REGULATION OF ASYMMETRIC NEUROGENESIS IN C. ELEGANS

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Introduction. Neural specification is further complicated when we consider that it needs to be coordinated across the left-right (L/R) axis. Disruptions in the bilaterally symmetric organization of the human brain are frequently observed in patients with neurological disorders. Furthermore, certain neurological disorders such as schizophrenia and Parkinson's disease present or progress asymmetrically, suggesting the possibility of underlying asymmetric genetic causes. The question of how early neural specification is regulated to produce both bilaterally symmetric and L/R asymmetric structures has been largely unexplored.

Neuron specification requires cells of the ectoderm to make a neuronal, rather than non-neuronal cell fate choice. This process requires proneural genes that are an evolutionary conserved family of basic helix-loop-helix transcription factors. We have identified earlier that *hlh-14* is expressed asymmetrically in the C-lineage of *C. elegans* and is required for the asymmetric specification of two neurons known as PVR and DVC. Furthermore, using forward genetic screen and promotor analysis they are beginning to identify several factors that are also expressed in C-lineage and act during neurogenesis and that may be upstream regulators factors of the *hlh-14/achaete-scute* proneural gene.

Materials and methods. In this project we have analyzed in detail one of the factors- *hlh-2/daughterless* by using a candidate gene approach. We have analyzed the phenotype of *hlh-2* both in terms of cell division and in terms of *hlh-14* expression. In order to perform this analysis we have conducted embryo scoring and 4D-lineaging of both mutant *hlh-2 (n5053)* and wild-type embryos with reporter transgenes *gmIs20[hlh-14::gfp]*

Results and discussion. Consequently, we have found that in the wild-type embryos *gmIs20[hlh-14::gfp]* is expressed in the DVC-lineage and no expression is detected in the PVR-lineage. This result suggests that the *cis*-regulatory elements that drive the expression in DVC is present in our transgene reporter, however the regulatory elements of PVR are further downstream or upstream of a reporter gene. Furthermore, the lineage of a mutant strain showed the precocious division of neuroblast that gives rise to DVC (and cell death), this led to the formation of two hypodermal cells instead of neuron (and cell death). The finding suggests that *hlh-2* has a role in establishment of DVC neuron specification. Finally, we have found by embryo scoring and 4D-lineage of mutant embryos, that loss of *hlh-2* affects *hlh-14* expression, which suggests that *hlh-2* is required for maintenance of *hlh-14* in *C-lineage* and they are likely to collaborate together as a heterodimers.

Conclusions. Collectively, the results presented here suggest that *hlh-2* is required for the *hlh-14* expression and show the same lineage defect as *hlh-14* mutant embryo, hence possibly *hlh-2* acts as one of the regulators of *hlh-14*. We suggest that *hlh-2* acts as a regulatory factor by binding to *hlh-14* and forming a heterodimer structure, which then binds to *hlh-14* gene and drives its expression.