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The Biochemistry and Clinical Importance of Ribonucleic Acid (RNA): A Review Article

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ABSTRACT: Ribonucleic acid (RNA) is a compound that is found in almost all the cells of animals, plants, microbial, and viral particles. It is constituted from a polymer of nucleotides that contain a ribose sugar. There are many main types of RNAs, but the major types that take part in protein formation: are transfer RNA (tRNA), ribosomal RNA (rRNA), and messenger RNA (mRNA). The alteration in nucleotide sequence of RNA in viruses may be responsible for development of different diseases in living organisms. There is a huge variation in RNA viruses, such as retrovirus, rhinovirus, coronavirus, which account for many human illnesses. In this review article, we shed light on the evidence-supported information about the biochemical aspects and clinical importance of RNA.

1. INTRODUCTION

Almost all animals, plants, microbial cells, and viral particles contain a molecule named Ribonucleic acid (RNA). It consists of nucleotides which consist of ribose sugars bound to nitrogenous bases and phosphate groups. The nitrogenous bases present in RNA are cytosine, uracil, guanine, and adenine. Although mostly single-stranded, RNA can also be found in special double-stranded forms, such as certain RNA viruses. With different lengths and structural configurations, the RNA molecule exhibits variability. Being the genetic material in some viruses apart from DNA has led to many diseases in humans through RNA production instead of transcription from DNA that is further used by eukaryotes or prokaryotes synthesis into proteins: two processes differ significantly between these two types of organisms. Moreover, specific molecules regulate gene expression; an important aspect— is understanding that these individual entities can act as potential therapeutic agents based on human diseases that they would otherwise affect. (Wang and Farhana, 2023).

RNA plays a role in cellular protein synthesis and acts as the genetic code carrier, taking over DNA duties in some viruses. RNA is an essential molecule within all living organisms — including animals, plants, viruses, and bacteria — serving various functions in the cell. Apart from being a structural molecule in cell organelles, it also participates in catalytic biochemical activities. Different types of RNA play different roles in various cellular processes (Pallan et al., 2007).

In this review article, we cast the light on the evidence-supported information about the biochemical aspects and clinical importance of RNA

STRUCTURE

Ribonucleic acid is a macromolecule that can be found in all living cells and has a similar structure to DNA. However, RNA is typically single-stranded unlike DNA which is double-stranded. The backbone of an RNA molecule is composed of alternating phosphate groups and a sugar called ribose (as opposed to deoxyribose in DNA) with one of the four bases— guanine (G), cytosine (C), uracil (U), adenine (A)— attached to each sugar. Cells contain various types of RNA including transfer RNA (tRNA), ribosomal RNA (rRNA), and messenger RNA (mRNA); others act as regulators for gene expression while certain viruses use RNA as their genetic material. As shown in figure 1. (Saenger, 1984).

RNA's ribose sugar takes the form of a five-carbon, one-oxygen cyclic structure. The occurrence of a chemically reactive hydroxyl (−OH) group at the second carbon atom makes RNA highly susceptible to hydrolysis. This inherent chemical instability in RNA, unlike DNA, which lacks such reactivity at the same position on its sugar component (deoxyribose), is considered a probable rationale for why DNA became nature's preferred genetic carrier over RNA in most organisms. R.W. Holley first unveiled the structure of the RNA molecule back in 1965. (Chatterjee and Wan, 2024).

Single-stranded is the usual characteristic of RNA, but when self-complementary sequences are present within the RNA strand, it leads to base-pairing within the chain— resulting in folding. This folding fashion of the ribonucleotide chain forms bulges-and-helices complexes at structural levels. The 3D structure of RNA plays a vital role in both stability and function; cellular enzymes modify ribose sugar along with nitrogenous bases through different ways by attaching chemical groups such as methyl groups (other modifications) at specific locations on the chain which result from specific bond formations that would involve distant regions — inducing complex contortions within the RNA chain and consequently enhancing further stabilization for RNA structure. (Pallan et al., 2007).

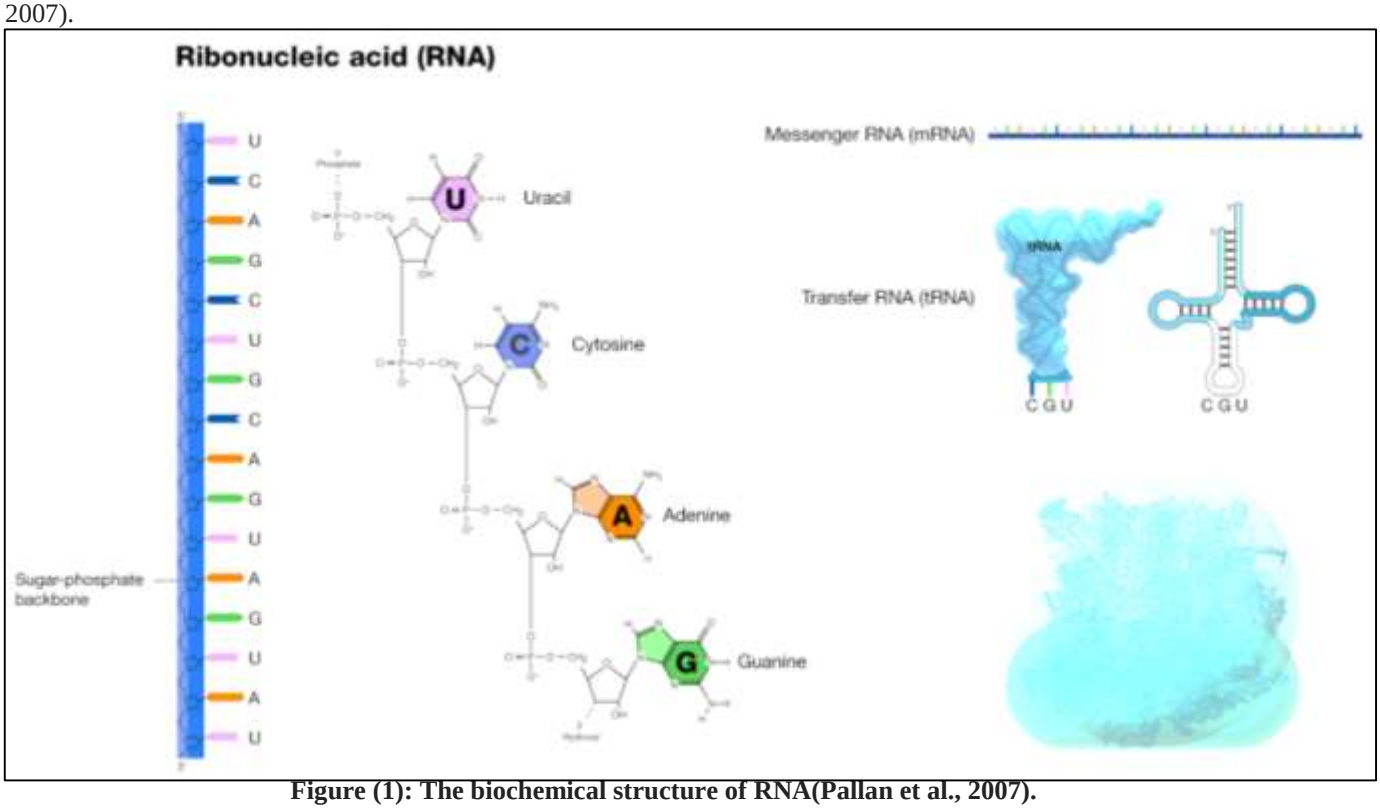

Figure (1): The biochemical structure of RNA(Pallan et al., 2007).

TYPES OF RNA

One of the most common RNA is messenger RNA (mRNA) along with other kinds like ribosomal RNA (rRNA) and transfer RNA (tRNA). They are universally present in all living organisms, and together with other forms of RNAs, including small nuclear RNAs plus small nucleolar RNAs, mostly function as enzymes that catalyze biochemical reactions. However, a few also have elaborate regulatory roles within cells. Because they participate in numerous regulatory processes due to their spread and diverse functions, RNAs are crucial biological molecules that impact both normal cellular processes as well as diseases (Minchin & Lodge, 2019).

There are several types of RNAs besides rRNA, tRNA, and mRNA. They can be broadly classified into noncoding RNA (ncRNA) and coding (cRNA). Among small ncRNAs are small nucleolar RNA (snoRNA), small-interfering RNA (siRNA), PIWI-interacting RNA (piRNA), small nuclear RNA (snRNA), micro RNA (miRNA); the miRNAs stand out. Micro RNAs are around 22 nucleotides long and have a regulatory role in gene expression in most eukaryotes: they can bind to target mRNA and inhibit translation leading to functional proteins not being produced, which has implications for cancer and other diseases. For instance, oncogenic miRNAs and tumour suppressors can control specific target genes contributing towards tumorigenesis; also noted for their functional significance are the piRNAs that range from 26 to 31 nucleotides long and widely present among animals. Transposons are controlled in germ cells by preventing their transcription, thereby ensuring that transposons are not transcribed. PiRNA mostly targets various transposons through complementarity and can specifically target those transposons (Mattick & Makunin, 2006; Hubé & Francastel, 2018).

One special aspect of Circular RNA (circRNA) is that it forms a closed loop structure due to the bonding of its 5′ and 3′ ends— this sets it apart from other types of RNA. CircRNAs are produced by a large number of genes that code for proteins, some in a manner similar to mRNA can function as templates for protein synthesis. They also have the ability to bind miRNA: they act like miRNA 'sponges' thereby stopping the miRNA molecules from binding to their targets. Furthermore, circRNAs are involved in controlling gene transcription and alternative splicing along which play pivotal roles in regulating cascades derived from genes that produce circRNAs (Zhao et al., 2022).

TRNA

The responsibility of the transfer RNA is to select the correct protein or amino acids (AA) that are needed by the body which in turn assists the ribosomes. Each tRNA is present at its amino acid-specific endpoints and is called as soluble RNA; it acts as a bridge between the messenger RNA and amino acids. The main role of tRNA is to carry AA to a ribosome complex through its 3' acceptor site with the help of aminoacyl-tRNA synthetase, an enzyme that attaches the proper AA onto tRNA. Protein synthesis occurs when aminoacyl-tRNA synthetases load appropriate AA onto free tRNAs; after binding with an AA, tRNAs are recognized as aminoacyl-tRNAs. The identity of an AA carried on tRNA is specified by the mRNA codon (a three-nucleotide sequence on mRNA that specifies AA). The anticodon arm of the tRNA is where the anticodon is located. The anticodon complements an mRNA codon and specifies the AA to be brought onboard. In addition, tRNAs control apoptosis as they act like a cytochrome c scavenger (Raina & Ibba, 2014).

MRNA

This is a kind of RNA that acts as a courier, delivering genetic information to ribosomes where protein synthesis takes place. It whispers sweet nothings about what protein cells are craving. By function, this is known as messenger RNA or mRNA— which plays an indispensable role either in transcription or protein synthesis; prokaryotic mRNA can go straight into protein synthesis without any processing while eukaryotic mRNA matures from pre-mRNA. Pre-mRNA has introns (non-coding regions) and exons (coding regions); during pre-mRNA processing, introns are spliced out and exons are joined together. A 5' cap (7-methylguanosine) is added at one end, and the other end is polyadenylated— ending production. Polyadenylation is when a poly(A) tail (consisting of adenine nucleotides) is added to the transcript. The cap at 5' end provides protection for the mRNA, and on the other end, the poly(A) tail at 3' contributes to the stability of mRNA while also helping it in transportation. Scientists have their eyes set on mRNA as an anti-cancer therapy; this molecule has the potential to alter cell structures (Van Lint et al., 2013).

RRNA

Ribosomal RNA, commonly known as rRNA, is responsible for the formation of ribosomes which play a crucial role in protein synthesis. A ribosome is made up of two main components: a large ribosomal subunit and a small ribosomal subunit. In prokaryotes, the 70S ribosome consists of a 30S and 50S subunit while in eukaryotes, an 80S ribosome is made up of by a 40S and 60S subunit. The rRNA molecules are primarily made up of cellular RNA components and they are the most abundant type of RNA found in all living cells. This underscores their importance in translation; acting as integral players alongside tRNA (transfer RNA) molecules in deciphering genetic information from mRNA to synthesize proteins (Raina & Ibba, 2014).

CLINICAL SIGNIFICANCE

Cellular operations are contingent on various protein-coding and noncoding RNAs along with RNA-binding proteins; these molecules come together to form ribonucleoprotein complexes (RNPs). Disruptions in mutations — whether it be the RNA or protein components of the RNP itself, or the factors required for their assembly — can prove deleterious. However, alternative splicing equips cells with an incredible ability to adjust their transcriptome and proteome according to need— a mechanism that is highly regulated because splicing relies on a complex code riddled with many RNA-binding proteins interweaved in an intricate network where mis-regulation could lead to disease. Unveiling disease-inducing mutations within RNAs promises a new stream of therapeutic targets sourced from understanding RNA biology: including its chemistry, leading to innovative RNA-based tools for drug development (Cooper et al., 2009).

An intriguing group of RNA molecules with repetitive sequences have a knack for trapping RNA-binding proteins (RBPs); this results in curious foci formations or protein aggregates within neural tissues. These little gatherings are major players in neurodegenerative disease development: think myotonic dystrophy and amyotrophic lateral sclerosis (ALS) because, let's face it, losing proper function or control over these essential proteins is bad news for any human. And speaking of not-so-great news for humans— particularly those with neurological disorders— an expanding non-coding RNA repeat seems responsible for more maladies than we can count on one hand (or even two hands) including Huntington's disease-like 2 (HDL-2), fragile X tremor/ataxia syndrome (FXTAS), frontotemporal dementia (FTD). The list goes on; but how does a simple repetition lead to such catastrophic consequences? Well, this expansion creates abnormal hairpin structures when certain areas fold back onto themselves along the RNA strand— kind of like when your plans fold in on themselves, only here it disrupts nucleolar functioning! In turn RNA toxicity is due to its deleterious effects which induce autophagy and splicing defects (Wang and Farhana et al., 2023).

In the realm of cancer, miRNAs play roles so significant that they have captured the attention of many researchers. Certain miRNAs are found to be at high levels in cancer cells, fueling the growth of these malignant masses; some even act as regulators for more than one type of cancer. For instance, miR-126 has been identified as highly expressed in colorectal and breast cancers; interestingly, Silva et al. recently brought to light its elevated presence in human B-ALL. When they artificially induced miR-126 expression in mouse hematopoietic stem progenitor cells, it led to the development of B-cell leukemia— a cascading effect unveiled down the line. The overexpression of this miRNA resulted in a down-regulation of p53 and its related genes while suppressing it

triggered apoptosis: an interesting inhibitory effect on B-ALL progression in xenograft mice was observed. On another note players like miR-155 come into play as oncogenes belonging not only to one specific kind but rather many kinds— liver or gastric or lung plus breast and colon (Al-Haidari et al., 2017).

Certain miRNAs have been identified as tumor suppressors— for instance, let-7 and miR-34a. The let-7 miRNAs consist of a large family. A majority of them are under-expressed in various cancer types that encompass pancreatic cancer, colon cancer, breast cancer, prostate cancer, non-small cell lung cancer and hepatocellular carcinoma (Yan & Bu, 2021).

HOTTIP, a lncRNA derived from HOXA gene, has also been identified as a major cancerously overexpressed RNA. Recent findings by Luo et al. (2019) reveal HOTTIP's involvement as an oncogene in acute myeloid leukemia (AML); they discovered that HOTTIP acts as an epigenetic regulator upon its abnormal elevation in AML, orchestrating hematopoietic gene-associated chromatin transcription through modulation of gene expression program. Notably, LncTCF7 stands as another lncRNA transcribed from TCF gene locus with distinct implications: Wang et al. (2015) reported high expression levels of lncTCF7 in liver cancer stem cells (CSCs), suggesting its role in governing CSC self-renewal that could be vital for liver CSCs maintenance. Like miRNAs, lncRNAs too function either as oncogenes or tumor suppressors to orchestrate tumorigenesis and cancer progression thereby playing regulatory roles during the course of disease evolution.

Even though both whole-exome sequencing and whole-genome sequencing have greatly revolutionized our comprehension of the genetic etiology of human diseases, we are still unable to diagnose about half of the patients at a molecular level. The large proportion of variants with uncertain significance — coupled with the difficulty in interpreting noncoding variants — has led scientists to introduce RNA sequencing (RNA-seq) as part of the diagnostic workflow. An assay with high throughput capabilities, RNA-seq acts as a complement to genomic data by providing functional evidence. Through RNA-seq data, scientists can unearth aberrantly spliced genes or detect allele-specific expression, or even identify gene expression outliers (Peymani et al., 2022).

Human diseases can be caused by a wide range of RNA viruses. These include retrovirus, rhinovirus, and coronavirus. The viruses can be categorized based on polarity in a positive or negative sense and can have either a naked or enveloped membrane structure. Among the RNA viruses, the Coronavirus is famously known for causing Severe Acute Respiratory Syndrome (SARS). It is transmitted through droplets and has shown higher viral loads in nasal mucosa than in the throat; it also leads to increased inflammatory cytokines like TNFa, IL10, IL7, IL2 with symptoms including pneumonia, sore throat, cough fever (Singhal, 2020).

A retrovirus is another notable RNA family that can result in dangerous human disease: a positive sense enveloped RNA virus composed of HTLV and HIV. HIV wipes out naïve and memory CD4+ T cells, often remaining asymptomatic until the final stage where it leads to AIDS— Acquired Immunodeficiency Syndrome. An immunocompromised host then fails to fend off opportunistic infections as well as viral-induced cancers. On a different note, rhinoviruses take center stage among agents causing common cold: gaining entry via endocytosis with the assistance of LDLR and ICAM-1, resulting in symptoms like sore throat or nasal congestion; some other notable human diseases resulted from RNA viruses include measles, polio, rabies— just to mention but a few (Simon et al., 2006 ; Blaas & Fuchs, 2016).

CONCLUSIONS

Ribonucleic acid (RNA) is a compound that is found in almost all the cells of animals, plants, microbial cells, and viral particles. It is constituted of a polymer of nucleotides that contain a ribose sugar. The are many main types of RNAs, but the major types that take part in protein formation: are transfer RNA (tRNA), ribosomal RNA (rRNA), and messenger RNA (mRNA). The alteration in nucleotide sequence of RNA in viruses may be responsible for development of different diseases in living organisms. There is a huge variation in RNA viruses, such as retrovirus, rhinovirus, coronavirus, which are account for many human illnesses.

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