Foxe3 in lens development

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ABSTRACT

In this thesis I describe the cloning and functional characterization of a novel gene, *FoxE3*, which encodes a forkhead transcription factor important for eye development. cDNA and genomic sequences from mouse and man, embryonic expression patterns, chromosome localization and DNA binding are described. A spontaneous mouse mutant and a human patient with mutations in Foxe3/FOXE3 are identified and functional characterization is performed by generation of two mouse mutants carrying either a targeted deletion, or a transgene driving ectopic expression of *Foxe3* in lens fibers.

Foxe3 is expressed in the developing lens from early placode stage and onward. As lens fiber cell differentiation is initiated, its expression gets restricted to the proliferating lens epithelium. Apart from the lens, *Foxe3* expression is also, for a short time, seen in the developing diencephalons. Foxe3 have several functions during lens development; in early stages, it is involved in proliferation, closure and detachment of the lens vesicle. Mutations in *FOXE3* can affect the detachment process, and have been found in a patient with persistent keratolenticular connection (Peters' anomaly).

Later in lens development, Foxe3 promotes epithelial proliferation by excluding expression of differentiation promoting genes like *Prox1* and *Cdkn1c* (p57 ^{kip2}). Around birth, lens epithelial signaling downstream of Foxe3 induces differentiation of mesenchyme in anterior chamber of the eye. The striking phenotypic similarity between *Foxe3* and *Pax6* ^{Sey} mutants, together with a demonstrated dependence on Pax6 for *Foxe3* expression, suggests that reduced *Foxe3* expression is a major contributor to the *Pax6* haploinsufficiency phenotype.

Ectopically expressed *Foxe3* in the fiber compartment interferes with several aspects of fiber differentiation. The cytoskeletal remodeling and organelle degradation is blocked in fiber cells of transgenic lenses, whereas fiber cell specific expression of MIP and crystallins seem so be undisturbed.

Key words: Forkhead, Foxe3, Pax6, Sey, dyl, lens development, lens epithelium, anterior segment development, proliferation.

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