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Sensory Cilia: Generating Diverse Shapes One Ig Domain at a Time

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How morphologically complex cilia form is not well understood. A key regulator of ciliary shape has now been identified that links the establishment of neuronal fate with the formation of cell-specific ciliary structures in *Caenorhabditis elegans*.

Animal nerve cells have the amazing ability to form highly complex structures with exquisite precision. How such structures are formed to ensure proper nervous system function is one of the key questions in neurobiology. Neurons exhibit a number of morphological adaptations that allow them to perform specialized functions. Sensory cilia are membrane-bound, microtubule-based organelles that protrude from the surface of sensory neurons and house components of the sensory signal transduction machinery, including receptors, second messenger-generating enzymes and ion channels. Sensory cilia are thus critical for the translation of environmental cues into neuronal activity. Cilia were first described more than 300 years ago, and extensive research in recent decades has revealed a wide range of ciliary morphologies, from canonical unbranched cilia to more unusual complex patterns of branching and membrane elaboration [1]. Dozens of ciliary proteins have been identified, including the highly conserved IFT (intraflagellar transport) proteins that play a core role in cilia formation. Surprisingly little is known, however, about how morphologically complex cilia form their specialized structures. A study by Howell *et al.* reported in a recent issue of *Current Biology* now shows that a cell surface protein with a single immunoglobulin domain is a key regulator of complex cilia morphology in the nematode *Caenorhabditis elegans* [2].

Small immunoglobulin domain proteins are found throughout the animal kingdom, and they have been previously implicated in nervous system development and maintenance [3–5]. Howell *et al.* undertook an extensive analysis of *oig* (one Ig domain) genes in *C. elegans* and uncovered a remarkable role for one gene, *oig-8*, in controlling the structural complexity of sensory cilia. *oig-8* is expressed in a small subset of neurons, including the olfactory sensory neurons AWA, AWB and AWC. This class of olfactory neurons share morphological and functional characteristics, but show striking differences in the precise organization of their ciliated receptive-endings [6] (Figure 1). AWB neurons exhibit the simplest structure, consisting of two thin ciliary protrusions. AWC neurons are characterized by a large wing-shaped cilium with an extensive membrane elaboration. AWA neurons show the greatest degree of morphological complexity in their cilia, characterized by a highly complex tree-like branched pattern. These neurons thus provide an attractive model for studying how distinct morphological specializations are generated within a class of related neurons.

OIG-8 is a transmembrane protein expressed on the cell surface and localizes to the complex cilia in these neurons. Loss-of-function mutations in *oig-8* result in highly penetrant defects in ciliary morphology for all three neurons, in which cilia show a reduction in branching and membrane elaboration. These defects could only be rescued to restore wild-type morphology when OIG-8 expression was at a level similar to its endogenous level, but not when OIG-8 was over-expressed, suggesting that the precise level of OIG-8 expression is important for its proper function. By carrying out a series of elegant experiments in which the expression levels of OIG-8 were manipulated, Howell *et al.* showed that the level of OIG-8 expression is sufficient to control the degree of ciliary complexity. When OIG-8 is over-expressed in AWB or AWC neurons, their cilia exhibit more complex branched structures similar to those usually seen in AWA neurons. Remarkably, sensory neurons that do not usually express OIG-8 and have simple unbranched cilia can be instructed to undergo ciliary branching by ectopic expression of OIG-8.

The observation that these three neurons with complex cilia each require *oig-8* for their correct ciliary morphology, and yet show striking differences in this morphology, raises the question of how these neurons produce such distinct structures. By performing single molecule fluorescent *in situ* hybridization (smFISH), Howell *et al.* showed that these neurons usually express different endogenous levels of *oig-8*, in a manner that correlates with the degree of structural complexity in their cilia, with AWA neurons expressing the highest level of *oig-8*, AWC neurons expressing an intermediate level, and AWB neurons expressing the lowest level. How are these different expression levels of *oig-8* generated? Expression of *oig-8* in these neurons is not dependent on *daf-19*, the conserved RFX transcription factor that controls expression of core cilia genes [1]. Instead *oig-8* expression is dependent on the activities of neuron-type specific terminal selector transcription factors, which are required for cell fate establishment and control expression of genes required for neuronal identity, such as neurotransmitter-related genes and olfactory receptors. Taking advantage of weak mutations in these terminal selector genes in which cell fates are switched, Howell *et al.* showed that the expression level of *oig-8*, and hence

the degree of ciliary complexity, depends on the pattern of terminal selector gene expression in each type of neuron. The authors have thus demonstrated that distinct ciliary morphologies exhibited by these neurons are controlled by the same terminal selector genes that control other molecular markers during cell fate establishment.

This beautiful study has laid the groundwork to explore several outstanding questions related to how nervous systems develop to form their precise morphological features, how these specific features influence nervous system function, and how nervous systems adapt to allow for appropriate function in a changing environment.

Further work is required to understand the mechanistic details of how *oig-8* transcription is regulated by terminal selector genes to provide distinct expression levels in different neurons. This regulation is likely to be complex, and may provide general insights into how morphological characteristics are acquired following cell fate decisions. The molecular mechanisms through which OIG-8 functions to control ciliary morphology also warrant further work. While OIG-8 expression is sufficient to induce ectopic ciliary branching in some neurons, not all OIG-8-expressing neurons have branched cilia. How do low levels of OIG-8 in AWB neurons promote membrane flattening of cilia, while high levels of OIG-8 in AWA neurons promote extensive branching? OIG-8 function is clearly context-dependent. Identification of genetic and biochemical interactors will help shed light on the molecular mechanisms through which OIG-8 functions. OIG-8 is a cell surface protein with an extracellular immunoglobulin domain that is likely to engage in interactions with extracellular matrix proteins or cell surface proteins expressed on neighboring cells. The ciliated receptive-endings of these neurons are ensheathed by a glial cell, the amphid sheath (AMsh) cell, which is known to express secreted and transmembrane proteins required for proper morphology of neuronal receptive-endings [7,8]. It will be interesting to see how OIG-8 interacts with these extracellular signals, as well as how it interacts with ciliary proteins within the sensory neurons to shape cilia. The distinct environments in which different neurons reside and the distinct levels of OIG-8 expression may influence the nature of these interactions and result in different ciliary morphologies in different contexts.

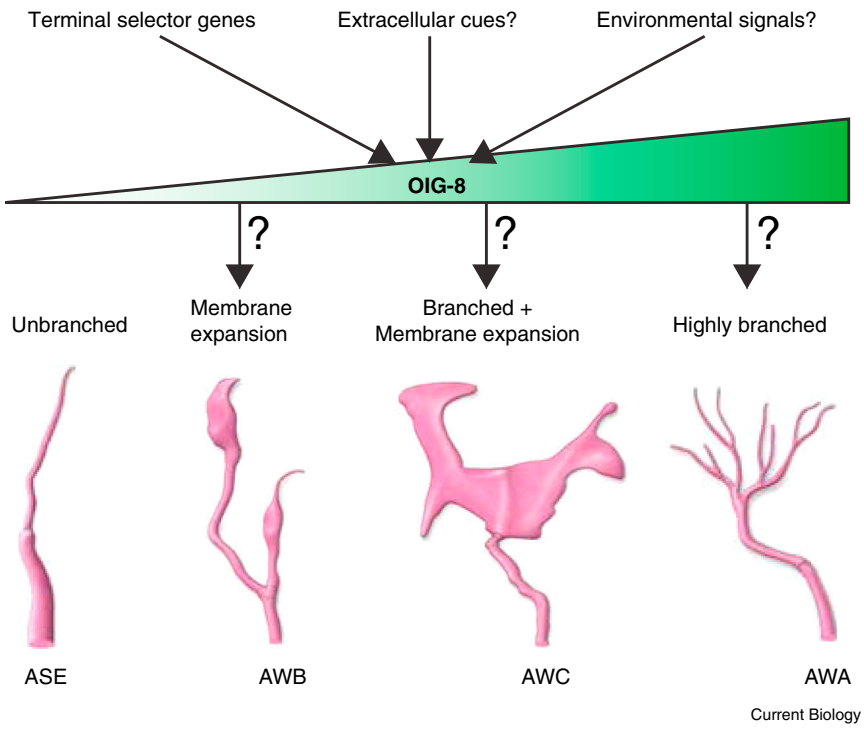

Figure 1. Morphological diversity of sensory cilia in *C. elegans*.
Different levels of OIG-8, which are dependent on terminal selector genes, are proposed to govern morphological complexity in the related neurons AWA, AWB and AWC. Image modified from [14].

Another fascinating question that can now be addressed is the functional consequence of the altered ciliary structures in *oig-8* mutants. It remains unclear why these neurons go to the trouble of developing such complex cilia when simple cilia can clearly function in sensation in other settings. Mutations in core ciliary genes have been extensively studied in *C. elegans* [1,9]. These mutations typically result in a general failure to form cilia, accompanied by strong defects in sensory function. The fact that *oig-8* is required specifically for the branching and membrane elaboration of complex cilia provides a great opportunity to study the role of these specializations. Recent data suggest that the highly branched cilia found on AWA neurons are not required for sensation *per se*, but for desensitization of sensory function following odorant exposure to prevent saturation [10]. It will be intriguing to see if the abnormal ciliary morphologies seen in *oig-8* mutants result in any defects in the dynamics of neuronal activation by odorants or any defects in sensory behaviors.

While the study by Howell *et al.* demonstrated a clear role for *oig-8* in regulating complex ciliary morphology, it remains unclear whether *oig-8* is required to maintain cilia in mature animals. It will be fascinating to see the extent to which *oig-8*-dependent remodeling of cilia can occur under physiological conditions. During larval development *C. elegans* can enter an alternative developmental stage, named dauer, in response to adverse environmental conditions. Entry into dauer is accompanied by remodeling of the cilia of AWC neurons, and Howell *et al.* showed that this remodeling requires *oig-8*. Adult *C. elegans* with mature nervous systems show some complex forms of learning in which olfactory responses are modified as a result of sensory experience [11,12]. Experience-dependent morphological plasticity of sensory receptive endings is an ongoing area of research, and indeed the ciliated receptive-endings of AWB

neurons are known to undergo remodeling in response to sensory deprivation [13]. It will be intriguing to see whether changes in *oig-8* expression levels play any role in this plasticity.

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Circadian Biology: Uncoupling Human Body Clocks by Food Timing

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Synchrony of circadian rhythms between tissues/organs appears critical for health. A new study reports that meal timing, a modifiable temporal cue for the circadian system, can selectively uncouple circadian rhythms in metabolic physiology from the central circadian clock in humans.

With obesity rates and metabolic disorders on the rise, the search for modifiable risk factors other than diet and exercise has received increasing attention. Circadian misalignment and sleep loss have recently emerged as key contributors to metabolic disease [1,2]. Both typically co-occur transiently when travelling across time zones, or more chronically in shift workers, who need to work, be active, and eat at times when the circadian system tunes the body to rest. The circadian system relies on a network of clocks, distributed across all tissues, from brain to periphery, and which are differentially sensitive to *Zeitgebers* (i.e., time cues). For example, while it has been long-recognized that light is the primary *Zeitgeber* for the central clock in the suprachiasmatic nucleus (SCN) of the brain, animal studies have shown that food intake can serve as a major time cue for metabolic tissue clocks, such as the liver, but not for the SCN. Conflicting *Zeitgeber* timing can lead to internal desychrony, a state where different clocks throughout the body are out of sync [3]. Long-term exposure to internal desynchrony is thought to contribute to the adverse metabolic effects of circadian misalignment, including the increased risk for type 2 diabetes among shift workers [4]. The insight that food timing can change the timing of some, but not other, clocks has so far primarily been based on experimental animal data. In a recent issue of *Current Biology*, Wehrens *et al.* [5] now report that this dissociation between central and peripheral clocks can also be induced in humans by manipulating meal timing.

In a seminal paper, Stokkan and colleagues [6] manipulated timing of food availability in rats, and effectively shifted clock gene expression rhythms in peripheral tissues, while the SCN