Seminar/Talk

'Closing the gap' in understanding vertebrate choroid fissure closure and ocular coloboma

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Host: Carl-Philipp Heisenberg

Proper development of vertebrate embryos requires fusion of epithelial cell sheets, resulting in closure of the developing neural tube, palate and retina. Within the eye, failure of the ocular fissure to close results in ocular coloboma, one of the leading causes of pediatric blindness worldwide. Our understanding of causative genetic lesions represents only a fraction of cases, highlighting the need for continued study of genes involved in regulating eye development. Previous work from our lab and others has defined key roles for TGF?/BMP and Wnt signaling pathways in regulating vertebrate ocular fissure closure, though our understanding remains limited. Here, I discuss work identifying novel mutations that implicate two genes in causality of ocular coloboma and microphthalmia, Frizzled-5 (FZD5) and Bone morphogenetic protein-3 (BMP3). The FZD5 mutation results in a truncated protein that retains the ligand-binding domain but lacks all transmembrane domains. In vitro assays suggest truncated FZD5 is a secreted dominant negative receptor that can antagonize both canonical and non-canonical Wnt signaling. We show in vivo that depletion of Fzd5 in zebrafish not only causes microphthalmia and coloboma, but also tissue-dependent effects on Wnt signaling, consistent with roles for Fzd5 on more than one Wnt pathway. Furthermore, ectopic expression of human truncated FZD5 highlights altered biological activity of the mutant transcript. This represents the first Wnt pathway member implicated in human structural ocular disease. In a separate study, we identified a novel missense mutation in BMP3 in a family with coloboma, and two additional missense mutations in an unrelated coloboma patient cohort. Consistent with a role for bmp3 in eye morphogenesis, zebrafish bmp3 mutants display fissure closure defects. Bmp3 is a known TGF? ligand and is expressed directly adjacent to the developing fissure. We therefore hypothesize that Bmp3 is a novel factor governing retinal TGF? signaling to control fissure closure. In summary, my work has contributed to our understanding of vertebrate ocular development and genetic lesions leading to ocular coloboma.

Tuesday, August 27, 2019 11:15am - 01:30pm
Meeting room 2nd floor / Bertalanffy Bldg. (I04.2OG - LAB)

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