CDB SEMINAR

Speaker: Shunichi Yoshikawa

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Title: "BMP signaling via ALK2 and ALK3 in the surface ectoderm cells is required for lens formation"

Date: Wednesday, August 11
Time: 16:00 -17:00
Place: 7th floor Conference Room of Building A,CDB

Summary:

Eye development has been studied as a classical model system of tissue-tissue interaction for many years. Recent analyses have shown that a number of secretory signaling molecules such as BMP, FGF and WNT are involved in the multiple developmental events, including lens induction, optic cup formation and lens differentiation. Mice mutant for the *Bmp* genes, which are members of *TGF-ß* superfamily, show defects in eyes during embryogenesis. Although it clearly indicates BMP signaling is necessary for ocular formation, its functional role in tissue-tissue interaction between the surface ectoderm (SE, future lens) and optic vesicle (OV, future retina) is poorly understood. To address this question, we designed tissue specific conditional gene disruption experiments by *Cre/loxP* system. Since BMP protein is secretory, we targeted the BMP receptor genes, which function in cell autonomous manner. Three type I BMP receptor genes are reported in mammalean genome, that is, *Alk2*, *Alk3* and *Alk6*. Single-gene mutant of each receptor gene showed minor or no phenotype. We tried double mutant of *Alk3/6* in OV and *Alk2/3* in SE.

OV-specific mutants were generated by mating with *Cre*-tarnsgenic mice of which expression is controlled by an OV-specific cis-element of the *Six3* gene. Adult double mutants of *Alk3/6* displayed severe microphthalmia or anophthalmia. Early events such as the formation of lens vesicle and optic cup, however, looked normal until E12.5. Retinal degeneration detected by TUNEL assay and lens growth defect were observed after E12.5: the latter may be a secondary effect of the former. SE-specific mutants were obtained by mating with SE-specific *Pax6-Cre* transgenic mice. Adult double mutants of *Alk2/3* had tiny or no lens. The lens induction was observed in mutant embryos but the size of lens vesicle was significantly small. The proliferation of mutant lens was very slow and lens differentiation (fiber cell formation) was poorly observed, while optic vesicle/cup was morphologically normal by E15.5. These results indicate that BMP signaling mediated by *Alk2* and *Alk3* in SE cells is required for lens induction and proliferation while it is dispensable in OV cells during early stages. At the Later stages, BMP signaling in retinal cells is essential for cell surviving and a certain signal (perhaps FGF) from the retina is necessary for lens proliferation.

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