SL101 Mechanisms of Neural Development in the Mouse Retina
시신경의 발생과 분화 메카니즘

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The molecular mechanisms which pattern the developing optic vesicle are only beginning to be understood. Important insights have come from the discovery of genes with asymmetric expression patterns within the developing optic vesicle. The eye develops from the optic vesicle which arises as an outpocketing of the rostral neural tube at E8 in the mouse. As the optic vesicle grows outward, it makes contact with the surface ectoderm which is induced to form the lens of the eye. The distal region of the optic vesicle subsequently invaginates to become the optic cup, while the proximal region narrows to give rise to the optic stalk. The inner layer of the optic cup forms the retina which surrounds the lens while the outer layer develops into the retina pigmented epithelium. The secreted polypeptide, shh plays a critical role in the specification of the optic vesicle to an optic cup or stalk fate. Ectopic expression of shh in the developing zebrafish leads to expansion of the optic stalk while loss of shh in the cyclops mutant results in the reduction of the stalk domain. Targeted disruption of shh in the mouse yields embryos lacking ventral forebrain structures. Shh (-/-) mutant mice also develop with a cyclopic eye, lacking stalk structures.

BF-1 is a winged-helix transcription factor whose expression within the neural tube is restricted to the rostral telencephalic neuroepithelium and the anterior half of the optic vesicle. We have shown that BF-1 is essential for the development of the cerebral hemispheres. Mice lacking BF-1 have hypoplasia of the telencephalon and lack structures arising from the basal telencephalon. In this study we focus on the consequences of deleting BF-1 on eye development. Analysis of the BF-1 (-/-) mutant reveals distortions in the contour of the anterior hemiretina, failure of the choroid fissure to close and the absence of the optic stalk. We find that the BF-1 (-/-) mutant has a deficit in a highly restricted domain of shh expression. The pattern of shh expression through E9.5 is indistinguishable in the BF-1 (-/-) mutant from that of WT littermates. However, by E10.5, shh expression in two discrete zones within the ventral telencephalic neuroepithelium is altered in the BF-1 (-/-) mutant. These zones of shh expression are immediately adjacent to the neuroepithelium of each anterior optic vesicle and are normally induced between E9.5 and E10.5. While we do not observe a signal above background in this region of the BF-1 mutant, we cannot exclude the possibility that low levels of shh are transiently expressed in the the ventral telencephalic neuroepithelium. The remainder of the shh expression pattern is unaltered in the BF-1 (-/-) mutant. We find normal expression of shh within the diencephalic neuroepithelium, the prechordal mesoderm, the floor plate and notochord. The localized loss of shh expression in the BF-1 (-/-) mutant precedes the onset of differentiation of the proximal vesicle.

We had previously found that proliferation of the telencephalic neuroepithelium is reduced in the BF-1 (-/-) mutant. Proliferation in the ventral telencephalic neuroepithelium, defined as the region which expresses the lacZ marker and does not express Emx-2, was sharply reduced at E10.5. In contrast, the dorsal telencephalic neuroepithelium continued to proliferate normally until E12.5. Because BF-1 is expressed uniformly throughout the telencephalic neuroepithelium, the molecular basis for the dorsal-ventral difference in the severity of the phenotype was not readily apparent. In the shh (-/-) mutant, ventral forebrain structures are completely absent. Markers of the dorsal telencephalon such as Emx-1 are present throughout the entire single prosencephalic vesicle. In the BF-1 (-/-) mutant, structures which arise from the ventral telencephalon, e.g. the basal ganglia are also not formed. The expression domain of dorsal telencephalic markers such as Emx-1 and Emx-2 is also expanded compared to normal. However, unlike the shh (-/-) mutant, Emx expression is excluded from a small region of the ventral telencephalon in the BF-1 (-/-) mutant. This suggests that ventralizing activity is present in the BF-1 (-/-) albeit at reduced levels.

Our finding that shh is not expressed within the telencephalic neuroepithelium of the BF-1 (-/-) raises the possibility that this loss may contribute to the severity of the ventral deficit. These observations suggest that shh functions to promote the proliferation as well as the specification of the ventral telencephalon. Our results are consistent with the view that shh activity from the prechordal mesoderm and/or the diencephalic neuroepithelium is sufficient for the initial specification of the ventral telencephalon, i.e. telencephalic neuroepithelial cells which do not express dorsal markers are present. However, these cells do not differentiate normally (Dlx-2 expression is missing), and they do not proliferate normally. Thus shh activity in the ventral telencephalon may be required for the complete differentiation of the ventral telencephalic neuroepithelium and their proliferation. Alternatively, ventral telencephalic cells lacking BF-1 may be unable to respond to the activities of shh.