Coming to our senses

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Summary

Sensory organs are specialized to receive different kinds of input from the outside world. However, common features of their development suggest that they could have a shared evolutionary origin. In a recent paper, Niwa et al.[1] show that three *Drosophila* adult sensory organs all rely on the spatial signals Decapentaplegic and Wingless to specify their position, and the temporal signal ecdysone to initiate their development. The proneural gene *atonal* is an important site for integration of these regulatory inputs. These results suggest the existence of a primitive sensory organ precursor, which would differentiate according to the identity of its segment of origin. The authors argue that the *eyeless* gene controls eye disc identity, indirectly producing an eye from the sensory organ precursor within this disc.
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Introduction

Except for rare individuals with synesthesia, who can smell colors or see music, we experience input from different sensory modalities as qualitatively different. However, the development of different sensory organs shares many features, suggesting that these organs may have evolved from a common primitive precursor.

Drosophila has three major types of sensory organs: external sensory organs, chordotonal organs and multiple dendritic neurons (reviewed in Ref. 2). The external sensory organs, which include mechanosensory and chemosensory bristles, form from a single precursor cell that divides to give rise to hair, socket, neuronal, sheath and glial cells. Multiple dendritic neurons can also be produced from this lineage in the place of the glial cell;[3] these neurons are internal and some of them have been shown to act as pain sensors.[4] Chordotonal organs, which are internal and sense deformations of the cuticle, consist of a neuron, a scolopale cell, a ligament cell and a cap cell, also derived from a single precursor. The precursor cells for sensory organs are specified by expression of basic helix–loop–helix (bHLH) transcription factors. For the external sensory organs, these transcription factors are encoded by proneural genes belonging to the *achaete–scute* complex;[5] a separate bHLH factor, Atonal (Ato), is responsible for establishing chordotonal precursors.[6] Ato likewise controls the differentiation of a set of modified chordotonal organs in the antenna that constitute the auditory organ of the fly, known as Johnston's organ.[7] More surprisingly, *ato* is also the proneural gene for photoreceptors in the compound eye.[8] Here Ato specifies a single neuron in each ommatidial cluster, the R8 photoreceptor; R8 then recruits additional photoreceptors and accessory cells by secreting Spitz, a ligand for the EGF receptor.[9] Similarly, chordotonal precursors are frequently arranged in clusters that include secondary precursors recruited by EGFR signaling.[10,11] In contrast, external sensory organs are formed from single precursors that send only inhibitory signals to their neighbors.

A single transcription factor, Cut, is sufficient to transform embryonic chordotonal organs into external sensory organs,[12,13] strongly suggesting that the two types have a common evolutionary origin. All these sensory organs also share a dependence on the transcription factor Senseless for their differentiation.[14] However, the parallels between more complex adult sensory organs such as the eye and the auditory organ are less well established.

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Requirements for sensory organ differentiation

Adult sensory organs develop from imaginal discs, but form at specific and invariant positions within these discs. Niwa et al.[1] examine three adult sensory organs that require *ato* for their specification: the eye, Johnston's organ, and a large chordotonal organ in the leg (Fig. 1). They suggest that the location of all three organs has a similar dependence on two morphogens, Decapentaplegic (Dpp) and Wingless (Wg). Blocking Dpp signaling by expressing Dad, an inhibitory Smad, locally represses *ato* expression in the eye, antenna and leg discs.[1] This is consistent with other studies showing that, in the eye disc, Dpp is essential for the initiation of differentiation,[15] and later promotes a "preproneural" state necessary for *ato* expression to be triggered by the Notch ligand Delta.[16,17] It is a pity that the authors do not investigate the role of Hedgehog (Hh) in sensory organ formation in the leg or antenna, as it is an even more critical signal than Dpp for photoreceptor differentiation.[18] Blocking Wg signaling at

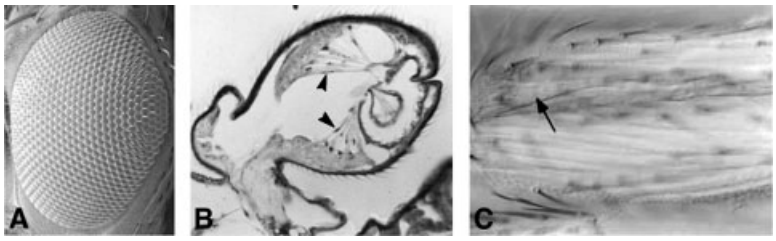

Figure 1. Structures of three *Drosophila* adult sensory organs. **A:** A scanning electron micrograph of the adult eye. **B:** A section through the adult second antennal segment. Arrowheads indicate some of the scolopales of Johnston's organ. (Reprinted from Jarman AP, Sun Y, Jan LY, Jan YN. 1995. Development 121:2019–2030 with permission from The Company of Biologists Limited). **C:** An optical cross-section of the adult femur; the arrow indicates the chordotonal organ. (Reprinted from zur Lage P, Jarman AP. 1999. Development 126:3149–3157 with permission from The Company of Biologists Limited).

least in the leg and eye discs leads to ectopic sensory organ differentiation.[1,19,20] However, Johnston's organ develops from a circular domain in the antennal disc that crosses stripes of both *dpp* and *wg* expression, making it unlikely that Wg antagonizes its formation. The presence of Dpp and the absence of Wg may be necessary, but are clearly not sufficient, conditions for sensory organ differentiation; they may set up a proneural zone from which sensory organs can form.

The temporal control of sensory organ differentiation is also of interest, as all three organs initiate their differentiation at approximately the same time.[1] A small increase in the level of the hormone ecdysone has been observed in mid-third instar larvae, around the time when sensory organ development begins, and is thought to direct wandering behavior and changes in gene expression.[21] Niwa et al. used a temperature-sensitive mutation to prevent ecdysone production at this stage. Although they claim that this abolished formation of all three sensory organs, the effects seem somewhat different in each tissue. The eye disc was dramatically reduced in size, suggesting an effect of ecdysone at a stage prior to *ato* expression, the proneural region for the leg chordotonal organ was not maintained although some sensory organ precursors still formed, and Ato staining in Johnston's organ was merely reduced.[1,22] Still, taken together, these results suggest that some common factors create an environment conducive to sensory organ differentiation (Fig. 2).

The regulatory region of *ato* itself may be a site for integration of this information. An enhancer located downstream of the gene has previously been shown to drive initial *ato* expression in the eye and leg discs.[23] Niwa et al. trace the Dpp responsiveness of this element to two predicted binding sites for the downstream transcription factor Mothers against dpp (Mad) that are essential for its expression.[1] The element is also sensitive to loss of Wg in the leg disc, perhaps because, in this disc, *dpp* is misexpressed in the absence of Wg.[24,25] Its temporal regulation matches that of endogenous *ato*,[1] but it has not been shown to receive a direct input from the ecdysone receptor. Unfortunately, this element is not sufficient for strong *ato* expression in Johnston's organ, which instead depends on a 5′ regulatory region.[23]

What is the role of Eyeless in eye development?

Despite their common activation of *ato*, the development of these sensory organs diverges as they form the specialized structures that allow them to mediate vision, hearing and pro-

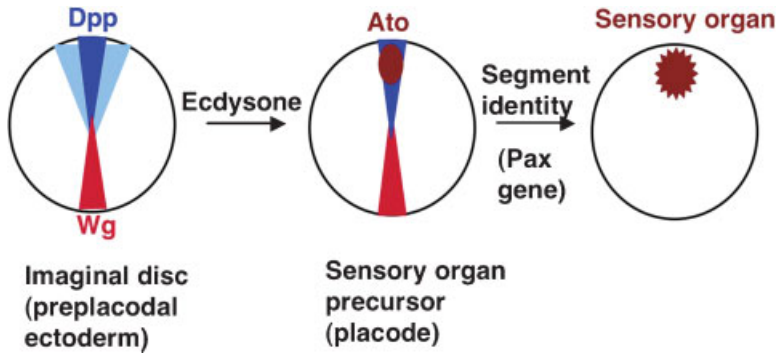

Figure 2. Model showing the requirements for sensory organ differentiation. The patterns of Dpp and Wg expression within the imaginal disc define a region that is competent to differentiate as a sensory organ (light blue). Differentiation is initiated by a temporal signal, most likely ecdysone, that leads to Ato expression. Segment identity genes determine the particular type of sensory organ that will differentiate. In vertebrates, the preplacodal ectoderm may correspond to the competence region, while the placode corresponds to the sensory organ precursor. *Pax* genes may distinguish between different sensory organ types.

prioception. What is responsible for these differences? Homeotic and other selector genes are an obvious possibility. In the absence of all the relevant selector genes, *Antennapedia, Sex combs reduced* and *homothorax* (*hth*), ventral imaginal discs develop into their ground state, shortened legs.[26] Since it does not require selector gene input, the leg chordotonal organ might therefore be the prototype for adult sensory organs. The homeodomain protein Hth transforms this ground state into an antenna,[27] setting in motion the modifications that produce the auditory organ.[28] While not members of a homeotic complex, the *Pax6* genes *eyeless* (*ey*) and *twin of eyeless* (*toy*) are also selector genes that are capable of initiating eye development in other imaginal discs.[29,30] However, they can do so only in restricted regions, close to sources of Hedgehog (Hh) and Dpp, and far from a source of Wg. The responsive regions can be expanded by providing Hh or Dpp pathway activity together with Ey, and coexpression of Wg can block the ability of Ey to induce eye development.[1,31–33] In addition, discs are only competent to respond to Ey at the time at which they normally initiate sensory organ development.[1] These limitations suggest that Pax6 proteins modify an existing program of sensory organ differentiation, rather than creating an eye de novo (Fig. 2).

Further evidence for this interpretation comes from loss-of-function studies. When the extensive cell death in the eye disc that results from loss of *ey* is rescued by expression of the baculovirus protein p35, clusters of Ato-expressing cells can form, although they fail to express the photoreceptor-specific protein Glass.[1] A homeotic function of Ey may thus have been masked by its role in preventing cell death. *ey* and *toy* control more than just the differentiation of the eye; complete loss of either gene results in the absence of the entire head,[34] and ectopic expression of Ey can induce apparent head structures surrounding ectopic eyes.[1] Although the state of the eye disc in the absence of *ey* and presence of p35 needs to be examined further, it would be interesting if it adopted a leg-like fate.

It is also notable that in the absence of *ey*, Ato-expressing cells form small patches or rings, but do not appear to be organized into a self-propagating wave as they normally are in the eye disc.[1,18] In the eye, Ato expression moves from posterior to anterior across the disc, essentially because the secreted protein Hh is both an upstream activator of Ato, and a downstream consequence of its expression. Differentiating photoreceptors shut off *ato* and turn on *hh*, allowing them to stimulate *ato* expression in more anterior cells.[18,35] Since Ey does not appear to affect *hh* transcription,[32] it may control the ability of Hh to regulate its target genes. An important eye-specific target gene is *eyes absent*, which is repressed by the transcription factor Cubitus interruptus (Ci) in the absence of Hh, and requires Ey for its activation.[31,36] Another potentially interesting connection in this regard is that Ski, encoded by a vertebrate relative of the Ey target gene *dachshund*, appears to alter the repressive activity of the Ci homologue Gli3.[37]

Do vertebrate sensory organs develop according to the same plan?

There are signs that vertebrate sensory organs might also have evolved from a common precursor. Many vertebrate sensory organs form from placodes, ectodermal thickenings that all arise in a region anterior or lateral to the cranial neural plate at roughly the same developmental stage.[38] Little is known about the specification of this preplacodal region, but the induction of neural crest, which also forms at the border of the neural plate, has been studied in detail. Neural crest is induced by intermediate levels of BMP signaling in combination with the posteriorizing Wnt, FGF and retinoic acid signals.[39] As Wnt antagonists are expressed in the cranial region that gives rise to placodes,[39] it will be interesting to learn whether placode formation, like *Drosophila* sensory organ differentiation, is dependent on BMP signaling and negatively affected by Wnt signaling.

The ability of *Drosophila Pax6* to specify eye disc identity and thus direct sensory organ development into the eye pathway may also have parallels in vertebrates. *Pax* genes are expressed in many of the placodes: *Pax6*, the *ey* homologue, in the lens and olfactory placodes, *Pax8* and *Pax2* in the otic placode, which gives rise to the ear, and *Pax3* in the trigeminal placode, which forms the sensory ganglion for the face.[38] It is certainly conceivable that these different *Pax* genes direct the differentiation of a prototypical sensory placode along different paths (Fig. 2). Vertebrates may have evolved to use *Pax* genes to specify the majority of sensory organs, while the eye and the chemosensory bristles dependent on *Pox neuro*[40] are the only known examples in flies. bHLH transcription factors are also important for vertebrate sensory organ development. The Ato homologue Math1 is required for the development of both types of hair cells in the mouse inner ear: sensory hairs in the cochlea that mediate hearing, and mechanoreceptors in the vestibular organ that are responsible for balance.[41] The related Neurogenin proteins are used in the trigeminal and epibranchial placodes,[42] while the olfactory system uses an Achaete–Scute homologue, Mash1.[43] The involvement of these gene families in sensory organ differentiation is consistent with the idea that diversification of Paired domain and bHLH transcription factors could have contributed to the evolution of different developmental paths for a primitive sensory placode. If common factors controlled the placement of identical sensory organs within the identical segments of our ancient ancestor, duplication and divergence in these gene families may have provided us with the diversity of sensory experiences we enjoy today.

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