quences with the growing public EST database, known as dbEST, searching for gene fragments that might code for them. They managed to find matches for 65 of the 69 potential spliceosome components. They then sequenced the full lengths of DNA represented by the ESTs to get the complete genes, which yielded insights into the nature and function of the proteins. Some of the 65 proved to be variants of the same protein, so in the end the team was left with 25 known spliceosome proteins and 19 new ones. To confirm that all the new proteins were really part of the spliceosome, the researchers linked the gene for each one to the gene for a fluorescent protein. They showed that the hybrid genes produced proteins that glowed in parts of the nucleus where spliceosomes were expected.

The spliceosome analysis "is a technical tour de force," says spliceosome researcher Thoru Pederson of University of Massachusetts Medical School in Worcester. Although it took 3 years, the researchers say they could perform it in a matter of months now that they have proven the techniques. Their success shows, for example, that the dbEST database now contains fragments of almost all the genes for the spliceosome—and, most likely, for many other multiprotein complexes, says molecular biophysicist Charles Cantor, of Sequenom Inc., a genomics company in San Diego. That had been in doubt because no one knew exactly how many of the more than 50,000 human genes were represented by the database.

The spliceosome work is also a pioneering example of "proteomics"—the effort to get from genome sequence data to protein function by analyzing many proteins at once. "We've all been excited by the genomics project," Pederson says. "This is the beginning of the proteomics project." **–DAN FERBER**

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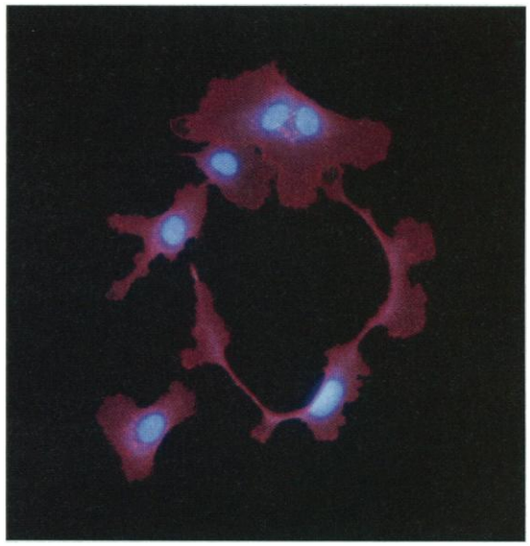
CELL BIOLOGY

Leptin Sparks Blood Vessel Growth

You can hardly find two hotter biomedical research areas these days than angiogenesis, the growth of new blood vessels, which has emerged as an exciting new target for anticancer drugs, and obesity, a field that was energized 4 years ago by the discovery of leptin, an appetite-suppressing hormone made by fat cells. Now, in a curious twist, biochemist M. Rocío Sierra-Honigmann of Yale University and her colleagues have forged a direct link between those two fields. They report on page 1683 that leptin triggers angiogenesis in experimental animals.

"No one would have thought that leptin has anything to do with angiogenesis. This is a paper that is going to change people's thinking," says angiogenesis pioneer Judah Folkman of Harvard Medical School in Boston. Just what leptin's double duty means for the workings of the body isn't clear yet. But findings by Sierra-Honigmann's team and others suggest several intriguing possibilities. One is that leptin contributes to the formation of the new blood vessels needed when fat increases in volume. Leptin may also spur blood vessel growth in the maturing egg and early embryo and in healing wounds as well.



M. R. SIERRA-HONIGMANN

Circle dance. Endothelial cells treated with leptin draw together to begin to form tubes.

Sierra-Honigmann decided to see whether leptin promotes angiogenesis because of a chance discovery she made a year and a half ago while helping out her husband, Jaime Flores-Riveros, who was then at the Bayer Research Center in West Haven, Connecticut. He had engineered cultured cells to make the cell surface receptor through which leptin exerts its effects—a receptor then known to be found mainly in the brain. Sierra-Honigmann was using antibodies to confirm that the cells actually contained the receptor. As a negative control for the antibody test, she used endothelial cells—the type of cells that form blood vessels. To her surprise, those cells scored positive, indicating that they naturally contain the leptin receptor. "It kept me awake at night," says Sierra-Honigmann. "If I were an endothelial cell, why would I want leptin receptors?"

To find out, Sierra-Honigmann enlisted the help of two postdocs from a nearby lab, Guillermo García-Cardeña and Andreas Papapetropoulos, who study angiogenesis. They found that leptin causes cultured endothelial cells to aggregate, forming tubes that resemble the early stages of blood vessels. Then with the help of Peter Polverini of the University of Michigan School of Dentistry in Ann Arbor, the team tested whether leptin would cause new blood vessels to form in the corneas of rats, the "gold standard" for an angiogenic molecule. Leptin passed the test.

Apparently, says Folkman, "nature used one molecule for two functions." In addition to its well-known role of controlling appetite and metabolism, leptin may, he suggests, "drive the blood vessels to match the fat." It does not appear to be essential for that second job, however, because the copious fat tissue in mutant mice that completely lack leptin manages to recruit an adequate blood supply.

But embryologist Jonathan Van Blerkom and his co-workers at the University of Colorado, Boulder, found a hint of another role for leptin-induced angiogenesis last year. They discovered that leptin is made in human ovarian follicles, which is where eggs mature until they are ready to be released and fertilized. What's more, Van Blerkom's team found that the protein is packaged with two known angiogenic factors in the follicle and in parts of the egg that develop into the cells responsible for forming the placenta. These findings led Van Blerkom to wonder if leptin is angiogenic. The discovery that it is, he says, suggests that it could help the follicles generate the many new blood vessels they produce as they mature and help the young embryo itself induce the mesh of blood vessels in the placenta.

Wound healing also depends on blood-vessel growth, and researchers had noted that healing is slow in leptin-deficient mice. In preliminary experiments, Sierra-Honigmann and her colleagues have now shown that extra leptin can speed healing. "A normal wound in a mouse heals in 5 to 7 days," she says, but with leptin treatment "it is completely healed by day 3 or 4." In addition, she says, the slow-healing wounds of leptin-mutant mice "heal like normal wounds" when treated topically with leptin.

The leptin-angiogenesis connection raises another possibility as well: that, like all other known angiogenic factors, leptin may be deployed by some cancers to recruit blood vessels. Folkman's team is checking to see if any tumors make leptin, which could then serve as a target for controlling cancer growth. Leptin made by tumors could in some cases also contribute to the appetite and weight loss that are common in cancer, he says. With all these new potential roles for leptin, this already famous protein is poised for even wider stardom.

–MARCIA BARINAGA