Program/Abstract # 47
Planar cell polarity and the coordination of cell behaviors during axis elongation
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The elongated body axis is an essential developmental feature of vertebrates and invertebrates and relies on the coordination of multiple processes – including polarized motility, selective adhesion and intercellular communication – across a three-dimensional field of cells. A widely used mechanism for tissue elongation is oriented cell intercalation. In Drosophila, the A–P patterning system acts to establish molecularly distinct planar polarized regions of the cell surface that are required for intercalary behaviors. We found that planar polarity in the Drosophila embryo is generated through a sequential enrichment of actin–myosin cables and adherens junction proteins in complementary membrane domains. F-actin accumulation at A–P interfaces represents the first break in planar symmetry and occurs independently of the proper distribution of adherens junction proteins at D–V interfaces. These polarized cytoskeletal and junctional proteins are dynamically reorganized during a novel program of cell behavior in which cells form multicellular rosette structures that assemble and resolve in a directional fashion. Contractile actin–myosin structures align across multiple pairs of polarized adherens junction assembly promotes rosette resolution. A–P patterning mutants selectively disrupt the frequency and directionality of rosette formation. We propose that the generation of higher order rosette structures links local cell interactions to global tissue reorganization during morphogenesis.

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Program/Abstract # 48
Multiple functions of Snail family members in palate development and craniofacial morphogenesis
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Palate development in mammals requires precise regulation of gene expression change, alterations in cell physiology and morphogenetic movements. Defects in any these processes can result in clefting of the secondary palate, one of the most common birth defects observed in humans. The fundamental changes that accompany palate shelf fusion, however, remain controversial, with epithelial–mesenchymal transition (EMT), cell migration and apoptosis providing alternate mechanistic explanations. Members of the Snail gene family are transcriptional repressors that play a central role in the growth and patterning of vertebrate embryos, including the regulation of EMT. We report here that deletion of Snai2 results in cleft

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Program/Abstract # 46
The role of Slit family guidance cues in breast
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Development of many organs, including the mammary gland (breast), involves dramatic changes in shape as tissues are molded into three-dimensional structures. The mammary gland is a tree-like structure composed of bi-layered ducts, comprising an outer layer of myoepithelial cells and an inner layer of luminal epithelial cells surrounding a central lumen. During development, the enlarged termini of ducts, termed end buds, establish the primary ductal architecture and drive the prodigious growth that establishes the mammary tree. My laboratory is interested in understanding mechanisms that regulate ductal architecture, and we have identified two signaling systems responsible for adhesive interactions between the two layers of mammary epithelium. SLITs, like NETRINs (Ntn), were originally characterized as guidance cues that direct neurons and their axons to targets during neural development. In mammary gland, SLIT2 and NTN1 are broadly distributed throughout the epithelial compartment, whereas their receptors, ROBO1 and NEOGENIN1, are restricted to the myoepithelial cell layer. Loss-of-function mutations in any one of the genes result in adhesive defects that are confined to the end bud. Ductal defects, in which the luminal cell layer peels away from the myoepithelial cell layer, are only revealed when both Slit2 and Ntn1 are deleted. These and other studies have led us to propose a model in which the two cues act in parallel through their respective receptors to mediate adhesive interactions between distinct epithelial cell types. We suggest this type of short-range adhesion maintains tissue structure, while allowing cell movement and re-organization during periods of tissue growth and remodeling.

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intermediate steps downstream of the early endodermal factor, Gata5, and that progressively lead to the induction of the pancreatic marker, Pdx1. On the basis of sequence identity, expression profile and functional analysis, we have defined a set of novel endodermal factors that are involved in the patterning of the dorsal/anterior endoderm, including signaling proteins, transcription factors and RNA binding proteins. Here, we have focused on Gata5 targets that modulate the TGFbeta/BMP signaling pathways. Functional analysis of these targets both in Xenopus and mammalian systems revealed that inhibition of BMP signaling is required for the establishment of pancreatic identity within the endoderm. Previous findings demonstrated a critical role for BMP signaling in determining dorsal/ventral fates in ectoderm and mesoderm, and our results now extend this trend to the endoderm.

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palate, the penetrance of which is increased to 100% in the presence of a single Snai1-null allele. This phenotype is due to a failure of the elevated palate shelves to fuse, caused by a lack of apoptosis and the persistence of periderm cells at the medial epithelial edge (MEE). Moreover, deletion of the remaining Snai1 allele using the neural crest-specific Wnt1-Cre results in multiple craniofacial defects, including a distinct cleft palate phenotype. Unlike Snai1+/−;Snai2−/− embryos, clefting in these embryos results from a failure of the Meckel’s cartilage to extend the mandible and thereby allow the vertical palate shelves to elevate, a defect similar to that seen in the Pierre-Robin sequence in humans. This work demonstrates that Snail family members play multiple, critical roles in craniofacial development in mice.

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Program/Abstract # 49
Cell-autonomous accumulation of the Drosophila HIF-α homologue Sima in tracheal cells contributes to tracheal extra-sprouting in hypoxia
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The Drosophila tracheal system is a network of ramified tubes that deliver oxygen to every tissue in the organism. Tracheal development relies mostly on guided cell migration in which the FGF homologue, Branchless (Bnl), is expressed outside the tracheae and attracts the extension of tracheal branches by binding to the FGF receptor homologue, Breathless (Btl), that is expressed in tracheal cells. By the end of embryogenesis, this genetically specified phase of tracheal development has been completed and later, in larval stages, terminal tracheal branches are plastic and have the capacity to sprout-out projections towards oxygen-starved areas in target tissues, very much like angiogenesis in mammals. This oxygen-dependent effect has been also reported to depend on the upregulation of Bnl in target tissues. Here we report that in hypoxic Drosophila larvae, the HIF-α homologue, Sima, accumulates mainly in tracheal cells, provoking transcriptional upregulation of Btl. Loss-of-function mutants for the HIF prolyl hydroxylase gene, fatiga, a well-known negative regulator of Sima, exhibit extra-tracheal branches but this effect is reduced by lowering btl dose. Specific over-expression of Sima or Btl in tracheal cells induce an increase in the number of terminal branches, suggesting that upregulation of the receptor is sufficient for tracheal extra-sprouting. We propose that upregulation of Btl in response to cell-autonomous accumulation of Sima in tracheal cells is a cardinal event in hypoxia-dependent tracheal terminal branching.

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Program/Abstract # 50
Regulation of growth by the Fat tumor suppressor pathway
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It has long been appreciated that organ growth is influenced by organ patterning, but the molecular mechanisms that link them have remained unclear. We have begun investigating a new intercellular signaling pathway, the Fat pathway, that links patterning to growth. fat encodes a large proteoglycan, mutation of which influences both tissue polarity and growth in the imaginal discs of Drosophila. Characterization of the functional relationships among Drosophila tumor suppressors led us to identify the kinases Discs overgrown and Warts as components of a Fat signaling pathway. fat, discs overgrown and warts regulate a common set of downstream genes in multiple tissues, including wingless, Serrate, four-jointed, Diap1, cyclin E and expanded. Fat signaling also interconnects with Hippo signaling at multiple levels, but both genetic and molecular experiments suggest that they act largely in parallel to regulate disc growth, with Hippo signaling regulating Warts phosphorylation, and Fat signaling regulating Warts stability. We will present our current understanding of the molecular basis for signal transduction downstream of Fat, and of the regulation of Fat by the graded expression of its ligand, Dachsous and the Golgi protein Four-jointed.

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Program/Abstract # 51
Fgf8 is essential for development of the male reproductive tract
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Fgf8 plays a major role in the development of several tissues, including the midbrain–hindbrain region, branchial arches, limb bud and metanephros. An examination of mutants with pan-mesodermal inactivation of Fgf8 due to tissue-specific recombination, using the primitive streak-specific TCre transgene, revealed a novel Fgf8-dependent phenotype in the male reproductive tract. Whole-mount immunohistochemistry and in situ hybridization using riboprobes for Fgf8, Pax2, Lim1 and Shh demonstrated that TCre; Fgf8 embryos lack the cranial aspect of the mesonephros, including the mesonephric tubules at E11.5. This results in the loss of the efferent ductules, the head and body of the epididymis and most of the vas deferens in