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A Messenger Ribonucleic Acid: A Platform for Protein Synthesis

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Abstract

The messenger Ribonucleic Acid (mRNA) has come to play as potential regulators of gene expression that is translates in the ribosome by the RNA polymerase and yields amino acid and protein. This plays a tremendous role in the protein synthesis and is not just mere template in translation but also contains essential regulatory elements as protein supplement, for therapy vaccine production and generation of pluripotent stem cells. This review highlights the new approaches and insights in the role of mRNA as a template in protein synthesis, functional approach, clinical uses and in vivo usage which is still a challenge underway.

Keywords: MRNA; Translation; Protein synthesis; DNA; Gene regulation.

Introduction

The mRNA is a single stranded RNA transcribed from the DNA in its orderly arranged manner that has two extreme ends of cap and tail, 5' and 3' untranslated regions (UTR) and coding sequence (CDS) in middle which translates to proteins. The amino acid synthesis starts in the coding region with the initiation codon AUG and runs to the termination codon AAA. The 5' terminal cap structure makes room for the correct binding between mRNA and ribosome. The ribosome is an enzymatic protein that catalyzes the mRNA for the translation process to yield protein [1]. The translation machinery is located in the ribosome which begins at the 5' end of the mRNA but the 3' end is still join to DNA. But for the protein synthesis, translation mechanism of mRNA is programmed in away to integrate the amino acid for its production [2]. In the 3'non coding region as the location of microRNAs (miRNAs) that regulate the gene expression. This also contributes to mRNA degradation and translational repression due to its interaction with mRNAs at 3'UTR mRNAs activate translation or regulate transcription [3]. However, the primary function of it is in protein synthesis. This mechanism happens in a way that the translation into protein occurs by the action of transfer RNA and ribosome and two major ribosomal RNA (rRNA) molecules [4]. This involves the breakdown of large and small subunits of ribosome by the initiation factors (Ifs), whereby the small subunit (SSU) bounds to mRNA and met-transfer RNA and forms the initiation complex. It is followed by the peptide change elongation (PCE) that integrates the met-tRNA at the P site coupled with the amino acyl –tRNA to elongation factors (EFs) and binds at a site. The 5' and 3' UTR provides stability for the mRNA. Within the ribosome the mRNA initiates proteins at coding region [5]. The publication of Avery, McLeod and McCarty led to the recognition of DNA and its role in genetics due to the transformational principle of pneumococcal bacteria [5, 6]. Later, the mRNA came to a firm resolution for the knowledge of gene function [7]. In 1957, Arthur Pardee during his sabbatical visit to the Institute, Pasteur recognized that genes produce a messenger molecule as the first time in Paris [5]. It was later on that the RNA fraction was called messenger RNA (mRNA) by Jacob and Monod [6]. But this was debated that Nirenberg was the first to isolate mRNA [10].

Functional Approach to MRNA

Recently, mRNAs have come into play as potential regulators of gene expression following the RNA modifications in coding sequences N^6 – methyl adenosine, (M^6A), 5 – methyl cytosine (M^5C); pseudouridine Y) and N^1 methyadenosine ((M^1A) have been discovered within open reading frames of mRNAs [12].

The modulation of mRNAs within a cell has helped in the direct mechanism of protein synthesis regulation. But, a link between the amount of mRNA and its corresponding protein has not been observed [13, 14].

The disruptions in the initiation factor in the protein synthesis is not the only factor but the structural motif and regulatory activities in the 5' or 3' untranslated regions (UTRs) of MRNA come into that[15 -18].

Furthermore, mRNAs are not just mere templates for translation, but contain essential regulatory elements which might be included in regulation of translation. Certainly, the modification of mRNA has opened way for N' methyladenosine (M'A) to be included in the messenger RNA bank and this led to the elevated translation rates [18, 19]. This is known to be of utmost interest in the genetic information at the RNA level

which is Adenosine – Inosine editing [21, 22]. The issue of mRNA modification which contributes a lot in the translation mechanism acts as markers to provide landing platforms for proteins which enhance other regulatory processes like MRNA degradation or localization [23-28].

Following the systematic approach to the mechanism of mRNA in processing and transport has made impact in the gene expression and when located in sub cellular level also influence polarity, migration and development [29, 30].

However, the protein elongation and co translational protein folding as shown by mRNA also its particular structure in the regulation of translation rate, but the actual supports to these potential mechanisms to the control of translation speed remain uncertain and debatable[31 -37].

Not withstanding, the shift in translational rates in the mRNA structure – dependent can bring changes thereby making enough protein that can cause major phenotypic impacts such as human disease [38].

Shabalina and colleagues went further in their studies that changes in translation speed regulated by secondary structure of mRNA has led to variations in post-translated modifications of the nascent polypeptide which was not earlier regarded in RNA level regulation [39].

Also, remarkable evidence is the mRNA-translation speed-change (MTSC) occurs during multi drug resistance I (MDR_1 or ABCBI) gene that attacks protein folding and changes the conformation, the structure and function of the multidrug transporter [40, 41].

This awareness of mRNA nucleotide modification has led to the invention of RNA mass spectrometry and the next generation sequencing (NGS) techniques which has broadened our horizon to understand the concept that M6A Pseudouridine(Y) in the mRNA is a part in biological role such as splicing and regulation of translation to mRNA decay[42,43].

Whereas the ribosomal associated ncRNA (rancRNAs) binds with mRNA and reduces the protein synthesis in stress dependent manner [44, 45].

The recent study has also led to the discovery of micro RNAs (m1RNAs)[46] small RNA molecules (18–25 nucleotides), which in their nature single stranded forms that acts as post transcriptional repressors through pairing with messenger RNA[47]. Elgar and colleagues in their approach to the field of genetic engineering discovered that synthesized mRNA (Syn -mRNA) has been of much value and safe than the DNA in the genomic integration for human clinical therapy [48].

Although Wolf and others have shown in 1990 that direct injection of 'naked' messenger RNA (mRNA) into the skeletal muscle of a mouse resulted in expression of the encoded protein development of mRNA vaccines, but this was considered unrealistic because of the expected mRNA instability during storage and after application *in vivo* [49].

More recently, Warren and his colleagues have demonstrated the success of mRNA- mediated reprogramming of human fibroblasts to induce pluripotent stem cells (iPSC) and in turn, the mRNA mediated differentiation to achieve desired mature cell type [50].

UTRs are sequences present at the 5' and 3' ends of a transcript that do not code for proteins but carry features that allow differential regulation of a gene [51].

In humans, the disarrangement in this region of UTRs results in deregulation of genes which leads to susceptibility to diseases [52].

MRNA and Evolution

The recent discoveries have shown that the outcome of new genes is fundamental to the evolution of lineage- specific traits, and several molecular mechanism s regarding the origin of new genes [53-57]. Ohno proposed that new functions could be derived through DNA based gene duplications, and has gone extensive study as a major source of new genetic material [58, 59].

Another form of new gene formation is mRNA based retropositioon where reverse transcription of mRNA generates new intronless retrocopies that are fractioned into random genomic regions [57, 60, 61]. The means of finding out the fundamental method of gene expression of evolution has been on the detection of cis-acting genomic regulatory elements and trans- acting regulatory factors that decodes differences between species and populations [62 - 65]. The regulatory changes caused by gene expression variations have been a factor in phenotypic differences between closely related species [69 - 71].

Meyer and Zhou discovered that 5' UTR M6A modification makes way for cap independent translation initiation that functions for selective mRNA translation mechanism [72, 23]. It is of universal concept that N6 methyladenosine M6A RNA transcript modification among high animals as discovered in genetic engineering [73-76], and its reversible nature [73, 76, 77, 79]. Its effects on mRNA life time and translation efficiency have its role in the regulations of key regulators of biological pathways in human disease [27, 28, 80, 81 and 75].

Conclusion

The MRNA has much impact in the field of genetics as a potential gene regulator and its modulation effects in protein synthesis. The mRNA modification acts as a marker in accessing a landing platform for proteins. A certain shift in translational rates in mRNA structure-dependent brings changes thereby increasing production which leads to human disease. However, the heterogeneous nature of mRNA has made it to be involved in genomic integration for human clinical therapy.

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