Biology

Viroids: Introns on the run?

It can be satisfying when two conundrums fit together — they may just form one big puzzle, but at least some loose ends have been tied together.

Viroids are the smallest infectious particles known, consisting solely of naked RNA. So far as scientists have been able to tell after years of study, the RNA doesn't code for a single protein — yet somehow this "silent" genetic material can cause disease in the plant hosts. Introns are silent, too — bits of genetic material that can be seen in most DNA, only to be snipped out of the complementary RNA before it is translated into protein (SN:5/3/86,p.280). Now comes evidence for an idea first proposed in 1979: that viroids are "escaped" introns.

According to Gail Dinter-Gottlieb, there is a striking similarity in the nucleic acid sequences, and possibly in the structures, of viroids and a certain class of introns. These "group 1" introns can be found in both plants and animals, and in all three cellular organelles (in chloroplast, nuclear and mitochondrial RNA); as a group, they are defined by a shared, 16-nucleotide consensus sequence. In the September PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.83, No.17), Dinter-Gottlieb reports that all of the viroids so far sequenced contain the consensus sequence as well. (Dinter-Gottlieb, now at Drexel University in Philadelphia, did the work at the University of Colorado in Boulder.)

There are other nucleotide sequences, called boxes, that are also more or less conserved within the group of introns. Complementary base-pairing within these boxes forces the intron RNA into its 3-dimensional configuration. The viroids contain the boxes, in the same order as in the introns. "When the boxes in [one viroid] are paired, a structure is generated in the viroid which is strikingly similar to that of group 1 introns," Dinter-Gottlieb writes. Previous studies have reported a rod-like shape for viroids, but Dinter-Gottlieb speculates that they may fold more elaborately when stabilized by cellular proteins.

The evidence is strong for a close relationship between viroids and introns, Dinter-Gottlieb says, though it remains unclear whether viroids evolved from introns, or merely share a common ancestor molecule. However, she adds, at least one group 1 intron shares yet other viroid sequences, stretches of RNA responsible for modulating the severity of infection. The similarity, she told SCIENCE NEWS, leads to the question of whether introns might be pathogenic. Perhaps, she speculates, some renegade intron escaped the normal regulatory processes of the cell, and took up an infectious "life"-style.

Half an antibody: Better than one?

Researchers at Genex Corporation have engineered an unconventional antibody that is structurally simpler than naturally occurring antibodies. Instead of a mirror-image pairing of two light and two heavy chains, the new formulation has just the "business ends" of one light and one heavy chain. The scientists stabilized the molecule by inserting a gene for a protein link between the chains, producing one continuous protein. According to researcher Robert Bird of the Gaithersburg, Md.-based company, recent tests show this "single-chain antibody" binds specifically to its antigen.

Once the technology matures, Bird says, it may hold some advantages over monoclonal antibodies (MABs). Production of these smaller units, by bacterial fermentation, should be much cheaper than the cell culture used for MABs, according to Bird, and because the new antibodies have just one chain, they should be less prone than MABs to be knocked off affinity columns during protein separations. The new antibody may also prove less problematic in long-term immunotherapy, Bird says, because it would present a smaller target for the host's immune system.

Biomedicine

Helping the body kick out cancer

With cancer, it's not that the body doesn't try to get rid of tumor cells, it's just that the effort fails. Steven A. Rosenberg and his colleagues at the National Cancer Institute have been investigating ways to boost the body's efforts; one such method has already had success in preliminary trials in humans (SN:12/7/85,p.359). But because the initial approach has some potentially serious side effects, Rosenberg and his colleagues are working on ways around the problem. In the Sept. 19 SCIENCE they report preliminary success in animal trials of one such method.

In their previous work, the researchers isolated a specific type of lymphocyte, or white blood cell, from the blood and incubated it with an immune system stimulator. They injected the resulting cells, called LAK (lymphokine-activated killer) cells, along with a booster of interleukin-2, into patients in whom all conventional therapy has failed. Of the first 55 patients treated, 21 showed a response and five of them have had a complete remission.

But the interleukin-2, while necessary for the process, also causes substantial side effects, primarily organ-damaging water retention. So Rosenberg is trying a more "dedicated" white blood cell, one that has already infiltrated the tumor.

In the mouse experiment, he and his colleagues collected white blood cells not from the blood but directly from tumors. In a series of experiments they found that the progeny of these cells, called tumor-infiltrating lymphocytes (TIL), had a dramatic effect on tumors.

When they combined TIL with only 10 to 20 percent of the interleukin-2 needed with LAK cells and an immune system suppressor to fight off the body's attempt to get rid of the foreign cells, the researchers say they were able to "cure" mice with induced cancer. In one experiment on 12 mice, they were able to clear up metastases in all the animals. The TIL cells, they found, are 50 to 100 times more potent than the LAK cells.

The researchers have been able to isolate the same class of white blood cells from human tumors. While they are currently awaiting U.S. Food and Drug Administration approval to try the procedure on humans, Rosenberg cautions that it is too early to tell whether the procedure will be successful. "A lot of things work in mice but don't work in people," he says. "I don't know if this will work."

Pictures of a sniffle stopper at work

With the help of a high-energy synchrotron and a supercomputer, researchers have discovered how an experimental drug blocks replication of cold viruses.

Last year Michael G. Rossmann and colleagues at Purdue University in Lafayette, Ind., used a synchrotron to bombard cold virus crystals with high-energy X-rays. They analyzed the diffraction pattern with a supercomputer, and generated a three-dimensional picture of the virus (SN:9/21/85,p.181). "Valleys" on the virus surface remain constant from generation to generation, while the exposed hills change — explaining why people can't build up permanent immunity to colds.

The Purdue group collaborated with researchers from the Sterling-Winthrop Research Institute in Rensselaer, N.Y., to study experimental antiviral agents developed by Sterling that have shown promise in test-tube experiments (SN:5/11/85,p.292). The new drugs prevent the virus from shedding its coat after it has infected a cell. The researchers studied the virus-drug interaction with the synchrotron and supercomputer, and describe the results in the Sept. 19 SCIENCE — a "picture" of the pairing, showing that the drug inserts itself into the valley, where they believe it works either by blocking ion flow into the virus or by shoring up the valley so it can't collapse during replication.