

## Functional Genomics in Zebrafish

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The zebrafish is now the pre-eminent vertebrate model system for clarification of the roles of specific genes and signaling pathways in development. I will talk about positional cloning of two developmental mutants in zebrafish. The first mutant is *headless*: The vertebrate organizer can induce a complete body axis when transplanted to the ventral side of a host embryo by virtue of its distinct head and trunk inducing properties. Wingless/Wnt antagonists secreted by the organizer have been identified as head inducers. Their ectopic expression can promote head formation, whereas ectopic activation of Wnt signalling during early gastrulation blocks head formation. These observations suggest that the ability of head inducers to inhibit Wnt signalling during formation of anterior structures is what distinguishes them from trunk inducers that permit the operation of posteriorizing Wnt signals. I describe the zebrafish headless (*hdl*) mutant and show that its severe head defects are due to a mutation in T-cell factor-3 (*Tcf3*), a member of the Tcf/Lef family. Loss of *Tcf3* function in the *hdl* mutant reveals that *hdl* represses Wnt target genes. I provide genetic evidence that a component of the Wnt signalling pathway is essential in vertebrate head formation and patterning. The second mutant is *mind bomb*: Lateral inhibition, mediated by Notch signaling, leads to the selection of cells that are permitted to become neurons within domains defined by proneural gene expression. Reduced lateral inhibition in zebrafish *mib* mutant embryos permits too many neural progenitors to differentiate as neurons. Positional cloning of *mib* revealed that it is a gene in the Notch pathway that encodes a RING ubiquitin ligase. *Mib* interacts with the intracellular domain of Delta to promote its ubiquitylation and internalization. Cell transplantation studies suggest that *mib* function is essential in the signaling cell for efficient activation of Notch in neighboring cells. These observations support a model for Notch activation where the Delta-Notch interaction is followed by endocytosis of Delta and transendocytosis of the Notch extracellular domain by the signaling cell. This facilitates intramembranous cleavage of the remaining Notch receptor, release of the Notch intracellular fragment, and activation of target genes in neighboring cells. In addition, I will introduce new transgene reporter system and insertional mutagenesis which are recently developed in my lab.