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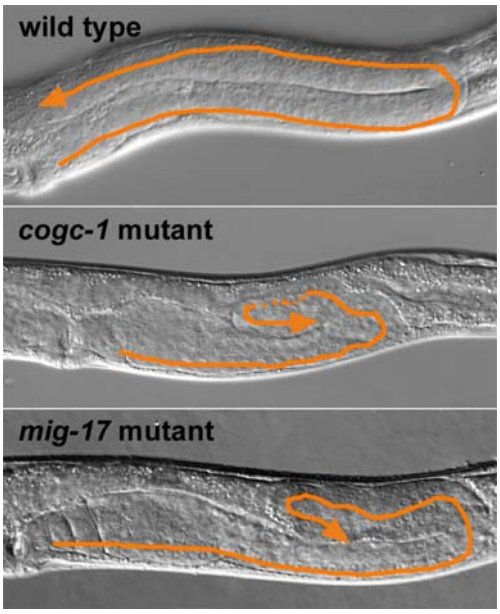
COG-driven machinery: Golgi complex function helps steer cell migration during *C. elegans* gonadogenesis

December 28, 2005 – Cells' ability to migrate, both individually and in coordinated groups, is a fundamental requirement for organogenesis. Migration takes place as the outcome of a collection of processes, from signaling by guidance molecules to rearrangements of the extracellular matrix and cytoskeleton, all of which must be meticulously choreographed and executed in order for cells to reach their appropriate destinations. The roundworm, *C. elegans*, provides a useful system for studying the dynamics of cell migration in its gonadal development, in which distal tip cells (DTCs) at the leading edges of two migrating arms wend their way through the larval body following contralateral U-shaped trajectories. Several labs have focused on how the developing roundworm is able to ensure that these gonadal pathfinder cells stay on course along these stereotyped routes, but the molecular mechanics have yet to be fully worked out.

Now, in a report published in an advance online issue of *Development*, Yukihiko Kubota, a research scientist and colleagues in the Laboratory for Cell Migration (Kiyoji Nishiwaki; Team Leader) describe the involvement of the (Conserved Oligomeric Golgi) COG complex in DTC migration and their interaction with previously identified guidance molecules belonging to the ADAM family of proteases.



U-shaped migratory pathway of wildtype gonad (top) is disturbed in *cogc-1* and *mig-17* mutants, as shown by the meandering phenotype (route marked in orange)

The Nishiwaki lab had previously shown that the ADAM protease MIG-17 is secreted from the body wall musculature in larvae and localize at the gonadal basement membrane, where it promotes the migration of distal tip cells. A pair of other genes, *mig-29* and *mig-30*, identified in the same mutation screen that yielded *mig-17* were found to code for homologs of components of the conserved oligomeric Golgi (COG) complex, which functions in many aspects of vesicle trafficking within the cell and has been identified in species from yeast to human. The genes were renamed *cogc-3*

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and *cogc-1* to reflect this homology, and Kubota et al set out to analyze their role in DTC migration.

In other species, the COG complex comprises eight protein constituents structured as a pair of lobes, which was shown to be true in *C. elegans* as well. The Nishiwaki team then demonstrated the functional importance of each of the COG components by showing that interference by RNAi with the function of any of the eight COGs produced defective DTC migration or malformed gonad phenotypes, an effect that was found to be stronger for lobe A COGs (which includes the proteins encoded by both *cogc-1* and *-3*) than for those in lobe B.

This led Kubota to the possibility that the COG complex might interact with other factors known to be involved in DTC migration, specifically to MIG-23, a Golgi membrane protein the lab's previous work had identified as a regulator of MIG-17 via the addition of sugar residues, a process known as glycosylation. COGC-3 was observed to co-localize with MIG-23 in muscle cells of the body wall, and when the team looked at cogc-3 and cogc-1 mutants, they found that MIG-23 was destabilized and decreased in quantity. Following the evidence trail, they looked next to MIG-17 glycosylation in these mutants and again found that its glycosylation was incomplete resulting in its failure to accumulate at the gonadal basement membrane.

The body of findings from these studies prompted the Nishiwaki lab to develop a picture of the molecular mechanisms underlying DTC guidance in which the COG complex functions to stabilize MIG-23, thereby ensuring the glycosylation of MIG-17 in muscle cells, which then secrete it to remodel the adjacent basement membrane and so steer the distal tip cells on their parabolic pathways. Their work provides the first evidence of the function of the COG complex in an organ-forming process, which is of some biomedical interest as well, as humans carrying a mutation for another COG component, COG-7, develop a glycosylation disorder characterized by multiple developmental defects. Here, as in many aspects of development, what is true in the worm may one day prove to be equally important in man.

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