

THE CED-2 CRKII, CED-5 DOCK180, CED-10 RAC PATHWAY CONTROLS CELL-CORPSE ENGULFMENT AND CELL MIGRATION, AND CED-10 FUNCTIONS REDUNDANTLY WITH THE MIG-2 RHO-TYPE GTPASE TO CONTROL AXON GUIDANCE

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The engulfment of cells undergoing programmed cell death is controlled by at least seven genes that define two parallel pathways. Mutations in genes of one pathway, which includes *ced-2*, *ced-5*, *ced-10*, and *ced-12*, result in defects both in cell-corpse engulfment and in the migration of the gonadal distal tip cells. *ced-5* encodes a protein similar to human DOCK180. DOCK180 interacts with the oncoprotein Crk and the GTPase Rac. We have cloned the *ced-2* and *ced-10* genes and found that they encode proteins similar to CrkII and Rac, respectively. That *ced-2*, *ced-5*, and *ced-10* act together in a pathway strongly indicates that mammalian CrkII, DOCK180, and Rac functionally interact *in vivo* as well. We have obtained genetic and biochemical evidence supporting a model in which CED-2 recruits CED-5 to the membranes of engulfing and migrating cells, thereby activating CED-10 to control the polarized extension of cell surfaces in both cell-corpse engulfment and distal tip cell migration.

Rac is a member of the Rho-family of GTPases, which includes Rac, Rho, and Cdc42. How Rho-family GTPases interact during animal development is largely unknown. We found that three *C. elegans* members of this family, *ced-10*, *mig-2*, and *rac-2*, function redundantly to control axon guidance. First, ultrastructural studies revealed that *ced-10; mig-2* double mutants show severely reduced axonal numbers and increased fasciculation defects in both the ventral and dorsal nerve cords; by contrast, neither *ced-2; mig-2* nor *ced-5; mig-2* double mutants show such defects. Second, *ced-10; mig-2* double mutants show defects in CAN cell migration and axonal extension and guidance, as determined using a *ceh-23::gfp* reporter that expresses in the CAN cell. Third, RNAi of *rac-2* shows synthetic CAN cell defects in animals mutant in either *ced-10* or *mig-2*. We also have analyzed how these three Rho-family genes, along with the *unc-73* GEF (guanine nucleotide exchange factor), interact during the processes of cell-corpse engulfment and distal tip cell migration.