A Neuron from Mesoderm: A Likely Case of *in vivo* Neuronal Reprogramming

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The ability to reprogram non-neuronal cells into neurons by defined transcription factors opens novel avenues for both the study and treatment of neurodegenerative and neuropsychiatric diseases that affect millions of patients worldwide. However, the reprogramming processes in mammalian systems are slow, inefficient, and highly variable, and our current understanding of molecular pathways and mechanisms that control reprogramming is limited.

In the *C. elegans* nervous system, most of the 302 neurons are derived from the ectodermal AB blastomere. However, six neurons are generated from mesodermal lineages. Furthermore, a transgene that expresses RFP under the *hlh-1*/*CeMyoD* promoter revealed strong reporter expression in the immediate ancestors of the mesodermally-derived neurons (http://epic.gs.washington.edu/genesPage2.html). This finding suggests that these neurons are generated through a mechanism that involves endogenous reprogramming. Therefore, identifying the molecular mechanisms that drive the development of these neurons might generate novel insights into neuronal reprogramming.

We have focused on one of the six mesodermally-derived neurons, the I4 neuron, which is generated as a sister of the pm5 muscle cell during pharyngeal development. Using a transgenic strain that labels I4 with GFP and the pharyngeal muscles with mCherry, we have performed genetic screens and identified 16 mutant isolates in which the I4 neuron is transformed into a muscle-like cell. So far, we have identified three genes defined by those mutants: *let-19*, *dpy-22*, and *hlh-3*. *let-19* and *dpy-22* encode homologs of conserved Mediator subunits, which regulate gene expression by recruiting RNA polymerase II to transcription start site. *hlh-3* encodes the homolog of Ascl1/Mash1, which can help drive mammalian neuronal reprogramming. Genetic analysis indicates that *hlh-3* and the Mediator genes act in parallel pathways to regulate I4 specification: while mutations in either *hlh-3* or the Mediator genes result in low penetrance of I4 transformation, mutations in both *hlh-3* and the Mediator gene causes high penetrance of the phenotype. We are investigating the mechanisms by which *hlh-3* and the Mediator genes regulate I4 neuronal reprogramming.

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