Program/Abstract # 213
The embryonic neural crest microenvironment as a model system to explore tumor cell reprogramming and metastatic ability
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The embryonic neural crest microenvironment represents an attractive model system to explore tumor cell reprogramming and metastatic ability. The neural crest (NC) is a pluripotent cell population that invade the embryo in a programmed manner to form many derivatives, including neurons, glia, and melanocytes to protect the body from UV radiation. Specification of the NC is thought to be endowed by signals within the neural tube, but can be reprogrammed by the environment through which NC cells migrate. We will show that when adult human metastatic melanoma cells, with ancestral origin to the NC, are transplanted into the chick embryonic NC microenvironment, the melanoma cells invade host NC targets, do not reform tumors and a subset of melanoma cells reprogram to a NC cell-like phenotype. Using high resolution 3D confocal imaging we show that invading melanoma cells display NC cell-like morphologies within the branchial arches, dorsal root and sympathetic ganglia. We will discuss analysis of melanocyte-specific phenotype markers in the subpopulation of invading melanoma cells. Monitoring of melanoma cell dynamics within the embryonic NC microenvironment combined with molecular analyses offer the potential to reveal the signals that alter melanoma cell identity and invasive ability.

doi:10.1016/j.ydbio.2007.03.540

Program/Abstract # 214
An in vivo role for neuropilin-1 in cranial neural crest cell migration
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During vertebrate development, the neural crest (NCs) is a pluripotent population of cells that delaminate from the neural tube and migrate in a stereotypical pattern to specific destinations. In the cranial region, discrete NC cell migratory streams invade the branchial arches to form facial structures and components of the nervous system, yet signaling mechanisms that produce the stereotypical NC cell migration pattern are still unclear. We are interested in exploring the function of potential cranial NC guidance factors, and use molecular perturbations and microsurgery in combination with time-lapse confocal analysis. We have identified a putative cranial NCCs guidance cue, neuropilin-1, by using a siRNA neuropilin-1 construct to knock down neuropilin function in ovo. When neuropilin-1 function is knocked down in ovo, NCCs fail to fully invade the 2nd branchial arch. Neuropilin-1 siRNA transfected cells sort into and maintain a directed migratory stream, but stop and collapse filopodia near the entrance to the 2nd branchial arch. Our results demonstrate that neuropilin-1 is a guidance cues that facilitates correct cranial NCC migration in vivo, and that distinct mechanisms shape NCC migratory stream formation and branchial arch invasion.

doi:10.1016/j.ydbio.2007.03.401

Program/Abstract # 215
Neural crest migration and dorsal root ganglia formation in zebrafish erbB3 mutant
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ErbB3 is a receptor-type tyrosine kinase that has been shown to have important roles in glial development and in sympathetic ganglion formation. In mice with a targeted mutation of ErbB3, neural crest cells make an ectopic cluster around the DRGs, raising the possibility that neural crest migration is defective. To learn whether erbB3 is required for normal neural crest migration, we have taken advantage of the transparency of zebrafish embryos and studied neural crest migration in erbB3 zebrafish mutants. We found that erbB3 mutants also have a defect in DRG formation, as revealed by
absence of neurogenin1-positive nascent DRG cells at 30 h postfertilization (hpf) and by absence of HuC/D-positive DRG neurons at 4 days postfertilization. However, markers that label migrating neural crest cells revealed no obvious defects in the pattern of neural crest migration in erbB3 mutants at 24 hpf. To learn whether other aspects of neural crest migration are affected in these mutants, we followed neural crest migration in live transgenic embryos in which GFP expression is driven by the zebrafish sox10 promoter. Treating embryos with the ErbB receptor inhibitor, AG1478, did not appear to affect overall neural crest motility, but did appear to affect the ability of migrating neural crest cells to stop near the position where the DRG normally forms. Although a few neural crest cells are present near where the DRG forms, they do not appear to become DRG neurons. These results suggest that erbB3 may be involved in the ability of DRG progenitors to recognize their target position during migration and to respond to DRG instructive signals.

doi:10.1016/j.ydbio.2007.03.402

Program/Abstract # 216
Diverse roles of Notch signaling in cardiac cell differentiation, migration and ventricular morphogenesis
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Heart development serves as an excellent model system for studying developmental processes such as tissue patterning, morphogenesis and cell differentiation. We found that a conserved signaling pathway, Notch, plays important and diverse roles in cardiac development, including cell differentiation, migration and ventricular morphogenesis. Expression of a constitutively active form of Notch (NIC) inhibits cardiac muscle differentiation, and promotes the differentiation of conduction cell, a specialized cell type responsible for setting and coordinating rhythmic heart beating. Conversely, by using a dominant-negative suppressor-of-hairless construct, we found that reducing Notch signaling resulted in an increasing cardiac muscle marker expression and a decrease of conduction marker expression. In addition, activation of Notch by expression of NIC or addition of soluble Delta1 ligand promoted cardiomyocyte migration in 3-D migration assay and caused an increase in trabeculae formation in the ventricles in vivo. Interestingly, the effect of Notch on promotion of cardiomyocyte migration can be separated from its effect on cell differentiation, thus representing a novel function of notch during development.

doi:10.1016/j.ydbio.2007.03.403

Program/Abstract # 217
Lipid phosphate phosphatases are necessary for the trans-epithelial migration of germ cells
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Drosophila germ cells form spatially and temporally separate from the somatic cells of the gonad and therefore migrate through the embryo to associate with them. Extracellular lipid phosphates are implicated in this migration because the lipid phosphate phosphatases, wunen and wunen2 are expressed redundantly in somatic tissues to repel germ cells during their migration and also in germ cells to promote their survival. We recently identified a role for Wunens in the process of trans-epithelial migration. In wild-type embryos the germ cells, which initially are tightly clumped, individualize and migrate across the midgut epithelium in order to reach the somatic cells of the gonad. In embryos lacking Wunens in germ cells and somatic cells, the germ cells remain tightly clumped and fail to migrate across the midgut epithelium. We visualized germ cell behavior in this background by live imaging. We see that germ cells inside the midgut are motile. We hypothesize that during trans-epithelial migration Wunens are required either to provide directionality to germ cells or to regulate cell–cell adhesion. We are currently distinguishing between these possibilities by testing for suppression of this phenotype with mutations in cell adhesion molecules.

doi:10.1016/j.ydbio.2007.03.404

Program/Abstract # 218
Identification of genes affecting Drosophila larval somatic muscle patterning
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Cell migration is required for biological processes as diverse as organ formation during embryonic development and metastasis of diseased tissues. During development of the musculature, migrating muscle cells are guided towards specific attachment sites. The Drosophila larval muscles provide a simplified system for studying cell migration and guidance during muscle development. Drosophila larval somatic muscle fibers are organized into an intricate, repeating pattern during embryonic development. This pattern depends on individual myotubes extending filopodia as they migrate and attach to specialized epidermal cells called tendon cells. These tendon cells release guidance cues to direct muscle fibers to their correct positions. Few molecules have been shown to function in this guidance process. Identification of genes involved in muscle guidance will provide a better understanding of what mechanisms may play a role in this process. We have isolated several Drosophila EMS mutations affecting the ability of somatic muscles to correctly select their proper epidermal attachment sites. The phenotypes of