Biochemistry

Evolving RNA with enzyme-like action

In modern organisms, RNA molecules convey genetic information from DNA to the cellular machinery that churns out proteins. Some even work like enzymes, catalyzing reactions.

But a few researchers think RNA once played a much broader role, serving as a key component in the earliest life forms. That ancient RNA would have needed the ability to perform the tasks of many modern proteins, such as binding to an energy-transfer molecule called adenosine triphosphate (ATP). Yet through the millennia, RNA somehow lost these abilities.

To turn back the clock, two molecular biologists have harnessed a technique called molecular evolution (SN: 8/7/93, p.90). Working at Harvard Medical School in Boston, Mandana Sassanfar and Jack W. Szostak first generated 100 trillion different RNA molecules, each with 169 nucleotide building blocks. They then filtered these molecules through a gel containing ATP, in the hope of catching any RNA capable of linking to ATP. Next they poured a solution containing ATP through the used filter, this time hoping to wash off ATP-bound RNA that preferred to link to water-borne ATP. The researchers made many copies of whatever RNA molecules washed out and repeated that procedure until they finally had enough ATP-binding RNA to work with.

They determined the nucleotide sequences of the 39 kinds of RNA molecules that had bound to ATP. It turned out that those 39 kinds represented just 17 different sequences of nucleotides. These sequences all shared a region of 11 nucleotides, seven of which were exactly alike and four of which were similar, says Szostak. So he and Sassanfar made a new 40-nucleotide RNA containing this sequence and discovered that it also bound well to ATP. It seems that part of the RNA molecule becomes double stranded, with the 11 nucleotides forming a loop sticking out of one side, they report in the Aug. 5 NATURE.

The researchers plan to incorporate this short RNA into sequences of a new set of RNA molecules and test those molecules for their ability to spur chemical reactions akin to those catalyzed by modern enzymes, Szostak says.

Protein pieces halt autoimmune response

In the disease known as myasthenia gravis, the immune system attacks regions where nerve and muscle meet, causing fatigue and loss of muscle control. At these junctions, a nerve ending normally sends chemical signals across a gap to stimulate muscle contraction. But in myasthenia gravis, antibodies destroy the muscle's receptor proteins that serve as docks for this signal, a chemical called acetylcholine.

Immune-system cells called T-cells play a key role in this autoimmune response. They break down acetylcholine-receptor proteins, creating two short fragments easily recognized by the immune system. The fragments then cause other immune-system cells to proliferate and make the antibodies.

Synthetic protein fragments that differ from the receptor's fragments by just one amino acid can inhibit this proliferation, says Edna Mozes of the Weizmann Institute of Science in Rehovot, Israel. Inhibition occurs both in cultured cells and in laboratory mice, she and her co-workers report in the Aug. 1 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

It seems the T-cells do not distinguish between the synthetic fragments and the receptor's own pieces, so they readily link to the lab-made versions, notes Mozes. However, the synthetic fragments fail to initiate the rest of the destructive immune-system response.

The researchers also report that the two most potent artificial fragments have quelled up to 100 percent of the response of T-cells taken from people with myasthenia gravis. This leads them to hope that such fragments will point the way to an effective therapy.

Chemistry

Oxidation strongly linked to aging ...

Though most living things need air to survive, they pay a price for it. Oxygen and many substances containing it can be chemically reactive — and quite damaging to tissues. While plants and animals have developed complex systems for neutralizing these oxidants, they seldom succeed in preventing all oxidative deterioration. Indeed, because oxidation can foster many disabling changes common in the elderly, many researchers now suspect that aging may merely constitute a lifetime's accumulation of oxidative damage.

A report in the Aug. 1 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES offers strong support for that theory. Working with houseflies, Rajindar S. Sohal and his co-workers at Southern Methodist University in Dallas have linked accumulations of protein carbonyl—a measure of oxidant-induced damage—with a fly's vitality and life expectancy.

In one experiment, they housed young adult flies in quarters that allowed them only enough room to walk. These insects lived twice as long as flies given room to fly. Suspecting that the sedentary life — and corresponding reduction in oxygen demand — caused less oxidation, the researchers measured protein carbonyl levels in the flies' tissue. And by day 14, flying flies had 55 percent more than their grounded counterparts.

Sohal's team also exposed young adult flying flies to sublethal periods of pure oxygen. These insects lived longer than flies breathing plain air. However, Sohal says, the reason seems to be that the exposure to pure oxygen sharply reduced the flies' metabolism, in effect rendering them as sedentary as the restricted insects. Moreover, he says, the high carbonyl content and immediate inability to fly seen in oxygen-treated flies suggests that their sedentariness reflects what amounts to rapid and premature aging.

... but quenched by ubiquitous hormone

Melatonin — secreted by the brain's pineal gland, but only at night — has been called the chemical expression of darkness. For years, scientists have puzzled over the primary role of this hormone. New research now indicates that this brain secretion may have played an important evolutionary role by helping many of the world's life forms, from algae to humans, survive the potentially dangerous oxygen-rich environment in which they developed.

Of the many oxidants to which our cells are exposed, the most potent tend to be free radicals — molecules or molecular fragments that contain an unpaired electron. And among free radicals, hydroxyl (•OH) is the most damaging, observes Russel J. Reiter of the University of Texas Health Science Center at San Antonio. So, "if you have but one free radical to scavenge, make sure it's the hydroxyl radical," he says. Reiter and his coworkers have now demonstrated that melatonin does just that.

The researchers gave rats safrole, a carcinogen that damages DNA by generating hydroxyl and other oxygen-based free radicals. They found that rats treated with melatonin prior to the safrole sustained 41 to 99 percent less DNA damage than untreated rodents. The amount of damage depended on the amount of extra melatonin each rat received, they report in the June Cancer Letters.

The doses needed to protect the rats from safrole were small and nontoxic -0.2 to 0.4 milligram of melatonin per kilogram of body weight. Moreover, says Reiter, the team's subsequent research indicates that melatonin also fights the hydroxyl radical in another way: by neutralizing its precursor molecule.

These findings suggest that melatonin, which can cross all barriers to enter every cell, "is the best free-radical scavenger known," Reiter contends. As such, it might hold promise in treating a number of disorders involving free-radical damage, such as Parkinson's and Alzheimer's disease, he says.

AUGUST 14, 1993 109