Forkhead Genes in Mammalian Development

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Abstract

This thesis concerns aspects of Forkhead gene biology and it's relation to mammalian development. Genes from three subclasses are discussed, *Foxj3*, *Foxf1* and *f2*, and *Foxe3*.

We have identified and characterized a novel forkhead gene, *FoxJ3*, that is expressed in neuroectoderm, neural crest and mytome, suggesting possible function in the nervous system and muscle. The myotome, which will develop into muscle, along with the mesenchyme lining the intestinal gut, originates from embryonic mesoderm.

Forkhead factors, *Foxf1* and *Foxf2*, are expressed in intestinal mesenchyme derived from splanchnic mesoderm. Foxf function is important for patterning of the gut tube. Removal of Foxf results in a range of intestinal phenotypes, such as agangliosis and megacolon. Both *Foxf1* and *Foxf2* are regulated by hedgehog signaling, Foxf mutants display mesenchymal increase in *Wnt5a* expression, and reduction in *Bmp4* expression. The extracellular matrix is depleted of collagens, and together with altered paracrine factors, this leads to a phenotype where epithelial cells lose polarization and become resistant to apoptosis.

The ocular lens develops from the head ectoderm and a critical factor in its formation is Foxe3. *Foxe3* is, after secondary fiber differentiation starts, expressed exclusively in the lens epithelium. These cells provide the precursors for lens fibers. Fiber cells are elongated, terminally differentiated cells that provide the specialized optical properties of the lens. Ectopic expression of *Foxe3* in the fiber compartment interferes with several aspects of fiber differentiation. The cytoskeletal remodeling and organelle degradation is blocked in transgenic lenses, whereas fiber cell specific expression of crystallins seems to be undisturbed.

Foxe3 is also involved in patterning of the anterior segment of eye. Heterozygous *Foxe3* mutants show defects in differentiation of the cornea, iris and filtration angle. The anterior segment similarities in *Foxe3* and *Pax6* heterozygous mutants provide, along with *Foxe3* expression being dependent on *Pax6* gene dosage, an indication that *Foxe3* is a major contributor to the phenotype of *Pax6* mutants.

Foxe3 can interact with many signaling pathways active in the eye. *Foxe3* expression can be altered by changes in growth factor ligands. Furthermore, components of different growth factor pathways can be controlled by Foxe3. Taken together, Foxe3 biology is regulated on many cellular levels in the ocular lens.

Keywords: Foxj3, Foxf1, Foxf2, Foxe3, development, lens, forkhead, transcription, intestine, anterior segment, Notch, Fgf, Bmp, Wnt.

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AKADEMISK AVHANDLING

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av

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