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A CED-2/Crk-II, CED-5/DOCK180, CED-10/Rac pathway controls cell-corpse engulfment and cell migration

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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, including *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* is known to encode a protein similar to human DOCK180 (Downstream of Crk 180KD) (1). DOCK180 has been found to interact with the the oncoprotein Crk and the Rac GTPase. We have now cloned the *ced-2* and *ced-10* genes and found them to encode proteins homologous to Crk-II and Rac, respectively. That *ced-2*/*ced-5*/*ced-10* exist together in a pathway strongly indicates that Crk-II, DOCK180, and Rac all functionally interact in vivo.

CED-2 contains an N-terminal SH2 (Src-Homology 2) domain followed by two SH3 domains, suggesting that CED-2 functions as an adaptor protein to mediate protein-protein interactions. Rac is a member of the Ras-like GTPase family. A subgroup of these GTPases, consisting of Rho, Rac, and Cdc42, regulate cell morphological changes by controlling the organization of the cytoskeleton. An analysis of the cell-migration defects in *ced-2* and *ced-10* mutant animals demonstrates that the distal tip cells, while competent for migration, are defective in maintaining correctly polarized pathfinding. Ectopic expression experiments suggest that CED-2 and CED-10 can act outside of dying cells for cell-corpse engulfment. We propose that CED-2/Crk-II localizes CED-5/DOCK180 to the plasma membrane, leading to the activation of the CED-10/Rac GTPase within engulfing and migrating cells. Such activation presumably regulates the polarity of cytoskeletal extensions in response to apoptotic or migrational cues. We are analyzing predictions made by this model, such as protein-protein interactions and protein localization.

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1. Wu, Y. C. and Horvitz, H. R. (1998). *Nature* 392, 501-504.