

Influence of the Vasculature on Pancreas and Liver Development

Kenneth Zaret¹, Hideyuki Yoshitomi¹, Yasushige Kashima¹, Patrick Jacquemin², Guy Rousseau², and Frederic Lemaigre²

¹Cell and Developmental Biology Program, Fox Chase Cancer Center, Philadelphia, PA

²Hormone and Metabolic Research Unit, Institute of Cellular Pathology, Université catholique de Louvain, Brussels, Belgium

Understanding the cellular niche in which tissue buds for the pancreas and liver develop from the embryonic endoderm, at the onset of organogenesis, provides a framework for rational approaches to control tissue repair, regeneration, and stem cell differentiation. Studies from a variety of laboratories, including our own, of the induction of liver and pancreas development in mouse embryos have revealed that sequential and combinatorial interactions between endoderm cells and different kinds of mesoderm cells define an organogenic code that specifies cell type and the initiation of tissue morphogenesis. For example, liver induction requires endodermal interactions with cardiogenic mesoderm (FGF signaling), septum transversum mesenchyme (BMP signaling), and endothelial cells (signaling unknown); and dorsal pancreas induction requires endodermal interactions with the notochord, aortic endothelium, and dorsal mesenchyme. Notably, our tissue recombination studies with embryo liver and pancreas bud explant cultures have shown that interactions with endothelial cells are intrinsic to the cells and not solely to endothelial function as a conduit for blood factors and oxygen. By reconstituting interactions between liver and pancreatic tissue buds from *flk-1* homozygous null embryos, which lack an endothelium, with different kinds of endothelial cells in three-dimensional cultures *in vitro*, we have discovered a surprisingly diverse array of inductive consequences. The tissue recombination assay reveals functionally distinct niche environments that are created by different kinds of endothelial cells. We also have discovered a relay pathway by which aortic endothelial cells selectively support mesenchymal cells, which in turn are needed to ensure the specification of dorsal pancreatic tissue in embryos. These studies show that tissue induction steps can be dependent upon interactions between different mesodermal cell types within an organogenic niche. Defining this network of interdependent relationships reveals the organogenic code for tissue development.