

HHMI's 1995 Holiday Lectures on Science
The Double Life of RNA

Lecture One

Catalysis: Chemical and Biochemical

Thomas R. Cech, Ph.D.

At the most fundamental level, life processes are chemical reactions. Left to themselves, however, those reactions would occur too slowly and nonspecifically to sustain life. Cellular enzymes serve as catalysts, taming the reactions by accelerating them, lending specificity, and regulating their time and place. Dr. Cech demonstrates some principles of biological catalysis with simple chemical examples.

Lecture Two

RNA as an Enzyme: Discovery, Origins of Life, and Medical Possibilities

Thomas R. Cech, Ph.D.

Like most scientific advances, the discovery of catalytic activity in RNA led to unexpected spinoffs. One of these spinoffs is a new, more plausible scenario for the origin of life on Earth. The ability of RNA enzymes (ribozymes) to cut and splice other RNA molecules has also sparked intense effort to develop ribozymes as pharmaceuticals directed against viruses, cancer, and genetic diseases.

Lecture Three

How to Accelerate a Reaction a Hundred Billion Times Using Only RNA

Thomas R. Cech, Ph.D.

RNA and protein are built from different chemical units and are assembled in different ways. Thus, the discovery that RNA exhibits catalytic activity rivaling that of traditional protein enzymes was unexpected. Recent studies of catalytic centers composed of RNA have revealed much about their structure and mode of action.

Lecture Four

Life at the End of the Chromosome

Thomas R. Cech, Ph.D.

Chromosomes of humans and other eukaryotes contain linear DNA molecules. The chromosome ends, or telomeres, are specialized structures necessary for DNA stability and replication. Telomere replication is carried out by an unusual enzyme, telomerase, whose RNA subunit acts as a template for telomeric DNA synthesis.

Key Concepts

- In a single cell too small to be seen by the human eye, thousands of chemical reactions take place under conditions that require less energy than normal thanks to biological catalysts called enzymes.
- Specific enzymes accelerate each of these reactions by bringing together the reactants in precisely the proper orientation and chemical environment.
- With only four different monomers, ribosomal RNA (rRNA) molecules cannot match the structural diversity of proteins, which contain more than 20 chemically diverse monomers known as amino acids.
- DNA molecules (genes) contain the blueprints for making proteins. Copies of genes in the form of messenger RNA (mRNA) carry the information from the genes to the ribosomes, where protein synthesis occurs.
- *Tetrahymena thermophila*, a single-celled eukaryotic organism, carries a gene that encodes rRNA. The *Tetrahymena* rRNA gene is not bound into a larger chromosome but occurs instead as a separate, easily isolated bit of DNA associated with regulatory proteins in the nucleus.
- The strategy of Dr. Cech's Nobel Prize-winning research team was to fractionate the crude nuclear extract; incubate the various fractions with purified, full-length, unspliced rRNA; and identify which fraction would be able to splice the rRNA. Samples containing the unspliced rRNA incubated with the same salts and RNA monomers (but no nuclear extract) served as controls. The researchers discovered that samples that contained the nuclear extracts could indeed splice the purified, full-length rRNA. But the control appeared to splice itself equally well.
- Bacteria, unlike *Tetrahymena* and other eukaryotes, do not contain introns and thus have no need for splicing activity.
- The *Tetrahymena* rRNA intron catalyzes its own splicing without the help of a protein enzyme.

- A *ribozyme* is a ribonucleic acid with enzyme-like catalytic properties.
- Some believe that rRNA, rather than protein components of the ribosome, may directly catalyze the formation of peptide bonds between amino acids as ribosomes assemble proteins. The catalytic capacity of RNA suggests that a randomly assembled RNA polymer may have the ability to catalyze its own replication.
- Because DNA is more stable than RNA, it performs the information—storage function.
- Because proteins are chemically more versatile than RNA, they perform the catalytic duties.
- The remaining catalytic duties of RNA may be vestiges left over from the earliest cells.
- Telomeres are repeated sequences of DNA at the ends of each chromosome in eukaryotic cells. RNA may play a unique role in telomere replication, which ensures that chromosomal DNA is faithfully duplicated.

References

About Protein Structure

Angier, N. "Light at the Bend of the Tunnel." In *Finding the Critical Shapes*, 6-23. Edited by Maya Pines. Chevy Chase, MD: Howard Hughes Medical Institute, 1990.

Branden, C. and J. Tooze. *Introduction to Protein Structure*, 272-284. New York: Garland Publishing Co., Inc., 1991.

"The Molecules of Life". Readings from *Scientific American*, 38-47. New York: W.H. Freeman and Company, 1985.

About Protein Synthesis

Pennsylvania Biotechnology Association. *Your World, Biotechnology and You* 2(2)4-5, 1993.

About Enzymes

Cech, T. "Group I introns: new molecular mechanisms for mRNA repair." *Biotechnology* 13:323-326, 1995.

Altman, S. "RNase P in research and therapy." *Biotechnology* 13:327-329, 1995.

Dressier, D. and H. Potter. *Discovering Enzymes*, 88-89. New York: W.H. Freeman and Company, 1991.

Culotta, E. "Forcing the evolution of an RNA enzyme in the test tube." *Science* 257:613, 1992.

About DNA/RNA/Gene Regulation

Micklos, D.A. and G.A. Freyer. *DNA Science: A First Course in Recombinant DNA Technology*, 87-93. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1990.

Pines, M., ed. "A Brief Key to Basic Genetics." In *Blazing A Genetic Trail*, 14. Chevy Chase, MD: Howard Hughes Medical Institute, 1991.

Pines, M., ed. "Why So Many Errors in Our DNA?" In *Blazing A Genetic Trail*, 17. Chevy Chase, MD: Howard Hughes Medical Institute, 1991.

Watson, J., et al. *Recombinant DNA: A Short Course*, 92-103. Scientific American Books, 1983.

Lab Activity Using *Tetrahymena*

Reames, S. *Ohio Science Workbook Biotechnology*, 165. Columbus: Ohio Academy of Science, 1993.

About Chromosomes/Telomeres

Oliwenstein, L. "By a Thousand Cuts." *Discover* Feb.:24-25, 1993.

About Catalytic RNA and Evolution

Orgel, L. "The origin of life on the Earth." *Scientific American* 271(4):77-83, 1994.

Lecture Bibliography

RNA Catalysis

Cech, T.R. "Self-Splicing and Enzymatic Activity of an Intervening Sequence RNA from *Tetrahymena* (Nobel Lecture)," 1989.

Cech, T.R. "Structure and Mechanism of the Large Catalytic RNAs: Group I and Group II Introns and Ribonuclease P." In *The RNA World: The Nature of Modern*

RNA Suggests a Prebiotic RNA World, 239-269. Edited by Raymond F. Gesteland and John F. Atkins. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1993.

Strobel, S.A. and Cech, T.R. "Minor groove recognition of the conserved G-U pair at the *Tetrahymena* ribozyme reaction site." *Science* 267:675-679, 1995.

Sullenger, B.A. and Cech, T.R. "Ribozyme-mediated repair of defective mRNA by targeted transsplicing." *Nature* 311:619-622, 1994.

Chromosome Termini

Blackburn, E.H. "Telomerase." *In The RNA World: The Nature of Modern RNA Suggests a Prebiotic RNA World*, 557-576. Edited by Raymond F. Gesteland and John F. Atkins. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1993.

Gray, J.T., et al. "Cloning and expression of genes for the oxytricha telomere-binding protein: specific subunit interactions involved in the formation of the telomeric complex." *Cell* 67:807-814, 1991.

Lingner, J., et al. "Telomerase RNAs of different ciliates have a common secondary structure and a permuted template." *Genes Dev* 8:1984-1998, 1994.

Fang, G. and Cech, T.R. "Telomerase RNA in the replication band and spherical subnuclear organelles in hypotrichous ciliates." *J Cell Biol* 130:243-253, 1995.