Using *C. elegans* as a Model to Understand the Relationship Between Primary Cilia Structure and Function
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**Introduction**

Primary cilia are non-motile sensory antennae that protrude from the surface of most human cells. They sense the environment and detect chemicals, light, osmolarity, temperature, and force. Once perceived, cilia then communicate these signals to the cell nucleus to elicit a cellular response.

Defects in primary cilia can cause diseases such as polycystic kidney disease and Bardet-Biedl syndrome (BBS). Thus, by understanding how cilia function, we can contribute to the understanding of human health.

All components necessary for cilia structure and function must be transported to and properly localized within the cilium. Our lab is interested in the relationship between receptor localization, cilia structure, and cilia function.

**C. elegans as a model for cilia structure and function**

[Figure 1. Hermaphrodite and male *C. elegans* (A). Head is to the left. Adult *C. elegans* have 302 neurons (hermaphrodites) or 383 neurons (males) and a subset of these have cilium (B). Panel B from Bae and Barr, 2008.]

Unlike in humans, complete loss of primary cilia in *Caenorhabditis elegans* does not result in death because *C. elegans* have primary cilia on only a subset of neurons. Thus, *C. elegans* are ideal candidates for testing the effects of mutations in genes that affect primary cilia in a living organism.

**Cilia Formation and the Role of XBX-1**

[Figure 2. Transport of ciliary components depends on molecular motors. XBX-1 is a component of the dynein complex, which transports components from the tip of the cilium back to the cell body.]

Primary cilia are constructed through an evolutionarily conserved process termed intrflagellar transport (IFT), which involves the movement of particles to and from the tip of the growing cilium. XBX-1 is a dynein protein that is a required part of the motor complex that transports cilia components.

[Figure 3. PKD-2 localizes to the cell body, cilium base, and cilium proper of *C. elegans* male-specific ciliated neurons. In xbx-1 mutants, increased PKD-2::GFP accumulation is observed in the cilium base (D and E) as compared to wild-type. [B and C]. (Bae and Lyman-Gingerich et al. 2008) The ciliated neurons of xbx-1 mutants also fail to fill with fluorescent dye, indicative of ciliary structural abnormalities (data not shown).]

**Identifying XBX-1 Interactors**

A number of proteins with potential interactions with XBX-1 have been identified both experimentally and computationally by other labs. Putative interactors include:

<table>
<thead>
<tr>
<th>Candidate Interactor</th>
<th>Protein Encoded</th>
<th>Ciliary Function</th>
<th>Neuronal Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHE-3[1]</td>
<td>Dynein heavy chain (DHC)1b isoform</td>
<td>Retrograde transport</td>
<td>+</td>
</tr>
<tr>
<td>DHC-1[2]</td>
<td>Dynein heavy chain</td>
<td>Mitotic spindle alignment</td>
<td>+</td>
</tr>
<tr>
<td>DAF-1[3]</td>
<td>TGFβ type I receptor</td>
<td>Regulation of dauer formation</td>
<td>+</td>
</tr>
<tr>
<td>DAF-19[3]</td>
<td>RXF family transcription factor</td>
<td>Sensory neuron ciliun formation</td>
<td>+</td>
</tr>
<tr>
<td>E01A2.6[5]</td>
<td>Unknown</td>
<td>Unknown</td>
<td>?</td>
</tr>
<tr>
<td>TWK-37[6]</td>
<td>TWik family of potassium channels</td>
<td>Unknown</td>
<td>?</td>
</tr>
<tr>
<td>DNC-1[7]</td>
<td>Dynactin</td>
<td>Unknown</td>
<td>?</td>
</tr>
<tr>
<td>SRI-5[8]</td>
<td>TTM chemoreceptor, see family</td>
<td>Unknown</td>
<td>?</td>
</tr>
<tr>
<td>SRT-61[9]</td>
<td>Serpentine receptor, class C</td>
<td>Unknown</td>
<td>?</td>
</tr>
<tr>
<td>K02A6.1[10]</td>
<td>Unknown</td>
<td>Unknown</td>
<td>?</td>
</tr>
</tbody>
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 wikipedia.org/wiki/celegans

We chose to further characterize the genes *twk-37* and E01A2.6 for the following reasons:

1. *twk-37* encodes a member of a family of potassium channels known to play a role in neuronal signaling
2. E01A2.6 was largely unidentified but was known to have neuronal expression.
3. Both of the genes are located on chromosome 1, and another research project in our lab is examining the role of genes on chromosome 1 using a different experimental approach.

**Ciliary Integrity of *twk-37* and E01A2.6 Mutants Appears Intact**

In wild-type, a subset of ciliated neurons take up lipophilic fluorescent dye. We use this ability as a measure of structural integrity of the cilia.

[Figure 4. A subset of ciliated neurons in the head of wild-type animals fill with dye (A). Anterior to the right. *twk-37* and E01A2.6 mutants both fill with dye similarly to wild-type (data not shown). The percentage of E01A2.6 and *twk-37* mutant worms that filled with dye was not significantly different from wild-type (p=0.93) and p=0.835, respectively, student’s t-test (B).]

We observed PKD-2::GFP mislocalization in *twk-37* mutant but not E01A2.6 mutant animals.

**Summary and Future Directions**

Normal dye-filling of *twk-37* and E01A2.6 mutants suggests hermaphrodite specific ciliated neuron structure is unaffected.

PKD-2 mislocalization in *twk-37* males, suggests male specific ciliary structure or receptor localization is affected by the mutation in *twk-37*.

Lack of phenotypes in the E01A2.6 mutants suggests cilia structure and function may not be dependent on this gene.

**Future Directions:**

1. Characterize localization and function of the wild-type *twk-37* gene product.
2. Continue to assess PKD-2::GFP localization of other genes predicted to interact with XBX-1.

**Funding and Acknowledgements**

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