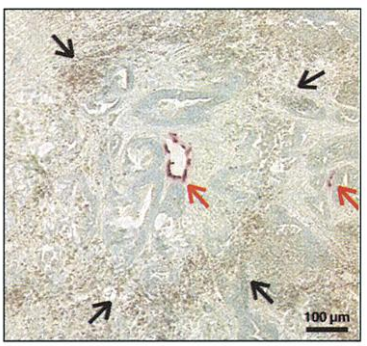
TUMOR ANGIOGENESIS

Gene Expression Patterns Identified

Researchers have obtained the most detailed sketch yet of how cancerous tumors secure the blood supplies that nourish their growth. On page 1197, a team led by Bert Vogelstein and Kenneth Kinzler of Johns Hopkins University School of Medicine reports the results of a large-scale comparison of the genes expressed in the blood vessels of human colon cancers and of normal colon tissue. They've found that the gene expression patterns of the two types of vasculature are distinctly different.

Researchers had previously identified a few "markers" that differ between normal blood vessels and the presumably newly formed vessels of tumors, but nothing on the scale seen by the Hopkins workers, who picked up differences in the activity of nearly 80 genes. "It is an important paper," says Erki Ruoslahti of the Burnham Institute in La Jolla, California, who studies tumor vasculature. "I found it surprising that there would be so many markers with such big differences."

Ruoslahti and other researchers interested in developing new cancer therapies are intrigued by the results. Philip Thorpe of the University of Texas Southwestern Medical Center in Dallas notes that the work could point the way to compounds that home in on the protein products of genes that are overexpressed in tumor vessels, in hope of shutting off the growth of blood vessels the tumor needs to survive. Angiogenesis researcher Judah Folkman of Harvard Medical School in Boston, who pioneered the idea of killing tumors by targeting their blood vessels, describes the paper as a "landmark."



Ring of difference. The cells immediately surrounding the purple-stained blood vessels in this colorectal tumor are living (red arrows), while those farther away are dead (black arrows).

Before achieving that landmark, the Hopkins team had to overcome a serious obstacle—learning how to isolate pure populations of the endothelial cells that form blood vessels. These cells are only one of many cell types found in tumor and normal tissues, and they are present in relatively small amounts. The task of sifting them out fell to postdoc Brad St. Croix, who spent 2 years on the problem. He eventually succeeded by using a protein called P1H12, which occurs mainly on endothelial cells, as a handle to separate out the cells. Angiogenesis researcher Noel Bouck of Northwestern University Medical School in Chicago describes the feat as a "tour de force."

Once the isolation method was worked out, Kinzler, Vogelstein, and their colleagues used a technique developed in their lab about 5 years ago to compare the gene expression patterns of endothelial cells from colon cancers and from normal colon tissue from the same patients. Called SAGE, for serial analysis of gene expression, the method involves making DNA copies of the messenger RNAs present in each type of cell and then combining up to 50 short nucleotide "tags" cut from each of these cDNAs into longer DNAs for sequencing (*Science*, 20 October 1995, pp. 368 and 484).

The Hopkins team found some 100,000 sequence tags, representing more than 32,500 active genes, in both normal and tumor endothelial cells. The expression patterns of 79 of these genes were significantly different in the two cell types: 46 were substantially more active, and 33 were less active, in tumor cells than in normal colon endothelial cells. What's more, the researchers found similar expression patterns for many of the same genes in vessels from other tumors, including lung, brain, and metastatic liver cancers. "It's clear that the tumor vasculature is different from normal vasculature," says Douglas Hanahan of the University of California, San Francisco.

Many of the genes expressed at higher levels had not been previously identified. But others are known genes, involved in such activities as forming or remodeling the extracellular matrix—necessary events in the formation of the new blood vessels thought to be present in growing tumors. In fact, the results indicate that the tumor vasculature is very similar to newly forming blood vessels elsewhere, such as in healing wounds. "Virtually all the genes expressed in the tumor vasculature were expressed in neovasculature that was not neoplastic," Vogelstein says.

In theory, this could pose problems for drug development. Compounds that block the overactive tumor vessel genes might also disrupt normal blood vessel growth, or angiogenesis. But, says Kinzler, "I don't think it means that there won't be good targets for therapy." Others agree. Hanahan notes, for example, that early studies of antiangiogenesis drugs haven't picked up any particular problems with normal angiogenesis, which in the adult is mainly confined to wound-healing and the growth of the uterine lining

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ScienceScope

Horseshoe Haven Scientists are uncertain if horseshoe crabs are being overharvested (see p. 1122), but the federal government is moving to set up a refuge for the animals anyway. Commerce Department officials last week proposed a 6164-square-kilometer sanctuary off Delaware Bay, believed to host the largest horseshoe crab population on the Atlantic seaboard.

Harvesters collected an estimated 3 million crabs in 1998 for use as bait—up significantly from past years. Despite a lack of rock-solid evidence for population declines, however, Commerce officials want to end harvesting in the new refuge by 30 October. "The last thing any of us wants is to see these creatures wind up on the fished-out stocks list," Commerce Secretary Norman Mineta said at an 8 August press conference. "We look at it as a risk-averse approach," adds biologist Paul Perra of the National Marine Fisheries Service. And conservationist Glenn Gauvry, director of the Ecological Research & Development Group in Milton, Delaware, says that "protecting spawners off the Delaware Bay is very sensible. It's the heart of the population."

A formal notice of the proposal, and a request for public comment, is expected later this summer.

Pig Tales Scotland's Roslin Institute, a pioneer in cloning sheep, made headlines again this week when reporters learned that it was halting its efforts to engineer pigs that could grow spare organs for transplant into humans. According to numerous press reports, Geron, the California-based company that financed the xenotransplant research, was pulling the plug over concerns that the pig organs might transfer dangerous viruses to people.

It just isn't so, company and institute officials said on 14 August. Disease concerns "were not the basis for the decision to refocus the funding" to other cell biology and genetic engineering projects, Roslin chief Grahame Bulfield said in a statement. "Our decision to allocate funding reflects current strategic priorities," which include harnessing Roslin's cloning expertise to Geron's work with stem cells, added Geron's David Greenwood.

The decision makes sense, industry watchers say, as other companies appear to be in a better position to profit from any xenotransplant breakthroughs. Says one: "Geron is playing to its strengths."

during the menstrual cycle.

Still, researchers have a great deal of work to do to find out what all the genes identified by the Kinzler-Vogelstein team do in normal angiogenesis, and whether any will be suitable targets for drug therapy. But the Hopkins workers are likely to have lots of help. "This paper will no doubt set off a flurry of work by other investigators," predicts Folkman. **–JEAN MARX**

MARINE CONSERVATION

Virginia Gets Crabby About Harvest Limits

Virginia is at odds with other Atlantic coastal states over a plan to protect horseshoe crabs. Virginia officials have refused to accept a quota on their harvest, arguing that it's not based on good science. Now, the Department of Commerce has scheduled a moratorium, to go into effect next month, that is aimed at preserving what many believe is a dwindling population.

The horseshoe crab is not really a crab at all, but a distant relative of spiders. Birdwatchers prize horseshoe crabs because their eggs provide nourishment for hungry migratory birds. Medical companies use crab blood to test injectable drugs for contamination. And the fishing industry uses crabs as bait for conch and eel. As demand from the growing conch fisheries has increased, crab harvest has skyrocketed, growing from 500 tons in 1990 to 3000 tons in 1997.

Ebb and flow. States disagree over how to protect horseshoe crabs.

The Audubon Society and other conservation groups fear that this demand may account for what appeared to be a sharp decline in horseshoe crab populations, originally noticed by volunteers in 1992. In response, Delaware and New Jersey officials in 1997 instituted stringent restrictions on their harvest. When fishers began landing their crabs in Maryland to avoid the restrictions, that state imposed its own 75% cut. That shifted the trade to Virginia, which now accounts for about a quarter of the harvest. In 1998, Maryland, Delaware, and New Jersey decided a coastwide management plan was needed, so they asked the Atlantic States Marine Fisheries Commission (ASMFC) to design one.

The scientists charged with the task soon realized that there was a lack of good data on horseshoe crab populations, says Jim Berkson, a fisheries scientist at Virginia Polytechnic Institute and State University in Blacksburg who participated in the stock assessment committee. But they were alarmed by the still-increasing harvest, fearing long-lasting effects on a species that takes 9 to 11 years to reach sexual maturity.

In February, ASMFC voted for a 25% reduction of the average harvest levels from 1995 through 1997. This was a compromise between the 50% cut desired by Maryland and other states and the status quo sought by Virginia. Virginia officials objected to what they said amounted to a 75% cut in what the state's conch industry needed. They argued that state laws require them to base their decisions on good science—which, they said, was absent here. State officials also argued that the problem needed to be quantified before a quota was established.

That position didn't pass muster with the commission, which saw it as a delaying tactic. In May, it found Virginia "out of compliance" and asked the Department of Commerce to shut down Virginia fisheries for not adhering to the commission's quota. "The bottom line is that decisions are made with whatever information is available," says Dieter Busch, director of ASMFC's Interstate Fisheries Management Program. Virginia's Marine Resources Commission has since reduced the legal harvest in half, to 355,000 crabs. But that still isn't good enough for federal officials. Last week the Department of Commerce proposed a moratorium for September, the start of the fall harvest.

Virginia hopes to convince the Atlantic commission at a meeting next week to ease its quota, and the fishing industry is watching closely. "We're hopeful," says Rick Robins, who runs Chesapeake Bay Packing in Newport News, Virginia, the largest exporter of conch. "But we're prepared to seek an injunction," he says, if the commission stands firm.

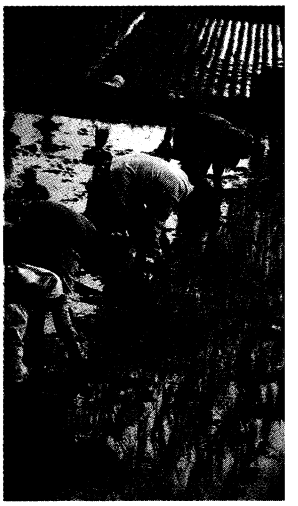
–ERIK STOKSTAD

AGRICULTURE

Variety Spices Up Chinese Rice Yields

The results of Chinese field trials reinforce the accepted scientific wisdom that planting different varieties of a crop in the same field holds down the spread of certain diseases and improves yields. And this time researchers seem to have convinced farmers, too.

Zhu Youyong, a plant pathologist at the Phytopathology Laboratory of Yunnan Province at Yunnan Agricultural University in Kunming, China, and colleagues report in the 17 August issue of *Nature* on a 2-year experiment that involved mixing two varieties of rice in the same field. Their work, involving thousands of local rice farmers, found an 18% rise in overall productivity, including greater profits for a premium-priced variety that is particularly susceptible to rice blast from a fungus.



Mixing it up. Monocultural plantings of rice, common in Yunnan Province and elsewhere, are more vulnerable to disease.

Most Yunnan farmers plant one variety of hybrid rice, with a few devoting some land to a more glutinous rice used for desserts and other regional specialties. Following Zhu's suggestion, however, farmers planted a single row of glutinous rice in the middle of a group of either four or six rows of hybrid rice. The experiment started on 812 hectares in 1998 and expanded to 3342 hectares in 1999. Monoculture control plots were grown at 15 small sites throughout the region.

The results show the power of variety. Researchers calculated that it would take an average of 1.18 hectares of monoculture cropland to produce the same amounts of hybrid and glutinous rice produced in 1 hectare of mixed crops. The most striking change was for individual glutinous plants grown in a mixed environment: They yielded up to 89% more rice than their monocultural cousins. What's more, because the glutinous rice fetches a premium price, the value per hectare of the mixed fields was 14% greater than the hybrid monoculture plots and 40% greater than the glutinous monoculture plots. In both years, blast destroyed about 20% of the glutinous rice grain in the monoculture plots but only 1% in the mixed plots. Blast damage in the hybrid rice, although much lower in general, also dropped, with a grain loss of only 1% in the mixed plots versus 2.3% in monoculture plots. The damage from blast was so reduced in the mixed plots that farmers stopped their periodic fungicide spraying. "The farmers are very happy," says Zhu.

Christopher Mundt, a plant pathologist at Oregon State University in Corvallis and a co-author of the paper, explains that different types of rice blast attack different varieties of rice. In a monoculture field of rice,

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