University of Massachusetts UMASS Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

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"Investigating the gene regulatory network underlying caudal hindbrain specification in embryonic zebrafish"

To understand the gene regulatory network (GRN) governing caudal hindbrain formation in embryonic zebrafish, several early expressed factors have been manipulated, and multiple genetic mutants have been characterized. Such analyses have identified morphogens such as Retinoic Acid (RA) and Fibroblast growth factors (FGFs), as well as transcription factors like *hoxb1b, hoxb1a, hnf1ba,* and *valentino* as being required for rhombomere (r) r4-r6 formation in zebrafish. Considering that the caudal hindbrain is relatively complex – for instance, unique sets of neurons are formed in each rhombomere segment – it is likely that additional essential genes remain to be identified and integrated into the caudal hindbrain GRN.

Our results reveal that r4 gene expression is unaffected by the individual loss of *hoxb1b, hoxb1a* or RA, but is under the combinatorial regulation of RA together with *hoxb1b*. In contrast, r5/r6 gene expression is dependent on RA, FGF, *hnf1ba* and *valentino* – as individual loss of these factors abolishes r5/r6 gene expression. Analysis of six mutant lines (*gas6, gbx1, sall4, eglf6, celf2*, and *greb1l*) did not reveal rhombomere or neuronal defects, but transcriptome analysis of one line (*gas6* mutant) identified expression changes for genes involved in several developmental processes – suggesting that these genes may have subtle roles in hindbrain development.

We conclude that r4-r6 formation is relatively robust, such that very few genes are absolutely required for this process. However, there are mechanistic differences in r4 versus r5/r6, such that no single factor is required for r4 development while several genes are individually required for r5/r6 formation.

Mentor(s)

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