A Degrading Way to Make an Organ

Jeff Hardin

Building an organ is a precise business. Organ rudiments must often navigate through a complex, three-dimensional terrain as their shape is transformed, and they must do so in a way that is carefully orchestrated with other concurrent developmental events. Many organ rudiments develop as tubular structures that are elaborated as the rudiment grows. In such cases, cells at the tip of the growing tube can be key regulators of organogenesis. Examples include gut formation in echinoderms, the tracheal system of Drosophila, and branching morphogenesis in vertebrates (1). As such growing organ rudiments extend, they must contend with a variety of extracellular matrices (ECMs), some of which may serve as barriers to migration. It has long been presumed that matrix metalloproteases, the major family of proteolytic enzymes responsible for degrading ECM components, play a key role in remodeling the ECM during cell migration (2). On page 2205 of this issue, Nishiwaki et al. (3) provide evidence that just such a protease, encoded by the mig-17 gene, is required for directional migration of another well-studied tubular organ rudiment, the gonad of the nematode Caenorhabditis elegans. Together with other recent experiments in C. elegans, these results provide clear evidence that metalloproteases are important regulators of organogenesis.

The hermaphrodite gonad of C. elegans has two U-shaped arms (see the figure). Both laser ablation (4) and genetic analyses (5, 6) indicate that the shape of the developing gonad is largely determined by the migration of somatic cells at the tips of the growing arms known as distal tip cells (DTCs). DTCs are born during the first larval stage, and they begin to migrate during the second larval stage. Normally, they migrate in opposite directions: the anterior DTC migrates anteriorly and the posterior DTC migrates posteriorly. During the third larval stage, the anterior DTC turns toward the right and the posterior DTC turns toward the left side of the animal, as each migrates across lateral epidermal cells toward muscle cells that lie in two dorsal quadrants. Upon reaching the dorsal muscle cells, the two DTCs turn again, this time leading their respective gonad arms back toward the center of the animal. This labyrinthine migration comes to an end in the fourth larval stage, after the tip of each arm has migrated hundreds of micrometers.

What role does the ECM play in the

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C

Germ cells

Muscle

DTC

Gland

Muscle

MIG-17

Basement membrane

C. elegans gonads on the go. (A) Mid-sagittal views of a C. elegans hermaphrodite larva showing the growth of the two gonad arms (dark gray). The two distal tip cells (DTCs) are shown in red. (B) A "filet" of a hermaphrodite at the first larval stage, opened up along the dorsal midline. Dorsal (D) and ventral (V) muscle quadrants are shown in purple; right (R) and left (L) lateral epidermal cells are shown in beige. The migratory routes of anterior (A) and posterior (P) DTCs in subsequent stages are shown (black arrows). (C) Hypothetical mechanism of MIG-17 release and activity. MIG-17 is produced by muscle cells, but can move to cover the surface of the migrating gonad primordium. It then acts on the extracellular matrix to support DTC migration. ([A] adapted from (9); [B] and [C] adapted from (3)]

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substrates have not been identified for either enzyme, there are several possibilities. One possibility is that both GON-1 and MIG-17 are required for structural remodeling of the ECM during DTC migration. In the absence of such remodeling, DTCs may be physically unable to make appropriate changes in direction. If this is the case, then GON-1 is clearly required earlier or more stringently than MIG-17, given the severity of defects in gon-1 mutants. This suggests that MIG-17 could be required for more subtle remodeling events, either subsequent to the action of GON-1 or concurrent with it.

Another intriguing possibility is that one or both proteases are involved in the modification of matrix-embedded guidance cues to which DTCs normally respond. Several extracellular cues appear to guide the DTCs during their journey, the best-characterized being those affecting dorsal-ventral migration (9). Ventrally, UNC-6/netrin, a secreted protein structurally related to laminin, serves as an extracellular cue whose effects are mediated by its receptors, UNC-5 and UNC-40/DCC (6). The transforming growth factor-β family member UNC-129 may play a similar role dorsally (10). Remodeling of the ECM could affect how migrating cells interact with both of these guidance systems. Although there is no evidence that GON-1 plays such a role, Nishiwaki and co-workers found a marked enhancement of DTC migration defects in mig-17/unc-6 double mutants. This suggests that MIG-17 may be involved in processing or presentation of guidance cues mediated by the UNC-6/UNC-5 system. However GON-1 and MIG-17 act, the demonstration that these proteases play an important role during organogenesis in vivo will likely stimulate the search for other proteases that regulate cell migration during development.