A larger role for RNA in life's emergence?

Primitive Earth more than 3.5 billion years ago offered little in the way of comfort, from a biological viewpoint.

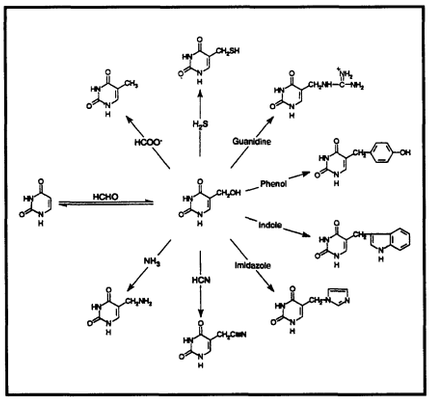
Lightning bolts tore through an atmosphere of carbon dioxide and nitrogen, blasting exposed rocks and perhaps mounds of ice — not a friendly place to start of family of evolving organisms.

Chemical evolutionists propose that modern organisms, based on proteins and DNA, may have arisen from a primordial RNA world. In that world, strands of so-called catalytic RNA participated in self-replicating chemical systems that made a variety of molecules, including amino acids and more RNA.

Michael P. Robertson and Stanley L. Miller, both chemists at the University of California, San Diego, contend that RNA may have played an "even larger role than has previously been assumed" in the evolution of biological molecules. They propose in the May 5 SCIENCE that ancient RNA differed slightly in its molecular makeup from modern RNA, allowing it to "catalyze a much wider range of chemical reactions."

Four molecular building blocks constitute RNA. One of these, uracil, tends to react with formaldehyde, a molecule that scientists think existed abundantly on prebiological Earth. The reaction forms 5-hydroxymethyluracil (HMU).

Robertson and Miller mixed HMU with several other chemicals postulated to be components of the prebiotic soup. The



A "reaction wheel" shows amino acid analogs (outer circle) formed when HMU (center) reacts with various prebiotic molecules.

compounds, they observed, "reacted extremely well with HMU," forming new molecules with many of the characteristics of modern-day amino acids.

The two contend that primordial RNA would have contained HMU at many sites where modern RNA has uracil. Noting the diversity of potential chemical paths available to HMU, they argue that ancient catalytic RNA would have had much greater "efficiency and versatility" than researchers have realized.

"The work described here demonstrates that the catalytic shortcomings of RNA can be overcome with simple modifications that would have been unavoidable under primitive Earth conditions," the two chemists state.

Moreover, their findings may offer a plausible explanation for the prevalence of the 20 amino acids that constitute modern proteins. HMU's reactivity, the researchers maintain, led to amino acid precursors armed with a specific set of "functional groups." Modern proteins taking over RNA's catalytic role would inevitably have had to retain the same functional groups.

Those critical functional groups are characteristic of the amino acids that make up today's proteins. Without them, enzymes could not carry out the catalytic duties crucial to life, Robertson and Miller point out.

Today, those same functional groups show up in proteins prevalent in the animal kingdom, as well as in the transfer RNA of cells.

"It's possible that the HMU present in modern organisms is a molecular remnant of the RNA world," Miller says. Indeed, HMU "may have acted as a bridge between the RNA world and the DNA-protein world of today." — *R. Lipkin*

Sabotaging the supply lines of neurons

In war, one of the most time-honored strategies for destroying forces far from home is to cripple the usually vulnerable supply lines that sustain them. Amyotrophic lateral sclerosis (ALS), a devastating neurodegenerative condition also known as Lou Gehrig's disease, may use just such a strategy as it slowly kills the body's motor neurons — specialized nerve cells that control the muscles.

Motor neurons, like all nerve cells, hook up to other cells via communication cables called axons. But the axons of motor neurons can be enormously long — 1 meter or more. For a neuron to stay healthy, its main cell body must constantly deliver important structural proteins and energy-producing organelles called mitochondria all the way to the distant end of the axon.

In the May 4 NATURE, a group of Canadian neuroscientists suggests that ALS patients may face a deadly blockade of those supplies within their axons. The researchers studied genetically engineered mice that make large quantities of a human protein that forms thread-like polymers called neurofilaments. More than 70 percent of ALS patients have excessive neurofilament accumulations in their motor neurons.

Whether these unusual neurofilament deposits were a cause or a consequence of motor neurons dying has been a mystery. But in their mice at least, says study leader Jean-Pierre Julien of McGill University in Montreal, the neurofilaments indeed play the villain.

Produced in the main body of the neuron, he explains, they clog the cell and form a plug at the beginning of the axon that slows or blocks structural proteins such as actin and tubulin from moving down the nerve fiber. This barricade, he suspects, also explains the virtual absence of mitochondria at the ends of the axons.

Julien and his colleagues suggest that these transport difficulties prompt the deterioration of the axon, starting at its far end; eventually, they believe, the whole neuron dies. Moreover, they argue, the length of motor neuron axons and their normal neurofilament content, higher than other neurons, make them especially vulnerable to overproduction of neurofilaments. ALS does not destroy other neurons, which seem to withstand better any excess buildup of neurofilaments.

This new mechanism is the fourth attempt in recent years to explain the progressive and selective killing of motor neurons in ALS (SN: 3/26/94, p.203). It's unclear whether any or all of these mechanisms are connected.

"Now, we need something to pull these four models together," says neurologist Stuart A. Lipton of Harvard Medical School in Boston, though he cautions that looking for a single chain of events to explain the neuronal death seen in ALS may be too simplistic.

If neurofilament blockades play an integral part in the ALS story, how might researchers prevent them from forming?

Julien suggests seeking out agents that could block production of the neurofilament protein, but he and others acknowledge that little has been published on the whole topic.

"I can't think of too many ways to change neurofilament accumulation. I don't know of anything practical," says neurologist Jeffrey D. Rothstein of Johns Hopkins University School of Medicine in Baltimore.

Then again, adds Scott Brady of the University of Texas Southwestern Medical Center in Dallas, who wrote an accompanying comment in NATURE on the new work, "if you identify a pathway, only then do you begin to think of manipulating it." — *J. Travis*