cells. Thus, by watching the dynamics of resynchronization, researchers are beginning to infer the network wiring of circadian oscillators in the brain.

Roberts *et al.* provide compelling evidence that in response to a light pulse the circadian circuit desynchronizes to resynchronize in a heterogeneous but consistent manner. This leads to the hypothesis that desychrony is an intrinsic and useful feature of the circadian circuit. However, key questions remain unanswered. What accounts for the differing responses among single cells? Does phase retuning change synaptic strengths? Roberts *et al.* like to refer to the ''new state of strengthened synchrony'' following a light pulse. This transient state should be contrasted with changes induced by weeks of gradually changing photoperiod. Does phase retuning occur regardless of the time and intensity of the light? Roberts *et al.* tested the effects of a 15-minute light pulse (approximately twice as bright as office illumination) delivered during the late night. Addition of VIP, for example, dose-dependently tumbles the phases of SCN cells and accelerates re-entrainment, independent of when it is applied [10]. Finally, how does synchrony within the circadian circuit translate to behaviors as diverse as sleep/wake, fasting/feeding, and mood? Once we understand the intricacies of circadian circuit entrainment, brief pre-treatments like phase retuning could work to realign the circadian circuit in people suffering from jet lag, shift work, and seasonal affective disorder. Travelers may desynchronize to synchronize.

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Cell Competition: Dying for Communal Interest

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Viable but slower growing cells are eliminated during embryonic development through the process of cell competition. Two new studies highlight a role for cell competition during adulthood as a surveillance mechanism that ensures tissue integrity during homeostasis, regeneration, and aging.

Forty years ago, Morata and Ripoll described a puzzling phenomenon while studying the proliferation of *Drosophila* cells mutant for *Minute* genes [1]. *Minute* mutations affect ribosomal proteins and are homozygous cell lethal; heterozygous flies are viable, but have a slower rate of development. When inducing a mosaic imaginal wing disc populated by both *Minute* heterozygous cells (*M*/+) and wild-type cells (+/+), *Minute* cells are eliminated over time. They termed this phenomenon 'cell competition', because *Minute* cells are eliminated only in the vicinity of wild-type cells (Figure 1A).

Cell competition is not restricted to *Drosophila* wing discs or *Minute* mutations, but is observed in many developmental contexts when mixed populations of cells with different growth rates coexist in the same tissue [2]. For example, overexpression of the oncogene *dMyc* in patches of cells in the wing disc generates 'supercompetitor' cells that can outcompete their wild-type neighbors and populate the whole tissue over time [3,4]. Therefore, wild-type cells can be 'winners' if they compete with less fit cells, or 'losers' if their neighbors are supercompetitors, suggesting that cell competition requires comparison of the relative fitness of different cell

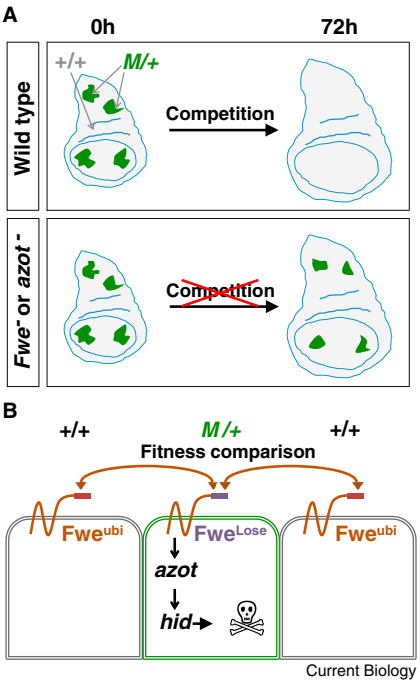

Figure 1. Cell competition in the *Drosophila* wing disc.
(A) In a wild-type background (WT), clones of heterozygous Minute cells (M/+, in green) are cleared from the wing disc 72 h after competition started (top). In a *fwe* or an *azot* mutant background, M/+ cells are no longer eliminated and are still present 72 h after clone induction (bottom). (B) WT cells express the fwe^{Ubi} isoform whereas M/+ cells express both fwe^{Lose} isoforms. Following flower-mediated fitness comparison, M/+ cells start to express *azot* and are eliminated from the tissue through Hid-dependent apoptosis.

populations. Using dMyc-induced cell competition, it has recently been shown that cells are labeled as losers or winners; the 'tags' are different isoforms of the gene *flower* (*fwe*), which encodes a transmembrane protein [5,6]. The *flower* locus can generate three different isoforms, fwe^{Ubi}, fwe^{LoseA}, and fwe^{LoseB}. The distinction between loser and winner cells is mediated by the differential expression of *fwe* isoforms: in the wing disc, loser cells expressing fwe^{Lose} isoforms are eliminated from the tissue through apoptosis while winner cells express the fwe^{Ubi} isoform (Figure 1B).

Although cell competition has been observed in a variety of systems, from the mouse epiblast [7] to the fly wing disc [1], its biological function has remained unclear. It has been proposed to participate in the homeostatic control of tissue growth [4,8]. However, the lack of overgrowth when cell competition or apoptosis is blocked challenged this model. Accumulating evidence now suggests that cell competition is a surveillance mechanism that allows the elimination of 'less-fit' or 'unfit' cells during development, ultimately enabling the production of the 'optimal' organism [8]. To tackle these issues, the Moreno group has extended the study of cell competition to adult tissues [9,10] and is providing substantial evidence in favor of a surveillance mechanism.

In a recent issue of *Current Biology*, Moreno *et al.* [10] use brain regeneration as a paradigm to study the role of cell competition in adulthood. They present evidence of a role for Flower-mediated cell fitness comparison during tissue regeneration. Adult neurogenesis was only reported very recently in flies where quiescent *Drosophila* neuroblasts (neural precursors) appear to be reactivated in order to promote neuronal regeneration upon injury of the optic lobes [11]. After apoptosis of injured cells following brain lesion, a second wave of apoptosis occurs three days after the injury. The second burst of apoptosis differs from the first one in that it depends on the Flower-mediated fitness comparison. Apoptotic cells during this second phase express the Fwe^{LoseB} isoform, contrary to the fit cells that express Fwe^{Ubi} and Fwe^{LoseA}. Forced uniform levels of the Fwe^{LoseB} isoform abolish the second wave of apoptosis, but not the first one. Therefore, after injury, damaged neurons are eliminated first while a subsequent fitness comparison is used to further eliminate unfit neurons.

Other molecules besides Flower, such as SPARC, have been implicated in conferring a 'fitness signature' to a cell [12]. How a cell integrates this information is literally a matter of life and death. In a study published recently in *Cell*, Merino *et al.* [9] identified one of the downstream effectors of Flower that promotes the elimination of loser cells. Using transcriptome analysis of loser cells during dMyc-promoted cell competition, the authors identified a new gene they baptized *ahuizolt* (*azot*), which is upregulated in loser cells (Figure 1B). *azot* is necessary for cell competition, as loser cells are not eliminated through apoptosis in *azot* mutants (Figure 1A). Different levels of Fwe^{Lose} during competition are required for the expression of *azot* in loser cells, indicating that *azot* integrates information from Fwe^{Lose} isoforms and, potentially, other fitness indicator molecules to activate the apoptotic program in loser cells.

The *azot* gene is also expressed in adult tissues following UV irradiation, which suggests that cell competition is not restricted to growth, and could occur throughout the life cycle. Indeed, the median lifespan of *azot* mutants is significantly decreased, whereas, more surprisingly, an extra copy of *azot* leads to increased lifespan. This suggests that elimination of unfit cells benefits the whole organism by maintaining organ function. Moreover, an increased number of neurodegenerative vacuoles were observed in neurons in *azot* mutants, suggesting an acceleration of aging. To directly assess whether the effects on aging and lifespan were due to the lack of *azot*-mediated elimination of unfit cells, the authors performed an elegant experiment: they created a knock-in allele of *azot* where the coding region of the gene has been replaced by the sequence of the proapoptotic gene *Hid*. The authors were able to remove *azot* function while maintaining apoptosis of 'unfit' *azot*-expressing cells. They observed an increase in lifespan compared to wild-type flies, and they were able to rescue the wing morphological defects observed in *azot* mutants. This experiment revealed that elimination of *azot*-expressing cells is sufficient to suppress morphological defects and to increase lifespan in *azot* mutant flies.

These results support the idea that cell competition works as a surveillance mechanism that guides the elimination of unfit cells. These cells, when not eliminated, accumulate, causing morphological defects and suboptimal organ function. At the organismal level this leads to decreased lifespan. A previous study reported that components of the innate immune system, the Toll and immune deficiency signaling pathways, are used to eliminate unfit cells [13]. This suggests that the conceptual similarities between cell competition and the immune system (elimination of unfit cells versus elimination of pathogens) are translated into similarities at the mechanistic level.

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