

## MOLECULAR ANALYSIS OF THE DEVELOPMENT OF THE VERTEBRATE VISUAL SYSTEM

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Spemann proposed that the development of the visual system requires inductive events between the optic vesicle and the overlying ectoderm. More recent evidence suggests that lens formation involves a multi-step process including competence, bias and final determination. Several genes have been discovered that are expressed in a spatial and temporal manner during these stages and consequently may be considered candidates for controlling at least some of these complicated processes.

One gene, *Pax6*, has been shown to be a key player in vertebrate and fly eye development. *Pax6* mutant mice and men exhibit a loss of eye formation. Also, when expressed ectopically in imaginal discs of *Drosophila* embryos *Pax6* can induce eye formation (Halder et al., 1995). We have studied *Pax6* in detail and have shown that besides a role in eye and nose development *Pax6* is also required for the development of forebrain structures. Specifically, loss of *Pax6* function causes a failure of the establishment of several expression boundaries that specify longitudinal domains within the developing forebrain (Stoykova et al.). The establishment of some expression boundaries along the dorsal/ventral axis of the secondary prosencephalon is distorted and the specification of several ventral structures and nuclei is abolished. Especially, the development of the hypothalamo-telencephalic transition zone and the ventral thalamus is distorted.

Our detailed analysis included a comparison of the expression of *Pax6*, *Dlx1* and several other genes during embryonic mouse brain development in wildtype and in the mutant *Small eye* brain. The results from the analyses of normal brain development show that the restricted expression of *Pax6* and *Dlx1* respect domains within the forebrain, consistent with the implications of the prosomeric model for the organisation of the forebrain as brought forward by Puelles and Rubenstein. Furthermore, we found an early restriction of *Pax6* and *Dlx1* expression in two presumptive histogenetic fields and correlate with the formation of distinct forebrain structures and nuclei.

Our results will be discussed in light of changes in adhesive properties in the *Sev* brain that might control segregation, assembly and cell migration of progenitors of specific forebrain regions. These results suggest that *Pax6* may promote changes in adhesive properties and underline the multiple roles that *Pax6* plays during the development of distinct structures. Our findings also indicate in particular eye development requires in addition to *Pax6* other genes regulating individual steps.

Based on existing *Drosophila* mutants we have screened for the presence and function of one specific gene that is involved in eye development in the fly, *sine oculis*. Indeed one member of this gene family we recently identified, *Six3*, seems to be a functional homologue of *sine oculis* in the mouse. Earlier on, *Six3* expression is restricted to the anterior neural plate and is later found in the region of the optic recess, the hypothalamus and optic vesicles. Using a gain-of-function approach we have demonstrated that *Six3* activity is sufficient to promote ectopic lens formation in fish embryos in the absence of an optic vesicle. Our results show that in addition to the lens placode, the ectoderm in the region of the optic placode is competent to respond to a lens promoting signal. These studies identify *Six3* as another key player in the development of the vertebrate eye (Oliver et al., in preparation).

Another gene, *Pax2*, is also expressed in structures of the developing visual system. Initially, *Pax2* expression is confined to the ventral optic vesicle and it is later been found mostly in the proximal regions that are destined to contribute to the optic nerve and optic chiasm (Nornes et al., 1990). We generated *Pax2* mutant mice which show the requirement of *Pax2* for the establishment of axonal pathways along the optic stalks and ventral diencephalon. In mutant brain, the optic tracts remain completely ipsilateral due to the agenesis of the optic chiasm. Also, *Pax2* mutants show extension of the pigmented retina into the optic stalks and failure of the optic fissure to close resulting in coloboma. Therefore, *Pax2* is a major regulator required for the closure of the optic fissure and also required for the correct optic nerve trajectory (Torres et al., 1996).

### References:

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