Genetic Control of the Maintenance of the AIA Cell Identity

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As development progresses in multicellular organisms, the developmental potential of an individual cell becomes increasingly restricted until a final differentiated cellular identity is adopted. Research in recent years has indicated that a cell's differentiated identity can be unstable. The roles of factors that maintain the integrity of a cell's differentiated identity are poorly understood. We are characterizing a *C. elegans* gene, *ctbp-1*, that might act in the process of the maintenance of cell identity. *ctbp-1* encodes the worm homolog of the C-terminal Binding Protein (CtBP) family of proteins, shown in mice and *Drosophila* to act as transcriptional corepressors during development. We discovered that *ctbp-1* adult worms misexpress an M4 neuron-specific reporter in the AIAs. Strikingly, *ctbp-1* L1 worms do not show this AIA misexpression. We hypothesize that *ctbp-1* worms properly establish AIA identity but fail to maintain AIA identity as the animal ages and, for example, misexpress genes normally specific to other cell types. Consistent with this hypothesis, we have observed that *ctbp-1* mutants similarly show age-dependent defects in AIA cellular morphology (they generate an ectopic neurite) and AIA function (they fail in an AIA-dependent chemotactic behavior), again suggesting a failure in the maintenance of AIA cellular identity.

To understand how *ctbp-1* acts to regulate AIA cellular identity, we performed a genetic screen looking for suppression of the AIA gene misexpression seen in *ctbp-1* animals. We have identified two homeodomain transcription factors, *unc-39* and *ttx-3*, each of which when lost results in suppression of the AIA misexpression phenotype of *ctbp-1* mutants. We are now examining the nature of the interactions between *ctbp-1* and these transcription factors, e.g., by seeking shared transcriptional targets, with the goal of understanding the consequences of their loss on the regulation of gene expression and the maintenance of AIA cellular identity. We hope that an understanding of the mechanisms that maintain cellular identity in *C. elegans* will offer insights into how the failure of the maintenance of cell identity can lead to human diseases, e.g., neurodegenerative diseases such as Alzheimer's, Parkinson's and ALS, which might in part involve a loss of neuronal identity.

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