whether CTGF is required in the pancreatic endodermal epithelium, vasculature, or β cells themselves.

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Program/Abstract # 348
Cross-talk between neural crest cells and developing pancreatic epithelium regulates beta-cell mass
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In the ventral hindbrain, mouse homeodomain transcription factor Phox2b works in concert with Nkx2.2 to determine subtype identity of neurons. In the periphery, Phox2b is expressed by neural precursors that colonize the gut to form the enteric nervous system. We found Phox2b briefly expressed by neural precursors that colonize the gut to form the enteric nervous system. We found Phox2b briefly expressed in E12.5 mouse embryonic pancreas, in cell nuclei along the epithelial–mesenchymal border, and down-regulated in an Nkx2.2-dependent manner shortly afterwards. Lineage tracing with β-galactosidase staining of Pdx1-Cre/Rosa26-LacZ embryos indicated that Phox2b-expressing cells did not originate from Pdx1-expressing pancreatic epithelium. Instead, the timing of pancreatic Phox2b expression, its mesenchymal localization and co-localization with SOX10 are all consistent with its expression in neural-crest derived cells in other parts of the gut tube. In addition, Pgp9.5-positive differentiated neurons were absent from both the pancreas and the stomach of mice lacking functional Phox2b alleles. On the other hand, its transient expression and Nkx2.2-dependency represent unique aspects of pancreatic Phox2b expression. Interestingly, the pancreas of Phox2bLacZ/LacZ transgenic mice contained unique aspects of pancreatic Phox2b expression. Interestingly, cell autonomous and cell non-autonomous effects of Wnt/b-catenin signaling, the other activated by Nodal signaling, function in parallel to pattern the early heart field. Wnt antagonists such as Dkk-1, Gsk3b and a dominant negative form of the transcription factor TCF3 pattern the heart indirectly by inducing expression of the transcription factor Hex in the endoderm underlying the presumptive heart field, whereas the Nodal homologue (XNr-1) functions by inducing the secreted molecule Cerberus. Since both pathways function in the endoderm fated to become liver and pancreas, we asked (1) whether these pathways influence differentiation of endodermal organs, and (2) the identity of the secreted factor(s) induced by Hex or Cerberus that induce heart tissue. Q-RTPCR and in situ hybridization analyses show that both Wnt/b-caten antagonists and XNr-1 re-pattern endoderm to express markers for differentiated endoderm, including liver and pancreas. Interestingly, cell autonomous and non-autonomous effects of Wnt/b-catenin signaling led to the induction of distinct endodermal derivatives. Moreover, in the case of Dkk-1, this tissue is capable of forming insulin-positive islet cells. Finally, we have identified several potential downstream factors by screening two Xenopus gene microarrays. The candidate inducing proteins are being testing for

In the ventral hindbrain, mouse homeodomain transcription factor Phox2b works in concert with Nkx2.2 to determine subtype identity of neurons. In the periphery, Phox2b is expressed by neural precursors that colonize the gut to form the enteric nervous system. We found Phox2b briefly expressed in E12.5 mouse embryonic pancreas, in cell nuclei along the epithelial–mesenchymal border, and down-regulated in an Nkx2.2-dependent manner shortly afterwards. Lineage tracing with β-galactosidase staining of Pdx1-Cre/Rosa26-LacZ embryos indicated that Phox2b-expressing cells did not originate from Pdx1-expressing pancreatic epithelium. Instead, the timing of pancreatic Phox2b expression, its mesenchymal localization and co-localization with SOX10 are all consistent with its expression in neural-crest derived cells in other parts of the gut tube. In addition, Pgp9.5-positive differentiated neurons were absent from both the pancreas and the stomach of mice lacking functional Phox2b alleles. On the other hand, its transient expression and Nkx2.2-dependency represent unique aspects of pancreatic Phox2b expression. Interestingly, the pancreas of Phox2bLacZ/LacZ transgenic mice contained unique aspects of pancreatic Phox2b expression. Interestingly, cell autonomous and cell non-autonomous effects of Wnt/b-catenin signaling, the other activated by Nodal signaling, function in parallel to pattern the early heart field. Wnt antagonists such as Dkk-1, Gsk3b and a dominant negative form of the transcription factor TCF3 pattern the heart indirectly by inducing expression of the transcription factor Hex in the endoderm underlying the presumptive heart field, whereas the Nodal homologue (XNr-1) functions by inducing the secreted molecule Cerberus. Since both pathways function in the endoderm fated to become liver and pancreas, we asked (1) whether these pathways influence differentiation of endodermal organs, and (2) the identity of the secreted factor(s) induced by Hex or Cerberus that induce heart tissue. Q-RTPCR and in situ hybridization analyses show that both Wnt/b-caten antagonists and XNr-1 re-pattern endoderm to express markers for differentiated endoderm, including liver and pancreas. Interestingly, cell autonomous and non-autonomous effects of Wnt/b-catenin signaling led to the induction of distinct endodermal derivatives. Moreover, in the case of Dkk-1, this tissue is capable of forming insulin-positive islet cells. Finally, we have identified several potential downstream factors by screening two Xenopus gene microarrays. The candidate inducing proteins are being testing for

Program/Abstract # 349
ptf1a determines pancreatic exocrine versus endocrine fates
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Understanding how progenitor cells of the pancreas are specified to differentiate into endocrine cells has profound implications on diabetes therapeutics. Although the bHLH encoding gene, ptf1a, is required for exocrine differentiation, ptf1a is expressed in the progenitor cells of all pancreatic cell types. To determine the function of ptf1a in endocrine cell fate specification, we examined the differentiation of ptf1a mutant cells using a zebrafish ptf1a mutant in the transgenic ptf1a:GFP reporter background. In contrast to previous conclusions, we find that endocrine cell neogenesis occurs independent of ptf1a function. Furthermore, we show that cells that would normally express ptf1a and become exocrine cells, are transdetermined towards an endocrine fate in ptf1a mutants, indicating that ptf1a represses endocrine differentiation. This transdetermination of ptf1a expressing cells is not observed in other embryos with defective exocrine differentiation suggesting that ptf1a plays a specific and crucial role in determining exocrine versus endocrine specification. We conclude that exocrine and endocrine cell fates are not predetermined, and that the down-regulation of Ptf1a function is required to allow for endocrine cell specification. This finding provides a potential mechanism for exocrine to endocrine cell transdifferentiation, which has substantial implications on pancreatic endocrine cell replacement therapy for diabetic patients.

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Program/Abstract # 350
Dkk-1 and Nodal function in parallel to induce both heart and endodermal organs such as liver and pancreas
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We recently demonstrated that two genetic pathways, one mediated by antagonists of canonical Wnt/b-catenin signaling, the other activated by Nodal signaling, function in parallel to pattern the early heart field. Wnt antagonists such as Dkk-1, Gsk3b and a dominant negative form of the transcription factor TCF3 pattern the heart indirectly by inducing expression of the transcription factor Hex in the endoderm underlying the presumptive heart field, whereas the Nodal homologue (XNr-1) functions by inducing the secreted molecule Cerberus. Since both pathways function in the endoderm fated to become liver and pancreas, we asked (1) whether these pathways influence differentiation of endodermal organs, and (2) the identity of the secreted factor(s) induced by Hex or Cerberus that induce heart tissue. Q-RTPCR and in situ hybridization analyses show that both Wnt/b-caten antagonists and XNr-1 re-pattern endoderm to express markers for differentiated endoderm, including liver and pancreas. Interestingly, cell autonomous and cell non-autonomous effects of Wnt/b-catenin signaling led to the induction of distinct endodermal derivatives. Moreover, in the case of Dkk-1, this tissue is capable of forming insulin-positive islet cells. Finally, we have identified several potential downstream factors by screening two Xenopus gene microarrays. The candidate inducing proteins are being testing for