View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

throughout the CNS including the lens placode and optic vesicle, the role of Ldb complexes during eye development has never been studied. We have generated Ldb1 conditional mutants abolishing Ldb1 expression in the surface ectoderm-derived structures of the eye, including cornea, lens, and conjunctiva to study the role of Ldb complexes in lens development. Adult and P3 mutants had small lens, eyeballs and minor defects in the cornea. Our study indicates a role for Ldb complexes in controlling early lens progenitor cell proliferation and/or fiber cells differentiation during lens development.

doi:10.1016/j.ydbio.2008.05.430

Program/Abstract # 450
Hoxa2 acts as a repressor in the developing murine palate

Tara M. Smith, Adil J. Nazarali
Laboratory of Molecular Biology, College of Pharmacy and Nutrition, University of Saskatchewan, SK, Canada

Cleft palate is one of the most common congenital birth defects in humans. Palate development in vertebrates is a complex and tightly regulated process involving the interaction of a network of signaling pathways. *Hoxa*2 null embryos display a high penetrance of cleft secondary palate (up to 81%). Cleft palate in these animals has been suggested to be a secondary defect to altered tongue musculature. In contrast, we show for the first time that *Hoxa*2 is expressed within the developing palate at both the mRNA and protein levels. Real-time RT-PCR results show that *Hoxa*2 mRNA is highest early in palate development, but is observed at low levels for the remainder of palatogenesis. Immunohistochemical analysis of *Hoxa*2 protein showed that it is expressed throughout the palate with the highest expression seen in the mesenchyme at E13. A number of downstream targets of *Hoxa*2 within the developing palate were also identified. *Msx*1 and Ptx1 have been shown to be expressed within the developing palate, and downstream of Hoxa2 in the branchial arches. In the palate of *Hoxa*2 null embryos *Msx*1 shows increased mRNA expression at E12.5 and Ptx1 expression is increased at E13.5. *Six*2 has been shown to be repressed by *Hoxa*2 in the murine branchial arches but has not previously been described in the developing palate. We show that *Six*2 mRNA and protein are expressed throughout palatogenesis in wild-type embryos and that *Six2* expression in *Hoxa*2 null embryos is significantly increased. These data suggest that *Hoxa*2 is playing a direct role within the developing murine palate through the repression of a variety of downstream genes. Supported by NSERC.

doi:10.1016/j.ydbio.2008.05.431

Program/Abstract # 451
Tbx-associated transcriptional corepressor, Ripply3, plays essential roles in pharyngeal development

Tadashi Okubo, Akinori Kawamura, Jun Takahashi, Akiko Ohbayashi, Shinji Takada
Okazaki Institute for Integrative Bioscience, NINS, Japan

The Ripply family of genes consists of three members, which are highly conserved among vertebrates; and they encode transcriptional corepressors that modulate the transcriptional properties of T-box proteins by recruiting the Groucho and HDAC repressor complex. While Ripply1 and 2, which are expressed in the presomitic mesoderm, are required for proper somite segmentation, the role of Ripply3 remained to be elucidated. We found that Ripply3 was expressed in pharyngeal pouches of mouse embryos from E8.5 to E10.5. This expression pattern suggests that Ripply3-mediated modulation of T-box proteins is also crucial for the development of pharyngeal apparatus. To investigate the role of Ripply3, we generated Ripply3 knock-out mutant mice by inserting a LacZ sequence in the gene. Interestingly, formation of the 3rd and 4th pharyngeal arches was severely disordered in the mutants. Subsequently, Ripply3 homozygous mutation resulted in abnormal development of the thymus, parathyroid gland and ultimobranchial body, all of which are normally generated from the 3th and 4th pharyngeal pouches. For instance, the thymus was reduced in size and mislocated in the oropharynx in the mutants. The mutant pups died soon after birth with severe outflow tract defects in their heart. These results suggest that Ripply3 is implicated in the development of pharyngeal arches and its derivatives. We suspect that Ripply3 is a potential transcriptional modulator of the T-box gene, Tbx1 that plays an essential role in pharyngeal development and whose deletion results in the DiGeorge syndrome.

doi:10.1016/j.ydbio.2008.05.432

Program/Abstract # 452
Antagonistic functions of Jagged–Notch and Edn1 signaling control dorsal–ventral patterning of the vertebrate face

Crump Gage, Elizabeth Zuniga, Frank Stellabotte
Center for Stem Cell and Regenerative Medicine, University of Southern California, Los Angeles, CA, USA

The development of the vertebrate face relies on the regionalization of neural-crest-derived skeletal precursors into distinct dorsal–ventral (DV) domains. In the current model, a ventral to dorsal gradient of the Endothelin1 (Edn1) morphogen specifies lower versus upper jaw identity. Whereas high levels of Edn1 signaling would promote lower jaw identity by activating ventral specifier genes, such as the *dlx3/4/5/6* set (*dlx*), dorsal skeletal precursors would be too far from Edn1 to activate *dlx* expression and thus would adopt upper jaw identity. Here we present evidence for an unexpected role of Jagged–Notch signaling in antagonizing Edn1 signaling in dorsal facial precursors. First, we observe *jagged1b* (*jag1b*) and *notch2* expression in complementary dorsal and ventral skeletal precursor domains. Second, by studying zebrafish with a *jag1b* mutation or reduced Notch2 function, we found that Jag1b and Notch2 are required to repress *dlx* expression in dorsal precursors and to promote upper jaw morphology. Conversely, Notch activation inhibits *dlx* expression in ventral precursors and leads to loss of the lower jaw skeleton, a phenotype seen in *edn1* mutants. Lastly, reducing Jag1b or Notch2 function rescues *dlx* expression and lower jaw defects in *edn1* mutants. Thus, opposing forces of Jagged–Notch and Edn1 signaling are integrated to generate distinct DV facial identities. As Jagged1 and Notch2 are also mutated in Alagille Syndrome, we suggest that a conserved function of Jagged–Notch signaling in DV patterning underlies the facial anomalies seen in this human disorder.

doi:10.1016/j.ydbio.2008.05.433

Program/Abstract # 453
A mouse model of Costello syndrome through tissue-specific activation of Kras

Anandaroop Mukhopadhyay, Suguna R. Krishnaswami, Benjamin D. Yu
Division of Dermatology, Department of Medicine, University of California, San Diego, CA 92093, USA

RAS acts as a downstream molecular switch in several growth factor signaling pathways. Congenital mutations in RAS have recently been identified in human syndromes, some of which are associated with developmental defects of the skin. To investigate the basis of the