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## Blood Vessels Trigger Development of the Pancreas

Scientists have known that developing organs communicate with blood vessels via chemical signals to ensure that they receive the proper blood supply to sustain growth. Now, researchers have discovered that blood vessels can send signals that trigger development of the pancreas. The finding provides the first glimpse of a new type of biochemical signaling pathway that may prevent the pancreas, and possibly other organs, from developing until a blood-supply pipeline is in place.

According to the researchers, the source of the blood vessel signal may prove useful to scientists who are hoping to guide the differentiation of embryonic stem cells into pancreatic islet cells, the insulin-producing cells that are depleted in people who have type I diabetes. The discovery was published September 28, 2001, in the journal *Science*, as part of the *Science Express* Web site.

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"Other biologists might already have thought of the possibility of such signaling, but it was definitely a surprise to me," said Douglas A. Melton, a Howard Hughes Medical Institute investigator at Harvard University. According to Melton, insights from histological studies provided the initial evidence that led them to search for blood vessel signaling.

"When we used histological sections to examine how the pancreas develops, what jumped out was that we could never find any evidence for pancreas development or differentiation when there wasn't a blood vessel touching it," he said. "Also, it has been long known that in mice the pancreas develops by initially forming three buds, which are subsequently reduced to two. These remaining two buds fuse to form the whole pancreas. We'd always been puzzled about why the third bud disappears, and our examinations showed that this bud invariably loses its contact with a blood vessel. Taken together,

these studies indicated to us that pancreatic development is closely linked with the presence or absence of blood vessels.”

Melton and colleagues Eckhard Lammert and Ondine Cleaver did three types of experiments that provided additional evidence that blood vessel endothelial cells transmit signals to embryonic endodermal cells that develop into tissues such as the pancreas.

In cell culture studies, Melton and his colleagues found that isolated, cultured endoderm cells showed no signs of becoming pancreatic cells as they grew. When the scientists added cells from the dorsal aorta — a vessel that lies next to those cells in the developing embryo — the endoderm cells began expressing insulin and the gene, *Pdx1*, which is a known marker of pancreatic differentiation.

In experiments using frog embryos, the scientists found that when they removed blood vessels that were adjacent to pancreatic tissue, the embryos did not show normal expression of genes or insulin production that would be characteristic of normal pancreas differentiation.

Finally, the scientists created transgenic mice in which the gene *VEGF164*, which triggers blood vessel development, was overexpressed. In these studies, the scientists found that a dramatic increase in blood vessel endothelial tissue accompanied a similar increase in pancreatic islet cells. The researchers also found insulin-producing cells in the stomachs of the mice — an area where such cells would not normally appear. The three lines of evidence warrant a rethinking of the role of blood vessels in organ development, said Melton.

“The fact that all tissues and organs in the body need blood has led many biologists, including myself, to consider blood vessels as tubing that provides sustenance for the body,” he said. “But beyond that, there are a special set of organs or tissues in the body that use blood to serve their basic functions. These include hormone-secreting endocrine glands, lungs, kidneys, the liver and the pancreas.

“So, these organs must arrange for intimate contact with vessels,” he said. “To do this, they could develop first and then send signals to blood vessels to come to them — as tumors do in the process of angiogenesis. Or, these organs could also use a mechanism involving signals from blood vessels to trigger their differentiation, to guarantee this intimate contact before they develop.”

Given the new findings that blood vessels signal pancreatic cells, Melton expects a similar signaling system to be found in other organs. While the discovery of this signaling mechanism will most likely aid efforts to trigger stem cells to become islet cells, which may be used to treat diabetes, Melton emphasizes that blood-vessel-signaling constitutes only one factor governing differentiation.

“This is not the answer by itself to the problem of making islet cells,” he said. “But it is an important finding because it reveals one of the signals in a

stepwise path in islet cell differentiation,” he said.