abl-1 Suppresses the Engulfment of Apoptotic Cells through a Novel Pathway that Contains *abi-1*

Mike Hurwitz[1], Pam Vanderzalm[2], Laird Bloom[1], Julia Goldman[1], Gian Garriga[2], Bob Horvitz[1]

[1]Massachusetts Institute of Technology, Cambridge, MA, USA, [2]University of California, Berkeley, CA, USA

In *C. elegans*, apoptotic cells are engulfed by neighboring cells. Two parallel and partially redundant pathways comprising at least eight genes (*ced-1, ced-6, ced-7, dyn-1* and *ced-2, ced-5, ced-10, ced-12*) function in this process. Loss-of-function (lf) mutations in these genes cause the persistence of unengulfed cell corpses. CED-7 is an ABC-type transporter that appears to signal through CED-1, a transmembrane receptor and CED-6, an adapter protein predicted to bind the phosphotyrosines of CED-1. The dynamin DYN-1, which regulates membrane dynamics, acts downstream of CED-6. CED-2, a homolog of CrkII, is an adapter that contains an SH2 and two SH3 domains and activates the CED-5/CED-12 heterodimeric guanine nucleotide exchange factor (GEF). The CED-5/CED-12 GEF, in turn, activates CED-10, a small Rac GTPase.

In mammals, the CED-2 homolog CrkII functions in cell migration by activating the CED-10 homolog Rac1, which regulates cytoskeletal reorganization. This process is negatively regulated by the oncoprotein Abl kinase via phosphorylation of CrkII. Mutations in Abl cause several cancers and wild-type Abl is involved in signaling pathways important in the development of other types of cancer.

By analogy, we postulated that the *C. elegans* Abl homolog *abl-1* might negatively regulate *ced-2* and the engulfment process. We found that *abl-1*(lf) suppresses the engulfment defects of strong lf mutations in the *ced-1/6/7* pathway and of *ced-2* but not of *ced-5* or *ced-12*, suggesting that *abl-1* opposes these pathways but not by directly blocking *ced-2* function. Instead, *abl-1* might act on a gene that is either downstream of *ced-2*, such as *ced-5*, *ced-12* or *ced-10*, or in a parallel pathway.

The *ced-2/5/10/12* genes are also required for normal distal tip cell (DTC) migration. By contrast to its effects in engulfment, *abl-1*(lf) suppresses the DTC migration defects of strong loss-of-function alleles of *ced-5* and *ced-12* as well as of *ced-2*, consistent with *abl-1*'s acting in a parallel pathway.

We found that a mutation in *abi-1* enhances the engulfment defects of mutations in both the *dyn-1* dynamin and *ced-10* Rac pathways. *abi-1* is the *C. elegans* homolog of Abl interacting protein 1 (Abi1), a cytoskeletal regulatory protein in mammals. RNAi of *abi-1* completely suppresses the effects of *abl-1* on engulfment and DTC migration. Thus, *abl-1* suppresses a novel *abi-1*-containing engulfment pathway that acts in parallel to the known engulfment pathways.

Contact: mhurwitz@mit.edu
Lab: Horvitz