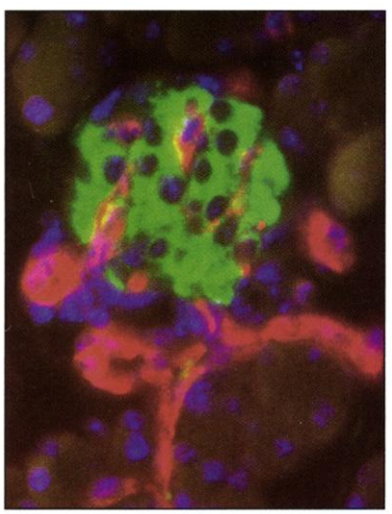
DEVELOPMENTAL BIOLOGY

Organs Await Blood Vessels' Go Signal

Blood vessels are the body's plumbing, supplying food and oxygen and removing waste. Now two papers published online this week by *Science* (www.sciencexpress.org) show that blood vessels play a more active role than previously believed: They help direct the construction of the body they serve. The teams, led by Douglas Melton of Harvard University and Kenneth Zaret of the Fox Chase Cancer Center in Philadelphia, report that blood vessels induce development of the pancreas and liver—even before the blood vessels are functioning.

Cancer researchers stumbled upon the first evidence that blood vessels do more than ferry food and waste around the body. In 1995, a team reported that endothelial cells, which make up blood vessel walls, produce growth factors.



Time to grow up. Blood vessels (red) direct islets (green) to differentiate.

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The new studies build on that work, showing that by sending another, as-yet-unidentified molecular signal, the embryonic blood vessels direct embryonic tissue not just to grow but to differentiate into complex structures. "The endothelial cells aren't just a bunch of pipes and tubing; they contribute to the formation of the organ," says liver regeneration researcher Robert Costa of the University of Illinois, Chicago. "That's really the most important part of the discovery."

Melton's team began scrutinizing blood vessels after noticing something odd about how cells in the mouse pancreas differentiate into islets, clusters of cells that produce insulin. The researchers observed that the endoderm—embryonic tissue fated to become middle organs such as the lungs, liver, pancreas, and stomach—directly touches a major blood vessel, the dorsal aorta. "It begs the question, is there a signal there?" says postdoc Ondine Cleaver, a co-author of the paper. The developed pancreas monitors blood vessels to assess blood glucose levels and tweak insulin production accordingly. The team suspected that the pancreas and blood vessels talk to one another chemically during development as well.

To test their hypothesis, the researchers first surgically removed cells fated to become the dorsal aorta from frog embryos. This dramatically reduced levels of insulin and two other pancreatic secretions in the developing embryos. To make sure the pancreas wasn't hobbled due to a lack of blood flow, Cleaver and fellow postdoc Eckhard Lammert grew undifferentiated mouse embryo tissue in culture with and without embryonic dorsal aortae. Only in the presence of the blood vessel did the tissue produce pancreas-specific markers, including insulin. Finally, the researchers overexpressed a blood vessel growth factor, VEGF, in mouse embryos. This increased blood vessel production as well as islet formation and insulin production.

The Philadelphia group, meanwhile, approached the blood vessel question from another angle. Zaret and colleagues examined liver development in mice with a mutation in a gene called *flk-1*, which encodes a receptor for VEGF. When such mice are developing, the team found, no blood vessels form in the part of the endoderm destined to turn into the liver. What's more, "in the absence of such endothelial cells, the liver bud stops dead in its tracks and doesn't develop further," Zaret says.

To verify that an absence of blood vessels prevented the liver from developing, visiting scientist Kunio Matsumoto of Osaka University in Japan invented a new cell culture system that permitted blood vessels to grow among cultured liver tissue. Once the system was in place, the researchers compared mutant cells with normal cells. The *flk-1* culture grew to the same size as the normal one. But whereas about 20% of the normal culture consisted of liver tissue, only 5% of the mutant culture became liver; the rest was connective tissue. Surprisingly, the endothelial cells' influence arose well before the cells turned into functional blood vessels, suggesting that the cells themselves—and not some component of the blood—were sending the growth signal.

Understanding how cells differentiate will be critical to any future stem cell–based treatments for disease, such as growing islets in the lab for transplantation into diabetics. "If we're going to induce organs to form, we have to have a thorough understanding of how the embryo develops them," says organ replacement biologist Michael Longaker of Stanford University School of Medicine in Palo Alto, California. "We will never do it in a more elegant way than the embryo."

—CAROLINE SEYDEL

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PLANETARY SCIENCE

New Visitors Set For Lunar Voyage

NAPLES, ITALY—Like flared jeans and disco, exploration of the moon is back in fashion. Next week, at a meeting of the International Astronautical Federation in Toulouse, France, Japanese and European scientists will present new missions that will probe the satellite's surface and interior.

Apart from two U.S. missions—Clementine in 1994 and Lunar Prospector in 1998—the moon has been largely ignored since Apollo 17 departed with a load of moon rocks in 1972. But plenty of good science remains to be done. "The moon still has many, many mysteries, such as its origin and evolution," says Hitoshi Mizutani, head of planetary research at Japan's Institute of Space and Astronautical Science (ISAS).

By far the most ambitious project is Japan's Selene—"we call it the Rolls-Royce for the exploration of the moon," says Bernard Foing of the European Space Agency (ESA). Costing $350 million and carrying 200 kilograms of instruments, Selene will be launched jointly by ISAS and NASDA, Japan's space agency, in 2005. The craft's 14 sensors include x-ray and gamma ray spectrometers to chart elements on the surface and an alpha-particle spectrometer to analyze radiation emitted by radon gas and polonium. A stereoscopic camera will also map the lunar topology.

Scientists expect that Selene will improve our understanding of the origin and evolution of the moon. Some observers,