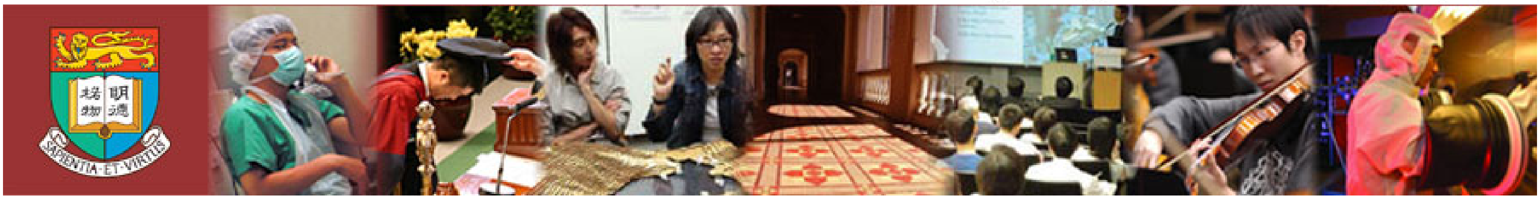

Title	Eya1 is essential for branchial arch segmentation and branchial epithelium development through regulating Notch signaling pathway
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Session III

Eya1 is essential for branchial arch segmentation and branchial epithelium development through regulating Notch signaling pathway

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Craniofacial anomalies are common features of Branchio-Oto-Renal (BOR) syndrome patients. Mutations in the Eya1 gene have been found in around half of the BOR patients, but the pathogenic mechanisms mediated by Eya1 in the craniofacial malformations remain unknown. In this study, we use Eya1 mutant mice as a disease model to study the abnormal early branchial arch (BA) development. Eya1-/- mutant embryos have hypoplastic BA2. The formation of branchial cleft was severely affected. Interestingly, Notch signaling was down-regulated in the mutant branchial epithelium. We hypothesize that Eya1 may interact with the Notch signaling pathway to regulate BA development. The aim of this study is to investigate the molecular mechanisms underlying the epithelial cell defects during abnormal BA development in BOR syndrome.

By cell lineage tracing experiments, we identified a group of Sox2 and Sox3-positive branchial epithelial progenitors in normal embryos. Analysis of Eya1-/- mutants suggested that these progenitors failed to contribute to the formation of branchial clefts. To test whether Notch signaling is involved in mediating these progenitors, we overexpressed an activated form of the Notch1 receptor (NICD) in Eya1-/- mutants. We found that over-expression of NICD resulted in ectopic epithelial progenitors, the branchial cleft defects of the Eya1-/- mutants were partially rescued. Furthermore, we showed that Eya1 could physically interact with the NICD protein and stabilize it. Our results indicate that the interaction between Eya1 and NICD is required for the specification and maintenance of epithelial progenitors, thereby controls the formation of branchial clefts and segmentation of branchial arches. In BOR syndrome patients who have mutations in Eya1 gene, some major craniofacial phenotypes, such as pinnae deformities and external auditory canal stenosis may be due to the abnormal development of branchial epithelium and branchial segmentation defects.

Loss of LIM-homeodomain genes, Lhx1 and Lhx5, disrupts dendritic spine morphogenesis of Purkinje cells and causes ataxia in mouse

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Abnormal development of Purkinje cells, the only efferent neurons in cerebellar cortex, damages cerebellum function and thus impairs motor coordination and body balance, leading to clinical symptoms like ataxia. Previously, we identified that LIM-homeodomain genes, Lhx1 and Lhx5, can regulate early Purkinje cell differentiation in developing cerebellum. However, their functional roles in postnatal development of differentiated Purkinje cells were poorly understood. Here both Lhx1 and Lhx5 were conditionally inactivated in Purkinje cells in postnatal mouse cerebellum, resulting in mutant mice suffering from motor disability and body imbalance. The control mice with one functional copy of Lhx1 or Lhx5 did not show any defects. Though the general morphology of Purkinje cells in the double Lhx1/5 mutant mice were comparable with the control mice, detailed examination showed that dendritic spine morphogenesis of Purkinje cell dendrites was disrupted in mutant mice. A large portion of dendritic spines of Purkinje cells in mutant mice failed to maturate. The mutant Purkinje cell dendrites had mislocalized F-actin cytoskeleton. In addition, we found that Lhx1 and Lhx5 could transcriptionally activate an actin-bundling protein, espin, indicating that Lhx1 and Lhx5 could govern F-actin cytoskeleton localization through espin. The F-actin mislocalization in Purkinje cell dendrites therefore caused the failure of dendritic spine maturation because F-actin is an important scaffold of dendritic spines. Overall, our findings illustrate that Lhx1 and Lhx5 are functionally redundant and essential for dendritic spine maturation, and thus maintain the proper functioning of differentiated Purkinje cells in mouse cerebellum.