Regulation of Developmental Timing and Cell-Fate Determination by Heterochronic Proteins LIN-29 and MAB-10

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During animal development, gene regulation needs to be temporally precise for proper cell-fate decisions to occur. The evolutionarily conserved *C. elegans* heterochronic pathway controls the temporal progression of development by regulating the activities of a sequence of genes. Components of this pathway control cell-fate decisions of proliferation versus differentiation, and mammalian homologs of these components play critical roles in stem cell regulation.

mab-10 was discovered in our laboratory to encode the *C. elegans* NGFI-A-binding protein (NAB) transcriptional co-factor. MAB-10 is involved in the terminal differentiation of the hypodermal stem-like seam cells and more generally in the larval-to-adult transition (Harris & Horvitz, *Development*, 138, 4051, 2011). LIN-29, the master regulator of the larval-to-adult transition, was shown to be an early growth response (EGR) protein that acts together with MAB-10 to control the expression of genes that regulate the onset of adulthood and terminal differentiation in the hypoderm. There is a striking parallel in mammals, in which EGR proteins interact with NAB proteins to cause terminal differentiation and the onset of puberty (Topilko *et al.*, *Mol Endocrinol*, 12, 107,1998). Furthermore, EGR1, the mammalian homolog of LIN-29, has been shown to act as a barrier during reprogramming to human induced pluripotent stem cells (Worringer *et al.*, *Cell Stem Cell*, 14, 40, 2014). Despite the importance of this pathway, mechanisms by which the terminal effectors LIN-29/EGR and MAB-10/NAB function and are regulated remain largely unknown.

We are studying the functions of LIN-29/EGR and MAB-10/NAB with the goal of understanding the mechanisms that control *C. elegans* developmental timing and providing insights concerning stem cell identity and development in mammals. Although MAB-10 has been identified as a co-factor of LIN-29, *mab-10* mutants have a weaker phenotypic defect than *lin-29* mutants. This observation suggests the existence of additional genes in this pathway that either function as co-factors of LIN-29 or that act in parallel with MAB-10. To identify such factors, we have performed genetic screens for enhancers of the *mab-10* mutant phenotype. We are currently characterizing these mutations. We hope that these studies will identify new molecules involved in stem cell regulation and facilitate advances in regenerative medicine.

Poster presentation
Primary session topic area – Development
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