BLMP-1/Blimp-1 Regulates the Spatiotemporal Cell Migration Pattern in C. elegans

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Abstract

Spatiotemporal regulation of cell migration is crucial for animal development and organogenesis. Compared to spatial signals, little is known about temporal signals and the mechanisms integrating the two. In the Caenorhabditis elegans hermaphrodite, the stereotyped migration pattern of two somatic distal tip cells (DTCs) is responsible for shaping the gonad. Guidance receptor UNC-5 is necessary for the dorsalward migration of DTCs. We found that BLMP-1, similar to the mammalian zinc finger transcription repressor Blimp-1/PRDI-BF1, prevents precocious dorsalward turning by inhibiting precocious unc-5 transcription and is only expressed in DTCs before they make the dorsalward turn. Constitutive expression of blmp-1 when BLMP-1 would normally disappear delays unc-5 transcription and causes turn retardation, demonstrating the functional significance of blmp-1 down-regulation. Correct timing of BLMP-1

down-regulation is redundantly regulated by heterochronic genes daf-12, lin-29, and dre-1, which regulate the temporal fates of various tissues. DAF-12, a steroid hormone receptor, and LIN-29, a zinc finger transcription factor, repress blmp-1 transcription, while DRE-1, the F-Box protein of an SCF ubiquitin ligase complex, binds to BLMP-1 and promotes its degradation. We have therefore identified a gene circuit that integrates the temporal and spatial signals and coordinates with overall development of the organism to direct cell migration during organogenesis. The tumor suppressor gene product FBXO11 (human DRE-1 ortholog) also binds to PRDI-BF1 in human cell cultures. Our data suggest evolutionary conservation of these interactions and underscore the importance of DRE-1/FBXO11-mediated BLMP-1/PRDI-BF1 degradation in cellular state transitions during metazoan development.

LIN-3/EGF Promotes the Programmed Cell Death of Specific Cells in Caenorhabditis elegans by Transcriptional Activation of the Pro-apoptotic Gene egl-1" is scheduled to be published in *PLOS Genetics* on 21 August 2014

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Abstract

Programmed cell death (PCD) is the physiological death of a cell mediated by an intracellular suicide program. Although key components of the PCD execution pathway have been identified, how PCD is regulated during development is poorly understood. Here, we report that the epidermal growth factor (EGF)-like ligand LIN-3 acts as an extrinsic signal to promote the death of specific cells in *C. elegans*. The loss of LIN-3 or its receptor LET-23 reduced the death of these cells, while excess LIN-3 or LET-23 signaling resulted in an increase in cell deaths. Our molecular and genetic data support the model that the LIN-3 signal is transduced through LET-23 to activate the LET-60/RAS-MPK-1/ERK MAPK pathway and the downstream ETS domain-containing transcription factor LIN-1. LIN-1 binds to, and activates transcription of, the key pro-apoptotic gene *egl-1*, which leads to the death of specific cells. Our results provide the first evidence that EGF induces PCD at the whole organism level and reveal the molecular basis for the death-promoting function of LIN-3/EGF. In addition, the level of LIN-3/EGF signaling is important for the precise fine-tuning of the life-versus-death fate. Our data and the previous cell culture studies that EGF triggers apoptosis in some cell lines suggest that the EGF-mediated modulation of PCD is likely conserved in *C. elegans* and humans.