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Sensory Organ Size Evolution: A View from *Drosophila*

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In this issue of *Developmental Cell*, Ramaekers et al. (2019) show that changes in *eyeless/Pax6* expression cause differences in compound eye size within and between *Drosophila* species. These findings reveal how changes in the underlying gene regulatory network facilitate eye size evolution and provide insights into organ size regulation.

The gene regulatory network underlying the development of *Drosophila melanogaster* compound eyes has been deciphered through many elegant experiments over the last 30 years or so and is understood in great detail (reviewed in Kumar, 2018; Casares and Almudi, 2016). The eyes develop from the eye-antennal disc (EAD), which is subdivided during the second larval instar by the expression of the transcription factors Cut and Eyeless/Pax6 that specify the antennal and retinal fields, respectively (Figure 1). Eyeless is necessary and, in some contexts, sufficient to trigger eye development by regulating downstream genes that promote retinal fate. This is achieved at the cellular level by a wave of differentiation from the posterior to the anterior of the disc that inhibits cell division and initiates the formation and maturation of the facets (ommatidia) that make up the eye (Figure 1). This serves as a paradigm for our understanding of how regulation of cell division and differentiation builds a complex sensory organ.

The compound eyes of dipterans and other insects exhibit great variation in size and shape as a consequence of changes in the number of ommatidia and/or ommatidia diameter, which results in differences in the contrast and/or acuity that is achieved, and sensory adaptation to different environments and lifestyles (e.g., Keesey et al., 2019; Gonzalez-Bellido et al., 2011). Within and between many dipterans species, changes in eye size are associated with reciprocal changes in other head capsule tissues—such as the antennae and/or interocular distance (face size) (Keesey et al., 2019; Norry and Gomez, 2017; Posnien et al., 2012). This suggests that there are tradeoffs that allow differences in the size of sensory organs as it has been previously reported in other animals (e.g., Hinaux et al., 2016). In contrast to our detailed knowledge of eye development, relatively little is known about how the final size of eyes is determined or how this can be tweaked during evolution to give rise to the great range of eye sizes and pervasive tradeoff with antennal and face size among *Drosophila* species and other insects.

In this issue of *Developmental Cell*, Ramaekers et al. (2019) explored the developmental and genetic bases of differences in eye size within and between *Drosophila* species. They found that a change in the timing of expression of *eyeless* contributes to differences in eye size between strains of *D. melanogaster* and between this species and *D. pseudoobscura*, which has even larger eyes. Furthermore, it appears that this change is also involved in the tradeoff between larger eyes and smaller antennae and face, and vice versa. Ramaekers et al. (2019) found that an intronic enhancer in the *eyeless* locus regulates the timing of *eyeless* expression involved in the partitioning of the EAD in to the retinal and non-retinal fields in both species. Remarkably, they were able to show that a single nucleotide change in this *eyeless* enhancer of *D. melanogaster* helps to determine differences in eye size between different strains of this species (Figure 1). The causative nucleotide in the *D. melanogaster eyeless* enhancer is located in a binding site for the transcriptional repressor Cut. This was demonstrated by using reporter constructs and CRISPR/Cas9 to test enhancer variants with the alternative nucleotides in the Cut binding site and examining the effects on eye development and size. When an "A" is present (as found in a strain of *D. melanogaster* with large eyes) rather than a "G" (as found in a strain of *D. melanogaster* with small eyes), the partitioning of the EAD in to eye and non-eye fields occurs earlier (reflected by faster posterior retraction of *eyeless* expression to the eye primordia), leading to the development of larger eyes, composed of more ommatidia, concomitant with a trend toward reduced antennal and face width (Figure 1). This shows that changing the expression of a single key regulator of eye development can contribute to natural variation in ommatidia number and overall eye size as well as to the tradeoff with antennal and face size. Interestingly, the authors also show that in *D. melanogaster*, the "A" allele appears to have evolved after this species migrated from Africa to other regions of the world including Europe. Therefore, it is possible that whether a fly has a "G" or an "A" at this position is a general mechanism for the evolution and development of smaller or larger eyes, respectively, in non-African populations of *D. melanogaster*.

Although the authors have revealed that *eyeless* underlies natural variation in eye size, there is evidence that evolutionary changes in additional genes also contribute to differences in the size of this important sensory organ within and between species. For example, the single nucleotide change in *eyeless* does not fully explain the difference in eye size between the strains and species examined, and genetic analysis of African populations of *D. melanogaster* suggests that other loci contribute to eye size variation in these

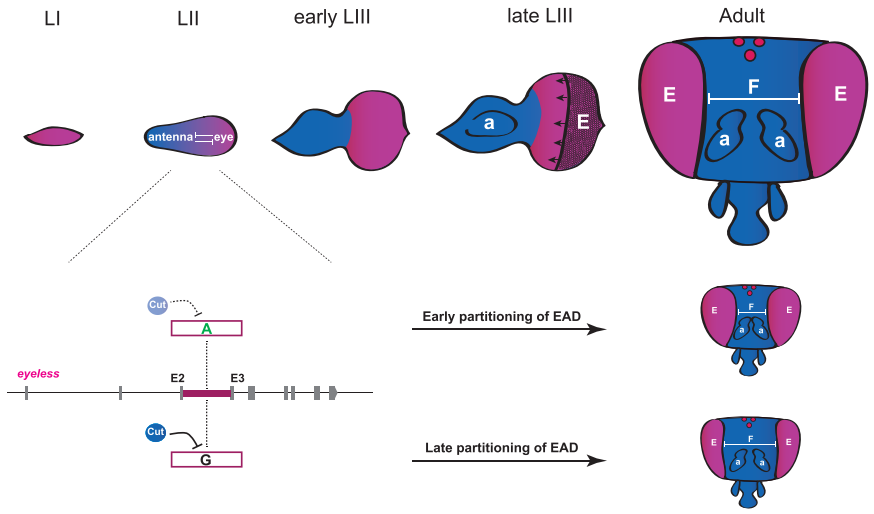

Figure 1. Transcription Factors Eyeless and Cut Determine the Eye and Non-Eye Field Territories during *Drosophila* Head Development

During LI, *eyeless* is expressed in the entire eye-antenna disc (EAD). Later, during LII, the EAD is partitioned in two main territories by the antagonistic activities of Cut and Eyeless to give rise to the future head capsule and antennae, and the prospective eyes, respectively. Results from Ramaekers et al. (2019) indicate that a SNP in a Cut binding site within an intronic *eyeless* enhancer modulates the temporal partitioning of the two territories, promoting relatively higher proliferation rates within the "A" allele flies versus the "G" allele in the eye field. This nucleotide change contributes to the size differences in the eye and the antennae/face of adult heads. LI, first instar larva; LII, second instar larva; LIII, third instar larva; a, antenna; E, eye; F, face; E2, exon 2; and E3, exon 3.

flies (Gaspar et al., 2019). Furthermore, there is also evidence that differences in eye size and face size can be genetically decoupled and potentially evolve independently in some *Drosophila* lineages (Arif et al., 2013). Nevertheless, the exciting findings of Ramaekers et al. (2019) will serve as an excellent platform to explore if *eyeless* and/or other genes contribute to eye size differences among other *Drosophila* populations and species, as well as other insects. This will allow testing of which genetic nodes of the well-characterized regulatory network controlling eye development can evolve to produce eyes of different sizes—crucial not only for understating how gene regulatory networks underlying organ size evolved to produce adaptations in vision but more generally how organ size is determined.

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