RNA INTERFERENCE

Mini RNA Molecules Shield Mouse Liver From Hepatitis

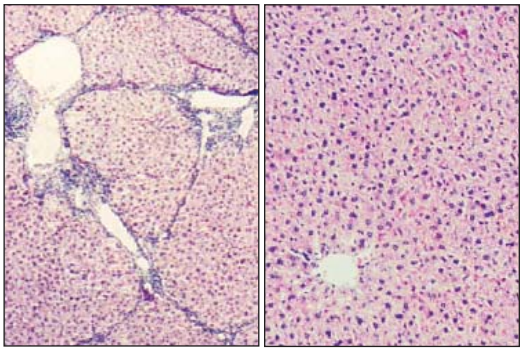
Shooting millions of tiny RNA molecules into a mouse's bloodstream can protect its liver from the ravages of hepatitis, a new study shows. It offers further hope that a novel approach to silencing troublesome genes will become a valuable disease-fighting tool. But the authors and others caution that the therapy must leap many hurdles before it can be safely applied to humans.

The technique, known as RNA interference (RNAi), utilizes short bits of RNA to silence specific genes. In this case, they blunt the liver's self-destructive inflammatory response, which can be triggered by agents such as the hepatitis B or C viruses.

Full-size RNA molecules convert genetic information into proteins. But in the late 1990s, researchers found that truncated RNAs could be coaxed to turn off the very genes that had helped generate them. Biologists exploring RNA's newfound versatility quickly recognized RNAi's potential as a powerful medical treatment (*Science*, 20 December 2002, p. 2296). But until now, that potential has been largely theoretical.

Harvard University immunologists Judy Lieberman and Premlata Shankar are apparently the first to unveil the therapeutic power of RNAi against disease in an animal. Infusing a solution of small interfering RNAs (siRNAs) into a mouse's tail—in a massive amount, equivalent to half the animal's blood volume—protected it against hepatitis. And in animals that were already ailing, RNAi shut down the inflammation enough to allow the liver to recover. Despite the traumatic delivery method, the mice didn't appear to suffer side effects.

"This is the first example that I know of where there's been a biological challenge and an animal [was] protected" by RNAi, says Phillip Sharp of the Massachusetts Institute of Technology in Cambridge, who recently co-founded a company called Alnylam to design RNAi-based therapies.



Interference. Mice given a placebo treatment for hepatitis suffered serious liver scarring (*left*, lines) from inflammation, whereas the livers of those receiving targeted siRNAs were protected (*right*).

CREDIT: E. SONG *ET AL.*, *NATURE MEDICINE*

In humans, liver inflammation is normally triggered by a virus or an autoimmune disorder. Although no viral analog exists in animals, scientists can induce autoimmune hepatitis. The disease has become popular in RNAi studies, largely because the liver readily absorbs siRNAs into its cells.

In a series of experiments published online this week by *Nature Medicine*, Lieberman's team gave mice injections of siRNAs designed to shut down a gene called *Fas*. When overactivated during an inflammatory response, it induces liver cells to self-destruct. The next day, the animals were given an antibody that sends *Fas* into hyperdrive. Control mice died of acute liver failure within a few days, but 82% of the siRNA-treated mice remained free of serious disease and survived. Between 80% and 90% of their liver cells had incorporated the siRNAs. Furthermore, the RNA molecules functioned for 10 days before fading completely after 3 weeks, lasting roughly three times longer than in previous studies. (*Fas* is rarely expressed at high levels outside the liver, so briefly disabling it has little effect on other organs.)

Another set of animals faced a different challenge: injections of cells called ConA, which compel the immune system to attack the liver and produce the scarring seen in viral hepatitis. Animals infused with siRNA developed no liver damage.

"It's amazing how well it worked," marvels Charles Rice of Rockefeller University in New York City. Still, he adds, the delivery method is clearly problematic. In humans, rapidly injecting a huge volume of solution is "not the way to go," Rice says. Researchers have yet to determine whether a gentler approach might work. In addition, biologists agree that the best strategy would be to aim siRNAs directly at hepatitis B or C viruses, but that would require a different siRNA than the one used by Lieberman's team. Evidence from several labs suggests that, in petri dishes, siRNAs can stop hepatitis C from replicating.

Lieberman, Shankar, and others are also testing RNAi's ability to battle HIV. At the Conference on Retroviruses and Opportunistic Infections, held in Boston this week, Shankar presented evidence that siRNAs can target a protein called CCR5 that helps shunt HIV into immune cells. The result: For 3 weeks, the RNAs barred HIV's entry. And in cells already infected, they put the brakes on viral replication altogether. –JENNIFER COUZIN

EUROPEAN UNION RESEARCH

Ethics Group Gives Qualified Nod to Placebos

BERLIN—A European ethics body has said that placebo-controlled trials can sometimes be justified in developing countries, even when proven treatments are available in wealthy countries. The statement departs from more stringent standards on placebos laid out in the Declaration of Helsinki, a document that sets worldwide standards for clinical research ethics.

The opinion from the European Group on Ethics in Science and New Technologies does not have the force of law, but it is expected to serve as a guideline for European Union–funded research, and especially for a $640 million European Commission project gearing up to test drugs against AIDS, malaria, and tuberculosis in the developing world. The opinion, released 4 February, states that placebo-controlled trials may be warranted when, for example, "the primary goal of the clinical trial is to try to simplify or decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of the cost." Two members of the group dissented from that conclusion, stating that it establishes an unethical double standard for research in wealthy and poorer countries.

The issue has been hotly debated since the late 1990s, when critics denounced several large HIV/AIDS trials in Thailand and Africa. In those studies, researchers compared a short course of treatment to a placebo, even though the effectiveness of a longer, more expensive course was well known (*Science*, 12 February 1999, p. 916). Patient advocacy groups, including the U.S.-based Public Citizen, argued that researchers had a responsibility to provide the best proven treatment to study subjects, even when that treatment would not normally be available in the local community.

The World Medical Association (WMA) agreed, amending its Declaration of Helsinki in 2000 to tighten the rules for placebo- ▶

controlled trials worldwide. Unless the condition is minor, said WMA, control-group participants must receive the "best current treatment." At the time, some scientists complained that the revision ruled out research that could save lives in poor countries by efficiently testing less expensive or simpler treatment options (*Science*, 20 October 2000, p. 418).

In its new statement, the European ethics group accepts that argument. Although in principle the best current treatment should be provided, exceptions can be made when they are approved by an ethics committee that includes representatives of the local community. "We open up a possibility for somewhat different exceptions [to the standard] than the Declaration of Helsinki [has]," says Göran Hermerén, chair of the group.

That approach puts the interest of the society ahead of the interest of individuals involved in clinical trials, says Delon Human, secretary-general of WMA, a premise rejected by the Declaration of Helsinki. "We do not believe that economic arguments should justify a lowered standard of research practice" for placebos or any type of research, he says.

Peter Lurie of Public Citizen says the new document is a missed opportunity. In calling for stringent ethical guidelines, "the object is to force researchers to think more creatively about alternative trial designs," he says. "This document provides more than adequate justification for business as usual."

–GRETCHEN VOGEL

AGRICULTURE

Study Shows Richer Harvests Owe Much to Climate

Since the 1940s, harvests across the United States have become ever more bountiful as farmers have planted better varieties of crops, generously fertilized them, and gained the upper hand against pests and weeds. But over the past 2 decades, they have had a little help: A new study shows that a surprisingly high percentage of the improvement in yield was due not to farm management but to climate change.

The finding suggests that food production in the United States may be more vulnerable to shifts in climate than was previously suspected, a fact that could affect global food security. "It's an eye opener," says agricultural meteorologist Gene Takle of Iowa State University, Ames.

On page 1032, graduate student David Lobell and Gregory Asner, both of the Carnegie Institution of Washington and Stanford University, report an analysis of the role of climate and other factors in U.S. agriculture. They investigated the interplay among temperature, rainfall, amount of sunshine, and bushels of corn and soybeans per acre from 1982 to 1998. During this time, summers in a large swath of the Midwest became slightly cooler. Lower temperatures in the region are known to boost the yields of corn and soybeans, which rose about 30% over the study period. The United States leads the world in production of the two crops.

Lobell and Asner wanted to tease out the impact of those gradual climate shifts relative to other influences on yield, such as farming practices. To spot correlations amid the statistical noise, they picked counties throughout the United States where yields had responded to climate in the same way, either rising in cooler summers or falling in warmer ones. That was the case in about half of the counties where corn or soybeans were being grown—618 for corn, 444 for soybeans. (The amount of sunshine or rainfall was unrelated to changes in yield.)

Using a statistical model to compare these climate variations among counties with changes in yield, the researchers found that the cooling climate was responsible for about 20% of the gains over the 17 years. The remainder they credit to management and other factors, such as increased carbon dioxide in the atmosphere. "Gains from management have not been as high as we thought," Lobell says. "This has important implications for projections of future food production."

Others agree. "This points out that our food production may be more vulnerable to shifts in climate than we thought," says Jonathan Foley, a climatologist at the University of Wisconsin, Madison. "It is a little scary." Lobell and Asner's analysis indicates that yields would drop by 17% for each degree that the growing season warms. That's three times as much as other studies have suggested. Most climate models predict that the Corn Belt of the U.S. Midwest will warm over the next few decades.

Nature's co-pilot? Farming practices such as crop dusting may have less effect on crop yields than previously thought.

CREDIT: JOEL SARTORE/CORBIS

"These yield trends in the U.S. have global implications," says Kenneth Cassman, an agronomist at the University of Nebraska, Lincoln. For example, Cassman explains, a drop in U.S. production might stimulate more planting of soybeans in environmentally sensitive areas such as Amazonian watersheds in Brazil.

If climate in the United States should take an unfavorable turn, farmers might be hard pressed to compensate, says agronomist Cynthia Rosenzweig of Columbia University and NASA's Goddard Institute for Space Studies in New York City. That's because U.S. agriculture may be nearing its maximum efficiency, she says. But Don Duvick, a retired plant breeder from Pioneer Hi-Bred International, is sanguine. "If there were a trend to higher temperature, the breeders would churn out hybrids that can take it," he says. More vulnerable to climate change are developing countries, where temperatures are already high, soils are often poor, and management has a long way to go. "Climate change will put them even further behind," Rosenzweig says.

The study is not the last word, Rosenzweig and others emphasize. Lobell and Asner looked at only one aspect of climate; its variability and the number of extreme events, such as floods, also strongly affect yields. In addition, temperature shifts might influence harvests in other ways, such as by bringing more or less land into production, says Mark Rosegrant, director of the International Food Policy Research Institute in Washington, D.C. It may also be dicey to generalize from these counties to the nation as a whole. "It's so simplified, it's hard to say that this is truly reality," Rosenzweig says.

No one, however, disputes the bottom line: Small, gradual shifts in climate can play an important role in yield trends and therefore food supply. What needs to be done next is to expand the study to other regions of the world—something that Lobell is already working on—and to other crops.

–ERIK STOKSTAD