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RNA

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Catalytic RNA; Messenger RNA; Nucleic acid; Ribosomal RNA; Ribozymes; RNA world; RNAi; Transfer RNA

Synonyms

Ribonucleic acid

Definition

Ribonucleic acid (RNA) is one of two principal types of nucleic acid found in all cellular life. The molecule consists of a polymer of ribonucleoside phosphates, each unit of which, in turn, is comprised of a ► pyrimidine base or ► purine base, a ► ribose sugar, and a ► phosphate. RNAs encode genetic information (e.g., RNA viruses), serve as intermediates in gene transcription (e.g., mRNA), and also play structural, regulatory, and catalytic (e.g., ► ribosome) roles in cellular biology.

Overview

Central Dogma of Molecular Biology

Francis Crick proposed a simple scheme, shown below, that he entitled "The Central Dogma of Molecular Biology" to serve as a unifying axiom for the emerging field of molecular biology: $\mathrm{DNA} \rightarrow \mathrm{RNA} \rightarrow \mathrm{Protein}$, i.e., "DNA makes RNA makes Protein." Information flow was held to be from left to right only, with DNA encoding genetic information, proteins as gene products serving as the main form of genetic expression, and RNA serving an intermediary role.

Although DNA encodes the information required for protein synthesis, it must first be *transcribed* into messenger RNA (mRNA), and then the three-nucleotide genetic code must be *translated* into an amino acid sequence during protein synthesis. In addition to mRNA, which serves as the physical template for translation, adapter molecules, known as transfer RNA (tRNA), match the ► nucleotide triplets of the genetic code in the mRNA to individual amino acids, which are covalently linked to each tRNA molecule. Protein synthesis takes place on the ribosome, an RNA-protein complex, whose structure is mainly comprised of ribosomal RNA (rRNA) molecules. The catalytic center of the ribosome is thought to be comprised entirely of rRNA, which also implies the peptidyl transferase of the ribosome is a ribozyme or a catalytic RNA. Bacteria, Archaea, and Eukarya all possess DNA genomes; however, a large subset of viruses possess single-stranded or double-stranded RNA genomes. RNA has recently been shown to be

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extensively involved in cellular gene regulation via pathways collectively referred to as RNA interference (RNAi).

Messenger RNA (mRNA)

The genetic information encoded in DNA is not immediately available for translation into protein sequences. Rather, this information must first pass through an RNA intermediary known as messenger RNA. Genes are transcribed by RNA polymerases, enzymes that copy a specific sequence of DNA in a template-dependent fashion, producing a complementary single-stranded RNA. Depending upon the organism, this primary RNA transcript may undergo additional processing steps (e.g., capping, splicing, 3′-polyadenylation) and nuclear export (in the case of eukaryotes) before it becomes a mature mRNA available for translation into a protein sequence.

Mature mRNA molecules typically possess a 5′-untranslated region (5′-UTR), a ribosome-binding and translational start site, a continuous coding region, one or more stop codons (a translational termination site) and a 3′-untranslated region (3′-UTR), and a polyadenine terminus. Both UTRs may contain regions of RNA that participate in translational (and sometimes transcriptional) regulation. The coding region may be discontinuous in the primary transcript, requiring that the intervening sequences of noncoding RNA (or introns) be excised and the remaining coding regions (exons) be ligated, a process collectively termed pre-mRNA splicing. The coding region in a mature mRNA is almost always continuous and consists of a linear sequence of nucleotide triplets, called *codons*, each of which codes for an individual amino acid. The mRNA thus serves as a mobile template for the assembly of a protein by the ribosome.

Transfer RNA (tRNA)

The one-to-one correspondence between an amino acid (the monomeric building blocks from which proteins are synthesized) and a nucleotide triplet codon is physically manifested in the form of transfer RNA (tRNA). Unlike mRNAs, tRNAs are comparatively small (~75 nt) noncoding RNAs that fold into a regular, well-defined globular three-dimensional structure. tRNAs serve as shuttle molecules, one end of which becomes covalently attached to a specific amino acid (via a reaction catalyzed by tRNA synthetase) and the other end, termed the anticodon, forms standard Watson-Crick hydrogen-bonded base pairs with the corresponding codon within an mRNA when both are bound to the ribosome. tRNAs having covalently bound amino acids are referred to as aminoacylated tRNAs, and these (along with the mRNA template) are the substrates used by the ribosome for enzymatic peptide synthesis.

Ribosomal RNA (rRNA)

The ribosome is an RNA/protein complex that catalyzes peptide bond synthesis reactions in a template-dependent manner to *translate* the genetic code into protein sequences. The substrates consist of aminoacylated tRNAs and an mRNA template. The ribosome itself is comprised of two subunits, conventionally termed the large subunit (which contains the peptidyl transferase reaction center) and the small subunit (which binds the mRNA template). Each of these subunits, in turn, is comprised of RNA and protein components. The RNAs define the core structure and appear to be primarily responsible for catalyzing the chemical step of peptide bond formation, as well as forming the binding sites for mRNA, the tRNAs, and the interface between the ribosomal subunits. The proteins are primarily found on the surface of the ribosome and appear to play more ancillary (but nonetheless essential) roles. The small subunit of the ribosome is comprised of several proteins and one RNA molecule (16S rRNA in prokaryotic systems and 18S rRNA in eukaryotic systems, where S indicates ► Svedberg units). The large subunit of the ribosome is comprised of several proteins and more than one RNA molecule (23S rRNA and 5S rRNA in prokaryotic systems and 28S, 5. 8S, and 5S rRNA in eukaryotic systems). The 23S rRNA in prokaryotes and the analogous 28S rRNA in eukaryotes are believed to possess all of the components required to catalyze the chemical step of the peptide transfer reaction; hence, these RNAs are examples of enzymatic RNAs or ► *ribozymes*.

Catalytic and Enzymatic RNAs (Ribozymes)

Until the early 1980s, it was presumed that all enzymes were proteins. It was then discovered that the self-splicing catalytic activity in group I introns in certain protozoans (e.g., *Tetrahymena*) and the enzymatic processing of precursor tRNA transcripts by the RNA/protein complex RNase P in bacteria were in fact catalyzed by RNA. Subsequently, several other RNA enzymes, or ribozymes, have been discovered. Inarguably, the most important of these, described in the previous paragraph, is the peptidyl transferase activity of the ribosome; hence, the ribosome is the most fundamental and important ribozyme. With the exception of the ribosome, all naturally occurring ribozymes catalyze either phosphodiester isomerization reactions (leading to both RNA backbone cleavage and ligation) or phosphodiester hydrolysis reactions (leading exclusively to RNA backbone cleavage).

Genomic RNA

All eukaryotic, archaeal, and bacterial genomes are comprised of double-stranded DNA. However, many viruses possess either single-stranded or double-stranded RNA genomes. An important subset of these viruses are known as retroviruses and are characterized in having a life cycle in which an RNA strand that invades the host cell is reverse transcribed by an RNA-dependent DNA polymerase into DNA and the complementary DNA becomes integrated within the host's genome (the human immunodeficiency virus (HIV) is one such example). RNA viruses that are not retroviruses include the common cold virus, influenza viruses, severe acute respiratory syndrome (SARS) virus, polio, and many others.

RNA Interference (RNAi)

Within the last decade, we have begun to understand that small (typically ~21-nucleotide) noncoding RNA molecules that are the products of cellular processing reactions are intimately involved in gene regulation via a series of related mechanisms collectively known as RNA interference (RNAi). Briefly, these mechanisms involve intermolecular interactions between the small noncoding RNAs and mRNAs, or in some cases, direct interaction with the nucleosome.

RNA World Hypothesis

The discovery that RNA can be catalytic provides a logical escape from the conundrum implicit in the Central Dogma of Molecular Biology. Specifically, if proteins are required to replicate ► nucleic acids and nucleic acids are required to encode proteins, which came first? This sort of paradox is typically invoked as an example of "irreducible complexity" by those arguing in favor of the necessity of a supernatural origin of life. However, if a single type of molecule, such as RNA, is capable of both information storage and catalysis, it means, in principle, that RNA has the capacity to self-replicate. A self-replicating RNA thus avoids the chicken or egg paradox objection of "irreducible complexity" and permits suggestion that some of the earliest self-replicating molecules may have been RNAs. This conjecture, originally articulated by Carl Woese and Francis Crick, has been formulated and given the title of the ► "RNA World." Of course, no one knows if life evolved from an RNA world, but it may be possible to give an experimental proof of principle by creating self-replicating RNAs in vitro. In vitro RNA evolution is now a commonly used laboratory technique for devising various aptamers and catalysts. Although ligase ribozymes have been developed that can copy other RNA sequences in a template-dependent manner (a prerequisite to propagation of RNA), a true self-replicase ribozyme remains elusive.

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See Also

► Evolution, In Vitro
► Nucleic Acids
► Nucleoside
► Nucleotide
► Oligonucleotide
► Purine Bases
► Pyrimidine Base
► Ribose
► Ribosome
► Ribozyme
► RNA World

References and Further Reading

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