Team conquers angiogenesis puzzle

Divide and . . . creep and coalesce? Endothelial cells do exactly that as they form new blood vessels—and whole vascular networks—in a process called angiogenesis. Physicians and scientists in Dartmouth's Angiogenesis Research Center have been trying to figure out how the process works.

They recently made an exciting discovery—in zebra fish and mice—about a genetic defect that affects the growth of arteries but not veins. When endothelial cells lack the intracellular protein synectin, their ability to form arterial networks is impaired; the vessels are smaller and there are fewer branches than in normal networks.

The report, published in the journal *Developmental Cell*, "is one of the first papers to show a molecular difference between arteries and veins," says DMS molecular and computational geneticist Thomas Chittenden, Ph.D., a principal author of the report. A follow-up paper, published in *Physiological Genomics*, provided further insights.

First: The finding is important because "it's the first description of an arterial branching defect," explains Michael Simons, M.D., chief of cardiology at DHMC and leader of the international team, which included researchers from Belgium and elsewhere in the U.S. In addition, the data suggests that there is "a fundamental difference in how arterial and venous cells respond to signals [and that] arteries and veins are different from the very beginning."

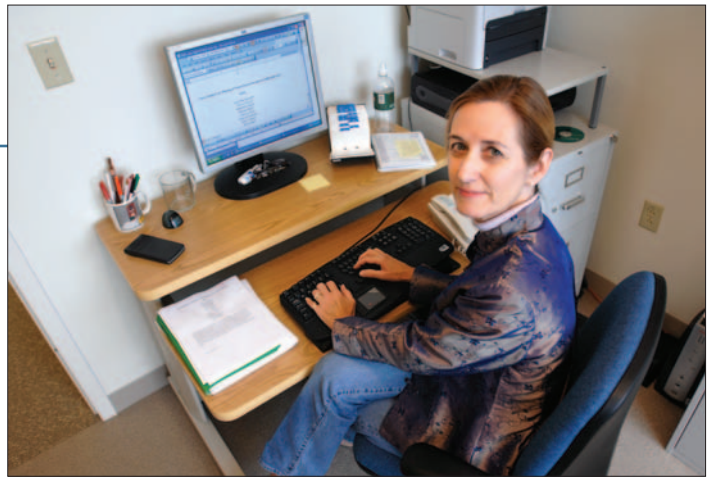
Scientists have long yearned to gain control over angiogenesis in the hope of developing therapies to counteract the over- or understimulation of blood vessel growth. Angiogenesis is a natural process by which the circulatory system is formed in developing embryos and blood flow is restored after injury in adults. Sometimes, however, angiogenesis goes awry, resulting in either too many vessels—such as in cancer, or too few—such as in coronary artery disease.

When tissues are damaged or diseased, they release angiogenic growth factors, which activate the endothelial cells lining nearby blood vessels. Those cells divide, migrate through tiny openings into adjacent tissues, then coalesce to form new vessels. The cells migrate by inching along on microfilaments called lamellipodia. But when synectin is missing, lamellipodia don't develop properly.

"It's amazing to watch the cells crawl along," says molecular biologist Anthony Lanahan, Ph.D., another member of the team. He made time-lapse movies of mouse endothelial cells as they migrated across culture dishes. The ones from "mice without the synectin gene crawled more slowly," he explains.

"Not only does this [study] have strong implications for cardiovascular disease, but for cancer, too . . . if we can figure out how to choke off the blood supply to a tumor," says Chittenden.

Their next target is "to see if abnormalities in synectin expression can explain some of the clinical findings in patients with coronary artery disease," adds Simons. LAURA STEPHENSON CARTER



FLYING SQUIRREL GRAPHICS

Titus-Ernstoff is looking into generational ripples from the use of DES decades ago.

DES effects run deeper than feared

A drug banned over 30 years ago still has implications today, a DMS epidemiologist is discovering. For 15 years, Linda Titus-Ernstoff, Ph.D., and a team of researchers around the country have been studying the long-term effects of diethylstilbestrol (DES)—a powerful synthetic estrogen once prescribed to millions of pregnant women in the United States. The dangers of DES, Titus-Ernstoff is finding, may extend further than anyone previously thought.

From about 1940 through the early 1970s, doctors commonly prescribed DES to reduce the risk of miscarriage—despite studies showing that it was potentially harmful and ineffective. The drug was finally banned in the early 1970s, when many of the prenatally exposed daughters developed an extremely rare vaginal cancer. Since then, researchers, including Titus-Ernstoff, have revealed numerous other side effects of DES: an increased risk of breast cancer in women who took DES while pregnant; of reproductive-tract abnormalities, menstrual irregularities, infertility, adverse pregnancy outcomes, and breast cancer in women who were prenatally exposed; and of urogenital abnormalities in men who were prenatally exposed.

Most recently, Titus-Ernstoff and her colleagues have found evidence that the children of the prenatally exposed may have DES-related abnormalities, too. While the drug "doesn't seem to create genetic mutations," says Titus-Ernstoff, "it may change gene expression in the prenatally exposed . . . and those changes in gene expression may be transmitted to the next generation." If proven, this would be a revolutionary finding in genetics, epidemiology, and numerous other fields. But, she is quick to caution, "these are very preliminary results. . . . Take it with a grain of salt until it's confirmed" by more research. Titus-Ernstoff is among those pursuing such research, as the lead investigator for a National Cancer Institute-funded study.

Impact: Whether these findings are confirmed or not, the DES saga is important as "a model for environmental and pharmaceutical estrogens and their impact," she says. "We can get estrogens through the environment, through our diet, through pesticide exposure . . . [or] pharmaceutically. [And DES] gives us some idea of what estrogen does when a fetus or embryo" is developing. JENNIFER DURGIN