salmonid fish (Figure 1). In the most classic cases, such as in the Atlantic salmon studied in Lorgen *et al.*, hatching occurs upstream in rivers and the young fish, the parr, grows in the rivers for one to four years [6]. Then, the darkly pigmented, bottom dwelling, sedentary and territorial parr transforms into a smolt: a silvery fish that starts shoaling, migrates to descend the river and acquires osmoregulation compatible with seawater acclimation. The smolt will reach the sea and grow there for several years before returning to its original river where it will spawn and, most often, die. Smoltification, the transformation of the freshwater-adapted parr to a seawater-adapted smolt, is often considered as a metamorphosis and in line with this notion THs are important regulators of this process. Plasma TH levels increase during smoltification and the pigmentation and behavioral changes observed during smoltification appear to be controlled by THs. In addition THs control the imprinting of the odor of the natal stream that occurs

