vision plays in the ordinary lives of animals.

References
1. Wallace, D.L., Greenberg, D.S., Sawinski, J., Rulla, S., Notaro, G., and Kerr, J.N.D. (2013). Rats maintain an overhead binocular field at the expense of constant fusion. Nature *498*, 65–69.
2. Walls, G.L. (1942). The Vertebrate Eye and its Adaptive Radiation. Reprinted 1967 (New York: Hafner).
3. Hughes, A. (1977). The topography of vision in mammals of contrasting life style: comparative optics and retinal organisation. In Handbook of Sensory Physiology VII/5, F. Crescitelli, ed. (Berlin: Springer), pp. 613–756.
4. Hughes, A. (1979). A schematic eye for the rat. Vision Res. *19*, 569–588.
5. Land, M.F., and Nilsson D-, E. (2012). Animal Eyes, 2nd ed. (Oxford: Oxford University Press).

School of Life Sciences, University of Sussex, Brighton BN1 9QG, UK.
E-mail: m.f.land@sussex.ac.uk

http://dx.doi.org/10.1016/j.cub.2013.06.015

Neuron Survival: Say It with Flowers

The Flower protein family is part of a cell–cell communication pathway that regulates cell competition, in which fit cells eliminate less fit neighbors. A new study demonstrates that this pathway can also govern the culling of unwanted neurons during development.

Franck Pichaud

Cell competition ensures the survival of the fittest cells and the elimination of the weaker ones during organogenesis. Morata, Ripoll and Simpson recognized this fascinating phenomenon in *Drosophila* tissues some 35 years ago [1,2]. The process presumably serves as a quality control process in normal tissues [3], but it can also be hijacked by rapidly proliferating cancer cells to kill their wild-type neighbors. It is not clear, however, how cells are able to evaluate the fitness of their neighbors or how fitter cells instruct less fit ones to die. The Moreno lab recently demonstrated that a conserved family of closely related transmembrane proteins encoded by the *flower* locus [4] sits at the core of the cell competition process [5]. In *Drosophila*, one gene locus encodes three Flower isoforms that are generated via alternative splicing — Fwe^{ubi}, $Fwe^{Lose\text{-}A}$ and $Fwe^{Lose\text{-}B}$ [4]. Remarkably, in the developing wing disc epithelium, cells of higher fitness can induce the expression of $Fwe^{Lose\text{-}A}$ and $Fwe^{Lose\text{-}B}$ in the surrounding less fit cells, as a required step in the elimination process [5]. This finding led Rhiner *et al.* to postulate a 'Flower code', in which Flower proteins tag cells according to their relative fitness, thereby enabling the fittest cells to recognize, eliminate and replace the less fit ones [5].

In this issue of *Current Biology*, Merino *et al.* [6] demonstrate that the Flower code is used in the developing fly retina to eliminate a subset of unwanted photoreceptor neurons [6]. These post-mitotic sensory neurons are culled, but not replaced, by fitter ones, which distinguishes the process from classical cell competition seen in proliferating tissues. This mechanism for eliminating newly differentiated neurons could have a crucial role in sculpting neural networks during neural development, as well as during adult neurogenesis.

Each of the 800 clusters of photoreceptors (ommatidia) that form

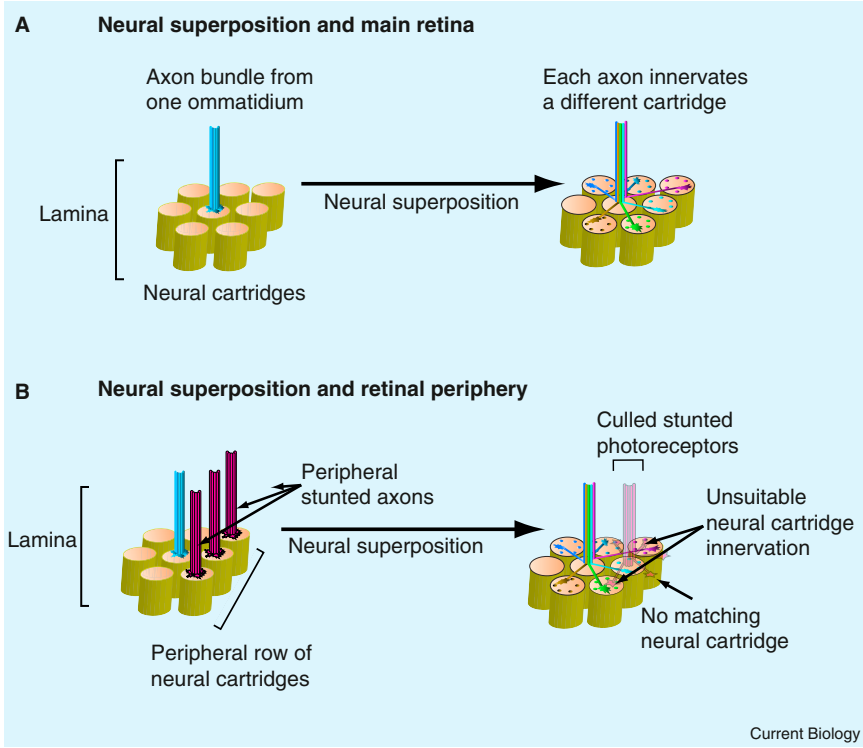

Figure 1. Wiring of the fly retina: neural superposition in the fly optic lobe.

(A) Each of the 800 ommatidial axon bundles promotes the morphogenesis of one neural cartridge in the fly brain. Subsequently, each of these bundles defasciculates such that each photoreceptor axon terminal projects and innervates neighboring neural cartridges. In each neural cartridge, the six pre-synaptic axons are contributed by six photoreceptors that are sharing the same optical axis in the retina (i.e. six photoreceptors that see to the same point in space). (B) At the retinal periphery, the row of stunted photoreceptors (red) contribute to the assembly of a peripheral row of neural cartridges. This row of neural cartridges is subsequently innervated by the axons of the photoreceptors that belong to the neighboring row of ommatidia in the retina. In this context, the unwanted peripheral stunted photoreceptors either innervate neural cartridges in their immediate vicinity or project outside of the lamina plexus. In either case, the elimination of the peripheral stunted photoreceptors prevents them from establishing inappropriate synapses in the lamina.

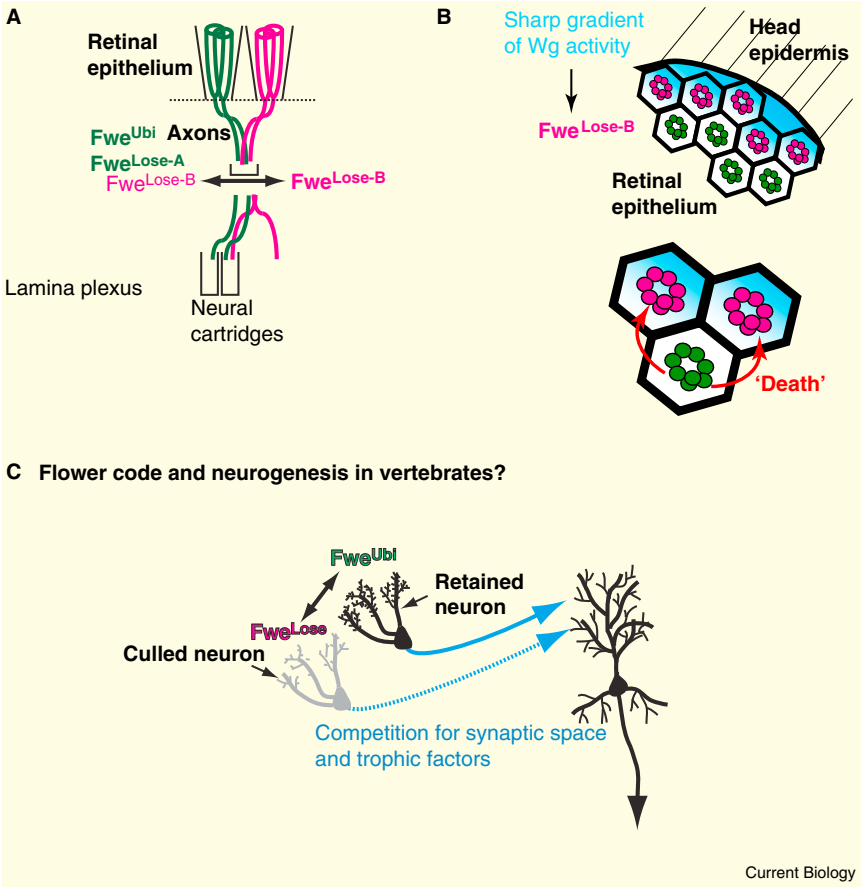

Figure 2. The Flower code and developmentally regulated photoreceptor apoptosis.

(A) Representation of two ommatidia. For simplification, only two photoreceptors per ommatidium are depicted. The photoreceptors that express Fwe^{Ubi} and Fwe^{Lose-A} are shown in green, while the peripheral stunted photoreceptors that express Fwe^{Lose-B} are shown in red. In this model all of these photoreceptors project their axon as part of a fascicle that contains both types of axon (i.e. Few^{Lose-B}(+) and Few^{Lose-B}(–) axons). Information is exchanged at this level (double-headed arrow). (B) The head capsule and accessory cells of the peripheral row of ommatidia promote the formation of a sharp gradient of Wingless activity in the retina. This translates into the expression of Fwe^{Lose-B} in the peripheral stunted photoreceptors. The death signal then comes from the neighboring Fwe^{Lose-B}(–) (i.e. green) photoreceptors, presumably as a result of the crosstalk depicted in (A). (C) Representation of hypothetical granular neurons as found in the adult dentate gyrus in the mammalian brain. These neurons synapse onto pyramidal neurons. In this speculative model and with analogy to the fly retina, Flower isoforms are used to cull unwanted neurons (grey) as they fail to join a neural circuit.

the fly retina is insulated from one another by accessory cells; each ommatidium contains eight photoreceptor neurons, which project to the optic lamina. The developing retina also contains a peripheral row of ommatidia, consisting of stunted photoreceptors that are culled after they have served their purpose, which is to promote the assembly of neural cartridges at the periphery of the lamina plexus (Figure 1). These peripheral neural cartridges are subsequently innervated by the surviving photoreceptors that belong to the adjacent row of ommatidia in the retina, following the principle of neural superposition (for review, see [7]) (Figure 1). The developing fly retina therefore provides an excellent model system to study how neuronal culling contributes to neural circuit formation.

Previous work has shown that Wingless promotes the death of these unwanted peripheral stunted photoreceptors at a precise time in development [8,9]. The head epidermis and accessory cells that surround the peripheral stunted photoreceptors are the source of a sharp gradient of secreted Wingless protein that acts upstream of the *snail* locus, which encodes several related transcription factors. It has been hypothesized that a short-range 'death signal' produced downstream of *snail* instructs these stunted photoreceptors to die [9].

Now, Merino *et al.* [6] show that Fwe^{Lose-B} is turned on specifically in the peripheral stunted photoreceptors at the time they die. They demonstrate that the culling of these cells requires an interface between neurons that lack Fwe^{Lose-B} and neurons that express Fwe^{Lose-B} in two elegant ways. First, they use the flip/FRT technique to create interfaces between photoreceptors ectopically expressing Fwe^{Lose-B} and wild-type photoreceptors that do not express Fwe^{Lose-B}, and they observe that the former cells die by apoptosis. Second, they express Fwe^{Lose-B} in all photoreceptors to abolish any Fwe^{Lose-B}(+)/ Fwe^{Lose-B}(–) interfaces and observe that photoreceptor death is suppressed.

Within the retinal epithelium, there is no direct contact between the Fwe^{Lose-B}-deficient photoreceptors and the unwanted Fwe^{Lose-B}-expressing ones. How then do the two types of photoreceptor communicate? As proposed by the authors, the most likely solution to this puzzle is that Fwe^{Lose-B}(+)/ Fwe^{Lose-B}(–) photoreceptors contact each other via their axons, as they project from the retina to the brain (Figure 2A). As previously shown [9], the *wingless–snail* pathway that functions in the surrounding accessory cells in the retina has already put these peripheral stunted photoreceptors on death row (Figure 2B), so that the Fwe^{Lose-B}-deficient axons just have to pull the trigger to induce their Fwe^{Lose-B}-positive neighbors to die.

Merino *et al.* [6] go on to link the expression of Fwe^{Lose-B} in the peripheral stunted photoreceptors to the Wingless pathway [6]. They show that inhibition of this pathway prevents the expression of Fwe^{Lose-B} in the peripheral stunted photoreceptors and blocks their death. In addition, they generate patches of photoreceptors in the retina that express Fwe^{Lose-B} but either cannot respond to Wingless or do not express *snail*; in either case, Fwe^{Lose-B} is still able to promote the death of these neurons. Together,

these findings indicate that Fwe$^{Lose\text{-}B}$ expression and function are downstream of *wingless* in promoting peripheral stunted photoreceptor apoptosis.

Many neurons are eliminated during the development of the vertebrate nervous system to help sculpt neural circuits. This process continues in the adult hippocampus, where neurogenesis occurs throughout life. In the adult dentate gyrus, 50% of the granular neurons produced are culled as they innervate their target pyramidal neurons [10,11]. In many cases, the culling of unwanted neurons coincides with the peak of synaptogenesis, suggesting that neurons may compete for synaptic space or trophic factors (for review, see [12]).

The Flower protein family is conserved through evolution [13] and it is tempting to speculate that something similar to the Flower code might regulate neuronal death in the mammalian brain (Figure 2C). The Flower proteins were first identified in the adult fly photoreceptor, where they were shown to function as synaptic-vesicle-associated calcium channels that regulate the endocytosis of synaptic vesicle membrane in pre-synaptic nerve terminals [4]. The stunted photoreceptors that Merino *et al.* [6] have used to study neuron culling do not get the opportunity to form synapses [7]. However, at the time of their death, their growth cones have presumably innervated neural cartridges or might have lost their way and wandered outside of the lamina plexus (Figure 1B). This situation might resemble that of newly formed neurons that are attempting to integrate a given neural circuit during brain development or in the adult dentate gyrus (Figure 2C).

The discovery of the Flower proteins and their roles in cell competition, calcium transport, endocytosis and, now, neuron elimination is a major breakthrough, but many questions remain. How is the Flower code recognized by cells? Are there Flower receptors? What intracellular signaling pathway(s) do the proteins activate? Is calcium involved? This new study will certainly spark interest and provide food for thought for future work.

References

1. Morata, G., and Ripoll, P. (1975). Minutes: mutants of drosophila autonomously affecting cell division rate. Dev. Biol. *42*, 211–221.
2. Simpson, P. (1979). Parameters of cell competition in the compartments of the wing disc of. Drosophila. Dev. Biol. *69*, 182–193.
3. Moreno, E., Basler, K., and Morata, G. (2002). Cells compete for decapentaplegic survival factor to prevent apoptosis in Drosophila wing development. Nature *416*, 755–759.
4. Yao, C.K., Lin, Y.Q., Ly, C.V., Ohyama, T., Haueter, C.M., Moiseenkova-Bell, V.Y., Wensel, T.G., and Bellen, H.J. (2009). A synaptic vesicle-associated Ca2+ channel promotes endocytosis and couples exocytosis to endocytosis. Cell *138*, 947–960.
5. Rhiner, C., Lopez-Gay, J.M., Soldini, D., Casas-Tinto, S., Martin, F.A., Lombardia, L., and Moreno, E. (2010). Flower forms an extracellular code that reveals the fitness of a cell to its neighbors in Drosophila. Dev. Cell *18*, 985–998.
6. Merino, M.M., Rhiner, C., Portela, M., and Moreno, E. (2013). "Fitness fingerprints" mediate physiological culling of unwanted neurons in Drosophila. Curr. Biol. *23*, 1300–1309.
7. Meinertzhagen, I.A., and Hanson, T.E. (1993). The development of the optic lobe. In The Development of Drosophila Melanogaster, Volume 2, 1993/12/01 Edition, M. Bate and A.M. Arias, eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory Press), pp. 1363–1493.
8. Lin, H.V., Rogulja, A., and Cadigan, K.M. (2004). Wingless eliminates ommatidia from the edge of the developing eye through activation of apoptosis. Development *131*, 2409–2418.
9. Lim, H.Y., and Tomlinson, A. (2006). Organization of the peripheral fly eye: the roles of Snail family transcription factors in peripheral retinal apoptosis. Development *133*, 3529–3537.
10. Cameron, H.A., Woolley, C.S., McEwen, B.S., and Gould, E. (1993). Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. Neuroscience *56*, 337–344.
11. Dayer, A.G., Ford, A.A., Cleaver, K.M., Yassaee, M., and Cameron, H.A. (2003). Short-term and long-term survival of new neurons in the rat dentate gyrus. J. Comp. Neurol. *460*, 563–572.
12. Bergami, M., and Berninger, B. (2012). A fight for survival: the challenges faced by a newborn neuron integrating in the adult hippocampus. Dev. Neurobiol. *72*, 1016–1031.
13. Petrova, E., Lopez-Gay, J.M., Rhiner, C., and Moreno, E. (2012). Flower-deficient mice have reduced susceptibility to skin papilloma formation. Dis. Model Mech. *5*, 553–561.

Cell Polarity & Epithelial Morphogenesis Laboratory, Medical Research Council, LMCB, University College London, Gower Street, London WC1E 6BT, UK.
E-mail: f.pichaud@ucl.ac.uk

http://dx.doi.org/10.1016/j.cub.2013.06.036

Ecology: The Lunch of a Lifetime

A single meal soon after hatching can reverberate through a lizard's entire life. More generally, events early in life may outweigh genetic factors in fashioning an organism's life history traits.

Richard Shine

One of the longest-running themes in biology is the interplay between nature and nurture: how much of the variation that we see among individuals is due to underlying genetic (heritable) factors, compared to the environmental challenges and opportunities that we encounter during our lives? Nobody doubts that both of these drivers are important. For example, my (regrettably modest) height reflects the diminutive nature of my lineage, ameliorated by my excellent nutritional input early in life (my mother cooked a wonderful roast lamb). But the impacts of my mother's culinary endeavors pale into insignificance compared to the effects now reported by Manuel Massot and Pedro Aragon in this issue of *Current Biology* [1]: a single meal two days after hatching can transform the entire subsequent life of a lizard.

All agree that most phenotypic traits — not just size and shape, but also performance measures like running speed and maze-learning ability — reflect the joint effects of genes and the environment. However, we can still disagree vigorously about the relative importance of those effects. Traditionally, evolutionary biologists have focused on the role of heritable factors — perhaps because these are easier to measure, and amenable to sophisticated quantitative-genetics analyses [2].

CrossMark