controls Wnt-mediated cytoskeletal reorganization during vertebrate gastrulation.

doi:10.1016/j.ydbio.2008.05.164

Program/Abstract # 153
6-Catenin regulates Xenopus developmental morphogenesis
Dongmin Gu a, Amy K. Sater c, Hong Ji a, Melissa Clark b, Sabrina A. Stratton b, Michelle C. Barton b, Qun Lu, Pierre D. McCre a a Department of Biochemistry and Molecular Biology, UT MD Anderson Cancer Center, Houston, TX, USA b Program in Genes and Development, UT GSBS, Houston, TX, USA c Department of Biology and Biochemistry, University of Houston, Houston, TX, USA d Department of Anatomy and Cell Biology, East Carolina University, Greenville, NC, USA

Catenins of the p120 sub-class display an array of intracellular localizations and functions. While the genetic knock-out of mouse 6-catenin resulted in mild cognitive dysfunctions and aberrant neuronal dendritic forms, we report severe effects upon its depletion in Xenopus. We find that Xenopus 6-catenin is transcribed as a full-length mRNA, or as three (or more) alternatively spliced isoforms. Further structural and functional complexity is suggested by three predicted and alternative translation initiation sites. Unlike the primarily neural expression of 6-catenin reported in mammals, Xenopus 6-catenin is detectable in most adult Xenopus tissues, although enriched in neural structures. To characterize 6-catenin’s functions in amphibian development, we employed anti-sense morpholinos targeted to inhibit pre-RNA splicing events. 6-catenin knock-down leads to developmental defects in gastrulation and neural crest migration, phenotypes that were specific based upon self-rescue experiments. Biochemical assays indicated that 6-catenin depletion results in reduced C-cadherin levels as well as activation of RhoA. Indeed, titrated doses of C-cadherin or dominant-negative RhoA significantly rescued 6-catenin depletion. Collectively, our experiments indicate that 6-catenin plays an essential role in amphibian development, with contributing functional links to cadherins and Rho family GTPases.

doi:10.1016/j.ydbio.2008.05.165

Program/Abstract # 154
Heterotaxin: A novel pyridine compound that perturbs left–right asymmetric organ morphogenesis
Meredith Parr a, Doug Young b, Michael Dush a, Alex Dieters b, Nanette Nascone-Yoder a a Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA b Department Chemistry, North Carolina State University, Raleigh, NC, USA

Proper orientation of internal organ situs is dependent on correct interpretation of left–right asymmetric cues by developing primordia. To investigate the molecular mechanisms of asymmetric organ morphogenesis, we employed a phenotype-based chemical genetic screen in embryos of the frog Xenopus laevis, which develop organ asymmetries analogous to higher vertebrates. In a pilot screen of 44 natural product-like compounds, synthesized and screened as mixtures of regioisomers, one compound mixture specifically reversed or isomerized the asymmetry of the heart and gut without affecting other aspects of development. Purification and rescreening of the individual components of this mixture revealed a single active pyridine compound, which we termed “Heterotaxin”. The effect of Heterotaxin on organ situs is both dose- and stage-dependent, and occurs with high penetrance. Heterotaxin-treated embryos have either unilateral left, unilateral right, bilateral or absent Pitx2 expression in the lateral plate mesoderm, suggesting that global left–right asymmetry is randomized by Heterotaxin. In contrast to control embryos, which have a well-defined, polarized intestinal epithelium, Heterotaxin-treated embryos have cohesive masses of disorganized, rounded cells protruding into the gut lumen, suggesting that epithelial morphogenesis is involved in the generation of digestive organ asymmetry. The discovery of Heterotaxin thus provides a novel tool to uncover the etiology of heterotaxia, and underscores the utility of a chemical genetic approach to organ morphogenesis.

doi:10.1016/j.ydbio.2008.05.166

Program/Abstract # 155
Basoluminal endoderm intercalation: A geometrically unique execution of convergent extension during gut tube elongation
Nanette Nascone-Yoder, Rachel Reed, Mandy Womble, Michael Dush, Stephanie Bloom, Read Tull, Allison Morckel Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, USA

The vertebrate gut tube undergoes dramatic elongation and rotation, but the morphogenetic mechanisms underlying these topological transformations are poorly understood. We found that endoderm cells in the late stage Xenopus embryo adopt a fusiform bipolar morphology and mediolateral orientation, reminiscent of axial mesoderm cells undergoing convergent extension in the gastrula. However, the endoderm cells rearrange in the unique three-dimen-sional context of the gut tube cylinder and appear to be “captured” as monopolar types at both the basement membrane and expanding central lumen, gradually reorienting themselves to radially-arranged basoluminal “spokes”. The novel geometry of these endoderm cell rearrangements accomplishes gut elongation, provides a morpho-genetic mechanism for generating curvature and rotation, and ultimately facilitates the development of the mature digestive epithelium. Moreover, gut-specific expression of a dominant negative mutant version of RhoA, or exposure of embryos to small-molecule inhibitors of Rho kinase and myosin II, perturbs the cell shape and adhesion patterns necessary for endoderm intercalation, and concomitantly induces severe defects in gut tube elongation, intestinal rotation and epithelial morphogenesis. These results provide insight into the etiology of human digestive deformities, and suggest that the morphogenetic events driving gut elongation via endoderm intercalation are surprisingly analogous to the mechanisms directing axial elongation in gastrulating mesoderm.

doi:10.1016/j.ydbio.2008.05.167

Program/Abstract # 156
Stiffening of the vertebrate embryo during axis elongation depends on actomyosin contractility
Lance Davidson, Hye Young Kim, Jian Zhou Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA