A secreted ADAM, MIG-17, controls cell migration in *C. elegans*

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ADAM family proteins play important roles in animal development. Four membrane-type and seven soluble ADAMs can be found in *C. elegans* genome. Of these, three ADAMs have been functionally characterized. One of them is a transmembrane ADAM, SUP-17, which is homologous to Kuzbanian in *Drosophila* and required for cell-cell signaling (Wen et al., Development 124: 4759, 1997). The other two, GON-1 and MIG-17, are soluble ADAMs required for gonadal leader cell migration (Blelloch & Kimble, Nature 399: 586, 1999; Nishiwaki et al., Science 288: 2205, 2000). We are studying migration of gonadal leader cells to understand the molecular system involving the MIG-17 ADAM.

The anterior and posterior gonadal leader cells called distal tip cells (DTCs) migrate in a U-shaped pattern to form the U-shaped gonad arms during *C. elegans* larval development. The migration of DTCs is coupled with the elongation of gonadal tubes and requires an appropriate interaction between the gonadal and body wall basement membranes. Although the DTCs in *mig-17* mutants can migrate, they meander or wander over the body wall basement membranes. Therefore, *mig-17* does not affect the migration itself, but rather the direction or route of migration. Unlike conventional membrane-type ADAMs, MIG-17 is a secreted protein without a transmembrane domain. MIG-17 is most similar to mouse ADAMTS-1 whose expression is up-regulated with tumor progression (Kuno et al., JBC 272: 556, 1997), although MIG-17 lacks thrombospondin type I repeats. *mig-17* mutation sites and deletion analysis revealed that any of pro-, catalytic, disintegrin-like and cysteine-rich domains are essential for normal DTC migration. Using GFP fusion genes, MIG-17 was found to be produced in and secreted from the body wall muscle cells and subsequently localized on the surface of the gonad (probably on the gonadal basement membrane). Interestingly, MIG-17 begins to localize on the gonad after the first turn of DTCs and this timing of localization coincides with the first sign of DTC migration abnormality in *mig-17* mutants. The disintegrin-like domain and the catalytic activity were required for MIG-17 to localize on the gonad. We recently found genetic interaction between *mig-17* and *mig-27*, another mutant with meandering DTC phenotypes. Furthermore, MIG-17::GFP localized on the gonad surface only weakly in a *mig-27* background, suggesting that *mig-27* may affect the mechanism of MIG-17 reception of the gonad.