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125. CED-12, A COMPONENT OF A RHO/RAC GTPASE SIGNALING PATHWAY, REGULATES CYTOSKELETAL REORGANIZATION AND CONTROLS CELL-CORPSE ENGULFMENT AND CELL MIGRATION IN *C. elegans*

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During animal development, cells undergoing programmed cell death, or apoptosis, are rapidly engulfed and degraded by neighboring cells. The engulfment of apoptotic cells by their neighbors is an evolutionarily conserved process. In *C. elegans*, mutations in genes that define two partially redundant pathways block the engulfment of cell corpses, causing cell corpses to persist abnormally. In one of these pathways, *ced-1*, *ced-6* and *ced-7* appear to act together to control cell-corpse recognition and to initiate phagocytosis. CED-1 is a transmembrane receptor similar to a mammalian scavenger receptor. CED-1 recognizes and clusters around cell-corpses to mediate their engulfment. *ced-7* encodes an ABC transporter that promotes the recognition of cell corpses by CED-1, possibly by exposing phospholipids on the outer surface of the cell corpses. *ced-6* encodes an adaptor-like protein that acts in engulfing cells. In the other engulfment pathway, *ced-2* CrkII, *ced-5* DOCK180, and *ced-10* Rac are part of a Rac GTPase signaling pathway proposed to mediate cytoskeletal reorganization.

We identified a new engulfment gene, *ced-12*, in a large-scale genetic screen for engulfment-defective mutants. Like *ced-2*, *ced-5*, and *ced-10*, *ced-12* functions in both cell-corpse engulfment and distal tip cell migration. Genetic interaction studies showed that *ced-12* acts in a pathway with *ced-2* CrkII, *ced-5* DOCK180, and *ced-10* Rac GTPase in cell-corpse engulfment. We cloned *ced-12* and found that it encodes a novel protein with a candidate SH3-binding motif. The CED-12 protein has both *Drosophila* and human counterparts. The *Drosophila* homolog *Dced-12* could partially replace the function of *ced-12* in *C. elegans*. CED-12 functions in engulfing cells to mediate cell-corpse engulfment. A CED-12::GFP fusion protein is localized to the cytoplasm in *C. elegans*. CED-12 interacts physically with CED-5, which contains an SH3 domain. When expressed in Swiss 3T3 fibroblast cells, CED-12 induced formation of filamentous actin structures in a manner dependent on the GTPase Rho. We propose that CED-12 is recruited to a CED-2/CED-5 protein complex through its interaction with CED-5 and regulates or effects Rho/Rac GTPase signaling, thereby leading to cytoskeletal reorganization by a mechanism that is evolutionarily conserved. We have performed a yeast two-hybrid screen for *C. elegans* proteins that interact with CED-12 and have identified a number of positive clones. Currently we are studying the functions of these potential CED-12 interacting proteins in the context of programmed cell death, cell-corpse engulfment, and cell migration.