modulating the differential response to FGF. Founder cells exhibit an enrichment of membrane protrusions on their anterior-ventral surface, where the heart daughter will arise. We have shown that delocalized, constitutive activity of Cdc42, a Rho GTase responsible for the formation of filopodia in many systems, disrupts the polarity of founder cell division. Founder cells expressing delocalized, constitutively active Cdc42 have membrane protrusions placed uniformly around the cell, and both daughters take on heart fate. Polarity can be restored by blocking Cdc42-directed actin polymerization using a truncated form of WASP. To further characterize the relationship between protrusive activity of the actin cytoskeleton and FGF signaling, we will employ live fluorescence microscopy to observe the localization and movement of several components of the signaling pathway downstream of FGF. These results highlight a potential role for the cytoskeleton in regulating differential fate induction events during development.

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Program/Abstract # 312
A feedback loop between xylt1 and sox9 controls chondrocyte differentiation
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Cells must interact with their extracellular environment as they differentiate. Here, we use zebrafish mutant embryos to reveal complex interactions between proteoglycans and chondrocyte differentiation that may regulate the timing of skeletal development in vivo. The enzyme Xylosyltransferase1 (Xylt1) catalyzes proteoglycan synthesis, and the transcription factor Sox9 drives chondrocyte differentiation. We find that xylt1 expression is restricted spatially to differentiating chondrocytes, which express both zebrafish sox9 co-orthologues. Supporting the hypothesis that Sox9 regulates proteoglycan synthesis genes, xylt1 expression appears reduced or absent in sox9 mutant chondrocytes. On the other hand, expression of sox9 genes is down-regulated in xylt1 mutants. These changes appear only after chondrocytes of wild-type siblings begin to secrete abundant proteoglycans, suggesting a positive feedback onto chondrocyte differentiation from their extracellular environment. Interestingly, this positive feedback loop between xylt1 and sox9 appears to control the timing of chondrocyte differentiation: xylt1 mutant chondrocytes express markers of chondrocyte maturation, such as collagen type 10a1 and indian hedgehog (Ihh) co-orthologues, earlier than wild-type siblings. Ihh is known to induce bone in the perichondrium, a tissue that overlies developing chondrocytes, and xylt1 mutants have early perichondral bone. Consistent with the idea that early Ihh expression in xylt1 mutant chondrocytes causes precocious perichondral bone, no early bone forms in xylt1;ihha double mutants.

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Program/Abstract # 313
Identification of a novel protein, LRRP, involved in primitive erythropoiesis and non-canonical Wnt signaling
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In Xenopus, signals from the ectoderm are required to induce mesoderm to adopt an erythroid fate. Our prior work demonstrated that the transcription factor GATA-2 is essential for this inductive signal. Using microarray analysis, we have identified a gene encoding a novel leucine-rich repeat protein (LRRP) that is upregulated by GATA-2 in the ectoderm, and required for erythropoiesis. Our microarray data also indicate that members of the non-canonical Wnt pathway are upregulated by GATA-2, whereas genes associated with the canonical Wnt pathway are downregulated by GATA-2. Reciprocal regulation of these two pathways by GATA-2 is intriguing given recent evidence that GATA proteins are involved in promoting the switch between canonical and non-canonical Wnt signaling in other developmental contexts. Moreover, coordinate regulation of these two often opposing pathways may be required for the transition between progenitor expansion, and differentiation to more mature cell types. Interestingly, in addition to its function during erythropoiesis, LRRP appears to be both necessary and sufficient to activate non-canonical Wnt signaling during convergent extension and heart development. We predict that non-canonical Wnt signaling is activated downstream of GATA-2, possibly in an LRRP-mediated fashion. We further hypothesize that these events are required to inhibit canonical Wnt signaling to allow blood progenitors to exit the cell cycle and adopt a hematopoietic fate.

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Program/Abstract # 315
Transcriptional control of dorsal-ventral polarity cues in C. elegans
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Embryos must undergo a series of asymmetric divisions to establish the three main axes of the body (anterior–posterior, left–
right, and dorsal–ventral) that function to provide polarity cues for cell fate specification and migrations. The *C. elegans* bodywall muscle cells are a great system in which to study spatial polarity cues because this tissue extends the length of the animal in four quadrants, occupying left and right positions on both the dorsal and ventral sides of the animal. One cue known to originate from bodywall muscle is TGF-beta/UNC-129 that is produced at higher levels in dorsal versus ventral muscle. This pattern of unc-129 expression is, in turn, generated by the activity of the transcriptional repressor UNC-130 that is preferentially produced in ventral bodywall muscle. To understand how these dorsal–ventral differences in expression are established, we determined the temporal pattern of factors required to establish ventral polarity by using a combination of reporter genes, imaging in live embryos, and antibody staining of fixed embryos. We can also define the cis-acting elements regulating unc-130, by identifying an evolutionary conserved sequence that is also sufficient to impose ventral polarity on a promoter element that normally is expressed uniformly in all body wall muscle. In order to find the trans-acting factor, we are performing a RNAi screen of candidate transcription factors in *C. elegans*. By identifying cell autonomous and non-autonomous factors regulating unc-130 expression we hope to understand the logic behind the establishment and maintenance of spatial and temporal polarity cues important for animal development.

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Program/Abstract # 316

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Program/Abstract # 317

Signaling through BMP receptors promotes respiratory identity in the foregut through repression of SOX2

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The mammalian foregut gives rise to the dorsally-located esophagus and stomach, and the ventrally-located trachea and lung. Proper patterning and morphogenesis of the common foregut tube and its derived organs is essential for viability of the organism at birth. Previous studies suggest that bone morphogenetic protein (BMP) signaling is important for early stages of respiratory development. However, its precise role in this process remains unclear. Here we show that conditional inactivation of BMP Type 1 receptor genes Bmpr1a and Bmpr1b (Bmpr1a;b) in the ventral endoderm led to tracheal agenesis and ectopic primary bronchi. Molecular analyses show that these mutants exhibit a reduction of ventral endodermal marker NKX2.1 and a complementary expansion of dorsal markers SOX2 and p63 in the prospective trachea and primary bronchi. Furthermore, we found that inactivation of Sox2 rescued tracheal formation, but did not suppress ectopic lung budding in Bmpr1a;b mutant mice. Together, our data suggest that signaling through BMPRIA:B performs at least two roles in early respiratory development: first, it promotes tracheal formation through repression of Sox2, and second, it restricts the site of lung bud initiation.

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Program/Abstract # 318

Ngn3 as a dosage sensitive driver for beta cell differentiation during embryogenesis and regeneration

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Ngn3 drives endocrine differentiation from endodermal progenitors during embryogenesis. We study how a specific portion of pancreatic progenitors is selected to activate Ngn3 expression, how Ngn3 level with each progenitor cell is controlled and how Ngn3 regulates islet cell differentiation. We show that during embryogenesis, Ngn3 must reach a high level to push pancreatic progenitor cells to endocrine islet cell fates. Reducing Ngn3 dosage pushes Ngn3+ cells to pancreatic duct and acinar cell fates, demonstrating that pancreatic progenitors maintain their multipotency before Ngn3 expression reaches a high level. Furthermore, we show that an absence of Ngn3 proteins reduces the transcription of Ngn3 in individual cells while increasing the number of progenitors that activate Ngn3 transcription, suggesting that Ngn3 utilizes both feed-forward and feed-back mechanisms to regulate its expression. In the adult stages, regenerative conditions, including partial pancreatectomy and partial duct ligation, could activate a low level of Ngn3 expression in both pancreatic duct and acinar cells. However, cell lineage tracing showed that most of these Ngn3+ cells do not differentiate into endocrine islet cells, as in embryonic pancreas. These data suggest that although the adult pancreatic cells maintain a degree of plasticity, a simple injury is not sufficient to induce these cells to become endocrine islet cells. These findings also suggest that microenvironments (factors) in the embryonic pancreas can cell autonomously reprogram the adult pancreatic cells.

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