BIOMEDICINE

New Genetic Tricks to Rejuvenate Ailing Livers

Some 20 million people in the United States alone suffer from liver diseases, and more than 40,000 of them die each year. Liver transplants could save many of those lives, but there are only enough to treat about 4000 American patients each year. Now, researchers have developed two new treatments that have proved successful in rodents with severe liver damage. The hope is that one day they may help prolong the lives of patients awaiting a donor organ—or perhaps even do away with the need for a transplant altogether.

On page 1253, Ronald DePinho of the Dana-Farber Cancer Institute and Harvard Medical School in Boston and his colleagues report that erosion of the telomeres, cap-like structures that protect the ends of the chromosomes, predisposes mice to liver cirrhosis, a degenerative liver condition that in humans is the main killer among liver diseases. What's more, the researchers restored liver function in the animals by using gene therapy that kept the telomeres from withering away.

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>
> —Ira Fox

And on page 1258, Philippe Leboulch of the Massachusetts Institute of Technology and Harvard Medical School, Ira Fox of the University of Nebraska Medical Center in Omaha, Naoya Kobayashi of Okayama University in Japan, and their colleagues report that they were able to grow enough liver cells (hepatocytes) in lab cultures to get rats through an acute liver failure. Ordinarily, cultured liver cells grow poorly, but the researchers overcame this handicap by first introducing a cancer gene that revved up their cell division machinery and then clipping the gene out again to curb the cancer risk.

Experts are hailing the studies. "This is very fascinating; the telomere system hasn't been implicated in liver damage and regeneration. And what's holding back the use of hepatocytes [in cell transplantation] is the inability to greatly expand them in culture," says Roger Williams, a hepatologist at the University College London Medical School. Still, he and others caution that there's a huge gap between bench and bedside. "There's a lot of ifs in here, and this is not immediately going to lead to a change in clinical practice," says physiologist Irwin Arias of Tufts University School of Medicine in Boston.

Cirrhosis results when the liver undergoes chronic damage, which in humans is often caused by excessive alcohol consumption or hepatitis virus infection. The organ tries to repair the damage by producing new cells, but the liver cells eventually stop dividing, and that in turn results in liver failure and death. Scientists have long known that telomeres in most normal human cells get a little shorter with each division until, finally, the aged cells no longer divide. So when Japanese scientists discovered in the mid-1990s that cells from cirrhotic livers have shorter telomeres than those from healthy ones, "this suggested to us that telomere attrition may be a crucial trigger for end-stage cirrhosis," says DePinho.

To test his hypothesis in mice, DePinho and his colleagues had to employ an experimental trick. In normal human cells, telomerase—the enzyme that makes telomeres—stops working when cells differentiate to form the various tissues, but in most mouse cells, it's active throughout life. As a result, mice have much longer telomeres. So the researchers used mice in which the gene for one telomerase component had been "knocked out." Through the generations, telomeres in these animals shrink, "making them more humanlike," as DePinho puts it.

Repair needed. Compared to the normal liver behind it, the damage to this cirrhotic liver is readily apparent.

CREDIT: R. MARKIN/UNIVERSITY OF NEBRASKA MEDICAL CENTER

When his team then subjected the animals to various liver injuries, their rate of liver cell death shot up, the cells' capacity to divide and regenerate was reduced, and they showed many of the symptoms of severe cirrhosis. The DePinho team also found that they could ward off the disease by injecting the mice with an adenovirus, which usually causes respiratory infections, that had been modified to carry the gene for the missing telomerase component.

One potentially serious issue would have to be resolved before researchers can even think about trying such a therapy in humans, however. As DePinho points out, telomerase often gets turned on in cancers—including, Arias says, about 75% of all liver cancers. Researchers will need to make sure that adding the enzyme to the livers of human cirrhosis patients won't facilitate liver cancer development.

To devise their liver cell therapy, Leboulch and Fox also took a cue from relentlessly dividing cancer cells. Hepatocytes, like all freshly isolated normal cells, are tricky to grow in culture. In 1996, Leboulch devised a technique to introduce a cancer-causing oncogene called large T antigen into primary cells, thus "immortalizing" them so that they would grow continuously in culture. As a safety device against the cells spiraling toward cancer, he designed the oncogene so that it could be chopped out of the cells' DNA by a "genetic scissors" that, upon introduction by an adenovirus, recognizes a pair of sequences bracketing the gene and deletes the portion in between.

When Fox, a liver transplant surgeon, heard about Leboulch's system, he immediately called him and proposed a collaboration to give it a try in hepatocytes. Leboulch agreed, and the team set out to see whether they could grow enough liver cells to save the lives of rats that had had about 90% of their livers surgically removed. This treatment is always fatal, but when the researchers injected the lab-grown hepatocytes into the animals' spleens, up to 60% of the animals survived. "This system may do away with the shortage of hepatocytes. You could keep [the immortalized cells] in the freezer and take them whenever you needed them, which is not possible with primary hepatocytes," says Fox.

Hepatologist Roy Chowdhury of the Albert Einstein College of Medicine in New York City calls the Leboulch-Fox team results "very encouraging." But he adds, "a 90% hepatectomy does not accurately reflect liver failure in humans where some insult like a virus or a toxin that caused the damage in the first place persists." These could also damage the transplanted cells. Achilles Demetriou, a liver expert at the Cedars-Sinai Medical Center in Los Angeles, agrees. Demetriou instead favors coaxing versatile fetal stem cells to differentiate into liver cells that could then be used for transplantation. "They're more promising and safer," he says.

No one can predict when—or if—the new strategies will provide relief for the thousands of patients awaiting liver transplants. Says Demetriou: "For about 20 years now hepatocyte transplantation has always

been 'promising.' But we still haven't delivered." And right now gene therapy doesn't have such a great reputation either. So, the new strategies may not be chopped liver, but they also don't appear to be magic bullets—at least not yet. –MICHAEL HAGMANN

AUSTRIA

Researchers Brace for Political Backlash

ZURICH—From its position at the crossroads of Europe, the former imperial capital of Vienna has attracted scientists from across the continent, east and west, for centuries. But earlier this month, after the Austrian president approved a new government incorporating members of a far-right political party, the nation's researchers suddenly found themselves living in a state shunned by much of the international community. "My colleagues are deeply worried," says physicist Arnold Schmidt, president of the country's basic research granting agency, the Austrian Science Fund. "We need international cooperation, and we don't feel that we should be held responsible for a government that many did not support." In an open letter sent last week, Schmidt appealed to foreign researchers "to maintain or increase contacts and cooperation with scientists in Austria."

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Other bodies have also been quick to reaffirm international ties and—in many cases—to distance themselves from the new government. Austria's university rectors issued a statement warning of possible "international isolation of Austria, which would be detrimental to its universities," and called on national leaders to show "openness and internationality." The University of Vienna's medical school pledged to intensify its efforts "to ensure that racism and prejudice are not tolerated." And the scientific directors of the Erwin Schrödinger Institute—a mathematical physics center in Vienna that draws visiting fellows from around the world—say on the institute's Web site that they oppose "the nationalistic and xenophobic sentiments expressed by some politicians" and reaffirm their commitment to "international scientific interaction and exchange."

So far, the actions taken by Western governments to protest the new Austrian coalition—in which six out of 12 ministers come from Jörg Haider's far-right Freedom Party—have been mainly symbolic. The European Union (E.U.) and many of its member nations have issued statements and snubbed some representatives of the new government, but a spokesperson for the E.U.'s research commissioner, Philippe Busquin, told *Science* that sanctions are unlikely to impact research programs and that Austrian scientists will not face discrimination in their applications for E.U. grants.

But there are some signs of unease in the international community: Manfred Horvath, an engineer who heads Austria's Office of International Research and Technology Cooperation, told *Science* that the Washington-based Interagency Environmental Technology Office asked last week that a conference planned for Vienna in October be moved elsewhere. "The situation is very unpleasant for Austrian science and research, which has been increasingly integrated into the E.U.'s research activities," he says.

So far, most Austrian scientists seem more worried about the reaction from outside than about changes in national science policy or funding. The new coalition purports to back science—reaffirming the previous government's commitment to increase research spending in coming years—but it raised some concern last week when it announced that it will split management of basic and applied research. The education ministry will now oversee basic research, while applied research will be combined with infrastructure in a ministry to be headed by Freedom Party member Michael Schmid. "I'm uneasy about splitting basic and applied research, and worried that the new government may focus less on research and more on development," says the Science Fund's Schmidt.

In the meantime, Austrian researchers are trying to reassure their colleagues around the world. Quantum teleportation pioneer Anton Zeilinger of the University of Vienna is urging international colleagues to continue their normal exchange with Austrian counterparts. And Erwin Heberle-Bors of Vienna's Institute of Microbiology and Genetics wants fellow Austrian researchers to "leave their ivory towers and discuss and explain the situation" to scientists abroad, and to continue their "full engagement with the international research community."

–ROBERT KOENIG

SCIENTIFIC COMMUNITY

Controversy Claims CDC Lab Chief

A senior manager at the Centers for Disease Control and Prevention (CDC) has been reassigned as agency officials scramble to quell a widening controversy about the reallocation of funds that Congress had earmarked for specific diseases. Testifying last week before Congress, CDC chief Jeffrey Koplan announced that virologist Brian Mahy has been replaced temporarily by James LeDuc as head of the division of viral and rickettsial diseases.

Mahy came under fire last year when an investigation by the Inspector General of the Department of Health and Human Services found that his division had spent between $8.8 million and $12.9 million that Congress had approved for research into chronic fatigue syndrome (CFS) on a variety of other diseases. The report angered lawmakers and CFS patient groups. In response, Koplan offered his apologies and promised to restore the CFS funds, but he didn't take action against Mahy (*Science*, 7 January, p. 22).

Earlier this month, however, Mahy's position was weakened further when a *Washington Post* report alleged that his division had also reallocated money earmarked for hantavirus programs. Testifying before the House appropriations subcommittee on Labor, Health and Human Services, and Education, Koplan said a preliminary inquiry has confirmed the allegation. CDC has hired private accountants to review the hantavirus program, Koplan said, followed by an investigation of all programs within the National Center for Infectious Diseases. In addition, Koplan has asked CDC managers to report within 90 days on any other cases where the agency provided inaccurate information to Congress.

Koplan stressed that the diverted money had not been wasted but used "to combat other life-threatening infectious diseases," such as Ebola and Nipah virus. He blamed the diversions on CDC's culture, "which emphasizes getting things done and taking care of the administrative niceties afterward." A CDC spokesperson said Mahy will stay at CDC but couldn't say in which position.

"It's a welcome piece of news," says Kimberly Kenney, executive director of the Chronic Fatigue and Immune Dysfunction Syndrome Association of America, a group that helped expose the diversion of CFS money. But scientists express sympathy for Mahy, who they believe was trying to deal as best he could with emerging epidemics. "It's kind of sad," says Charles Calisher, a virologist at Colorado State University in Fort Collins. "A guy does what he thinks is the right thing, and he gets lambasted." –MARTIN ENSERINK