appears random, although the old cell end is more likely to inherit large stress-induced aggregates. In asymmetric budding yeast, cell polarity ensures the retention of toxic aggregates in the old mother compartment, but the underlying mechanisms are hotly debated [7–9]. The links between environmental stress, protein aggregation, and cell aging appear to operate in a wide range of cell types and organisms [3]. Thus, uncovering the mechanisms that generate, move, and respond to protein aggregates in yeast cells might identify conserved principles in eukaryotic cell aging. Moreover, control of aggregate formation and movement may be coordinated with additional components of a larger aging system. Cellular aging programs appear to function as dynamic systems that are modulated by the environment. Cell shape and symmetry play an important role in the makeup of an aging program. Asymmetric eukaryotic cells such as S. cerevisiae and Candida albicans display a defined aging program [2], whereas symmetric Schizosaccharomyces pombe cells escape this fate [4]. This may be reflected in prokaryotes, where asymmetric Caulobacter crescentus cells age [10] but symmetric Escherichia coli may not. Initial studies suggested that E. coli cells, which look like a miniaturized fission yeast cell, segregate aging with the old cell pole [11]. However, subsequent work using more optimal growth conditions found a lack of clear aging [12]. The mechanisms that allow symmetric cells to reveal hidden aging programs under stressful conditions may have implications for controlling the growth of immortalized cells such as cancer. Symmetry does not provide cells with immortality, but continued work on these systems may reveal unexpected twists and turns on the way to mortality’s final stop.

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Evolution: Skipping School

Some individual fish like to be close together in ‘schools’, while other individuals like to be alone. A pair of recent papers dissects the genetic basis of schooling behavior, showing that genetic changes in sensory systems are involved when this social behavior is lost during evolution.

Alison M. Bell

Did you ever stand in a Cavern’s Mouth—
Widths out of the Sun—
And look—and shudder, and block your breath—
And deem to be alone

Emily Dickinson

For the small cave-dwelling fish Astyanax mexicanus, the world must indeed appear to be a dark and lonely place. They can’t see — not only because it’s dark, but because they don’t have eyes. It turns out that compared to their sighted relatives of the same species that live in surface waters, A. mexicanus in caves are indeed often alone. While their surface-dwelling relatives swim together in tight aggregations known as schools, cave-dwellers lead a more solitary existence. In many species, individuals aggregate in order to guard themselves against predators or to find food. Within-species variability in schooling behavior has been documented in other fishes. Two new papers [1,2] in this issue of Current Biology tackle the genetic basis for schooling behavior. In the case of A mexicanus, Kowalko et al. [2] show that vision is required for this social behavior, but the loss of schooling behavior in cave-dwellers evolved independently of the loss of vision. In another paper, Greenwood et al. [1] show that this social behavior can be broken into different components that map to different regions of the genome in sticklebacks (Figure 1).

Both cavefish and sticklebacks have proven to be profitable systems for identifying the genetic basis of how traits are lost during evolution. Crosses between surface- and cave-dwelling fish followed by genetic mapping have narrowed-down genomic regions harboring genes related to the loss of eyes [3] and pigmentation [4]. Similarly, genetic mapping based on crosses between marine and freshwater sticklebacks has revealed genomic regions (and even genes) related to the loss of social behavior is more challenging. Behavioral traits are notoriously complex, and social behaviors are particularly fraught with environmental
influences, including, in particular, the behavior of other individuals [7]. That being said, while schooling behavior might at first glance appear to be hopelessly complex given that it requires coordination among school-mates, relatively simple decision rules can generate complex coordinated group movement [8]; therefore, it might be genetically tractable after all. Indeed the two new papers [1,2] show that it is possible to track down regions of the genome that influence schooling behavior. One of the key insights from the stickleback study [3] is that by carefully measuring different elements of schooling (attending to the behavior of others versus position while schooling, for example), the authors could dissect this complex behavior into more manageable components, which then could be mapped to different regions of the genome.

The lab must have been like a science fair while the series of experiments by Kowalko et al. [2] were ongoing. Not only did they build an artificial school of fish that ‘swam’ around a tank, they ran experiments in the dark, put fish on antidepressants and gave their subjects the cavefish equivalent of choices at the optometrist’s office: which do you prefer — light or dark? The authors complemented these studies with surgery (ablating the lateral line, removing lenses from embryos), genomics and QTL mapping.

Altogether this paper comprises a series of diverse and often clever experiments to answer some hard questions.

First, the authors establish that cave-dwelling fish really don’t school, and show that there is a heritable basis to this trait. Why did they lose schooling behavior? The authors mention a few possible reasons — perhaps because there are few predators in caves, and therefore no benefit to hiding behind the group. But their real interest is in how schooling was lost, i.e. the underlying mechanism. One possibility is that the loss of schooling is related to the enhancement of the lateral line in cave-dwellers. The lateral line system is a peripheral mechanoreceptive sensory system that is more developed in cave-dwellers because it improves their ability to find food in darkness [9]. However, the cave-dwellers’ hyperactive lateral line system might interfere with schooling — providing a repulsive rather than attractive force. Kowalko et al. [2] rejected this hypothesis after experimentally ablating the lateral line, and observing no effect on schooling behavior.

Another possibility is that cave-dwellers don’t school because they have higher levels of monoamines such as serotonin and dopamine in the brain compared to surface-dwellers, probably because these systems have been co-opted by cave-dwellers to focus on finding food rather than fighting with others [10]. The authors find some support for this idea — fish on the antidepressant R-deprenyl schooled less.

But the crux of the Kowalko et al. [2] paper is about the possibility that cave-dwellers don’t school because they can’t see each other. It turns out that surface-dwellers like to be in the dark, but when they’re in the dark, they don’t school. Moreover, when the eye lenses of surface-dwelling fish are removed, they don’t school — strong evidence that vision is required for schooling. These observations suggest that when A. mexicanus first entered a pitch-dark cave (probably because they like to be in the dark), they could not see each other, and as vision is necessary for schooling, they didn’t school. Other studies have shown that there is a genetic basis to the loss of vision in cave-dwellers [3]. Therefore, at first the authors thought vision and schooling might have been lost together over evolutionary time if the same genes influence vision and schooling.

Kowalko et al. [2] address this possibility using the time-honored method of a simple genetic cross between cave and surface fish. When the F1 hybrids are crossed, a wide range of schooling behaviors among the F2 hybrid offspring between surface- and cave-dwellers is observed, but schooling segregates independent of vision. For example, there are sighted F2 hybrids who don’t school, and there are F2 hybrids that strongly prefer the dark and don’t school. Therefore, vision is necessary but not sufficient for schooling behavior, and vision, schooling and preference for dark can be uncoupled at the genetic level.

The authors then harnessed the power of genomics to determine whether the same or different regions of the genome influence schooling, preference for dark and vision. Like most interesting questions in science, the answer is a mix of all of the above. By performing QTL analysis on the subset of the F2s that were light-perceiving, the authors could remove the effects of vision on schooling. Altogether they found QTL that influence vision only, QTL that influence schooling only, and some QTL that influence both preference for dark and schooling. In other words, there are both vision-dependent, and vision-independent loci influencing
schooling. This suggests that the loss of schooling in cave-dwellers evolved by multiple genetic changes, only some of which are vision-dependent.

The paper by Greenwood et al. [1] offers a different evolutionary scenario for the loss of schooling in threespine sticklebacks. Like *A. mexicanus*, there are populations of sticklebacks that differ in schooling behavior, and the populations are inter-fertile. Unlike *A. mexicanus*, though, in the stickleback case the populations differ in how tightly they school — sticklebacks from the ocean school tightly together, while sticklebacks in lakes still form schools, but they are looser. Moreover, while the lateral line has a small effect on schooling in *A. mexicanus*, Greenwood et al. [1] found a genetic link between schooling and the lateral line in sticklebacks.

Together, these studies show that schooling behavior in both species was lost through modifications to sensory systems, but that convergent loss of schooling occurred via different sensory mechanisms (vision versus lateral line [11]). It will be fascinating to learn whether this generalization also applies within species. That is, was schooling lost via the same genetic changes in different populations of cavefish, for example? And did the genetic changes originate once (selection on standing genetic variation) or multiple times? How close to this question is tractable in both the cavefish and stickleback systems as there are multiple populations of both species that have independently lost schooling behavior. Another outstanding question is whether the loss of schooling behavior is actually an adaptive response to relaxed predation pressure in caves or lakes, or if it reflects neutral evolution and genetic drift. Perhaps genes influencing schooling accumulate mutations, which eventually result in loss of function and disappearance of the trait. Finally, there will be great interest in knowing the identity of the mutations that can turn a socialite fish into a loner.

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Chromosome Segregation: Not to Put Too Fine a Point (Centromere) On It

Localization of the histone H3 variant Cse4 (CENP-A) at the ~125 base pair point centromere in budding yeast directs assembly of a kinetochore that binds one microtubule. Recent work suggests there is more Cse4 at point centromeres than originally thought.

Thomas J. Maresca

Budding yeast kinetochores assemble at ~125 base pair (bp) sequence-specific centromeres in budding yeast. Specialized centromeric nucleosomes, which contain the histone H3 variant CENP-A (Cse4 in budding yeast) in place of histone H3, serve as an epigenetic marker for centromeres and play a central role in directing assembly of kinetochores from yeast to human. While utilization of a centromeric nucleosome may be well-conserved, the budding yeast centromere is different from most other organisms, which typically have megabase long ‘regional’ centromeres, in that it is genetically encoded by a specific and relatively short sequence of DNA — characteristics that led to its designation as a ‘point’ centromere. The fact that the point centromere is ~125 bp long and a comparable amount of DNA wraps around a conventional nucleosome [2] led to the logical proposition that the budding yeast centromere possesses a single Cse4-containing nucleosome — a theory that was later supported by chromatin immunoprecipitation experiments [3,4]. However, recent tests of the single nucleosome hypothesis have made the ‘pointiness’ of the point centromere a point of contention. Conflicting findings suggest that there could be enough Cse4 molecules for anywhere between 0.5–3 Cse4-containing nucleosomes per centromere [5–9]. A new study by Haase and Mishra et al. [10] appearing in this issue of *Current Biology* argues not only that point centromeres have more Cse4 than is required to support kinetochore assembly but that two distinct populations of Cse4 exist at metaphase kinetochores.