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mRNA Export Mechanism from Nucleus to Cytoplasm- A Critical Review

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Abstract

mRNA transcripts must undergo substantial processing prior to being exported from the nucleus. A 5′-cap incorporation, the splicing out of introns, cleavage at 3′ end and polyA tailing in addition to mRNA processing are all examples of these dispensation events. The mRNA export is basically well controlled, which allows for flexibility in modifying gene expression. Expression of genes can be regulated on a variety of levels. The movement of mRNA across the nuclear envelope (NE) barrier is a significant step in the process of gene expression and is essential for both robust gene expression and cell survival. The development of the nucleus during the evolution of the eukaryotic cell required the creation of a transport system to move mRNA from the nuclear transcription site to the cytoplasm's ribosomes. Nowadays research has explained how the processes that initiate before and after transport through nuclear pore complexes, affect nuclear mRNA export. They include mRNA processing, transcription, activation of genes, and mRNP assembly and disassembly. Here, the most current discoveries regarding the processes that define each route and emphasize the gene expression cascade has been outlined. We also study the process by which the proteins needed for the following stage in the mRNA assembly line replace those from the previous phase.

Keywords: 3′-end processing; mRNA; mRNA-binding proteins; mRNA export; mRNA processing

Background

mRNA transcripts must be extensively processed before they can be disseminated from the nucleus. Each of these processing stages, including the addition of a 5′-cap, intron splicing, 3′-end cleavage and polyadenylation, and mRNA export itself, is strictly regulated, allowing for flexibility in modifying gene expression [1]. These processing events are all associated with mRNA export. A single transcript can be produced on this assembly line in thousands of copies or just a few copies at a time throughout an organism's growth.

A multifaceted network of transcriptional regulators as well as an equally intricate network of RNA-binding proteins those associate with the mRNA transcript during post-transcriptional activities controls the complex regulatory system that determines when and where a gene will be expressed. These mRNA-binding proteins are involved in a variety of activities, including splicing and the localization of cytoplasmic RNA. A transcript must first gather mRNA export factors in order to depart the transcription machinery in the nucleus and transported to ribosomes in the cytoplasm. Export factors are typically assumed to actively escort mRNA transcripts through the nuclear pore complex (NPC) and out of the nucleus since they have the ability to bind both the RNA transcript and components of the NPC [2]. In eukaryotic cells, the nuclear pore complex (NPC), which is made up of hundreds of proteins, are anchored in the nuclear envelope and acts as a barrier which is selectively permeable, regulating the bidirectional movement of macromolecules between the nucleoplasm and cytoplasm [3].

mRNA is likely exported from the nucleus to the cytoplasm through a number of sub-steps in eukaryotic cells, including trafficking within the nucleus, anchoring at the nuclear basket of the NPC, moving through the NPC, and finally releasing into the cytoplasm for subsequent translation [4-7]. It has been well reported that, in brief, nascent mRNAs are processed within the nucleus and then put together into mRNA: protein complexes (mRNPs) with protein cofactors before docking at the NPC [8-12]. Nuclear transport receptors and the transcription-export complex are mediated by some of these cofactors [13-19]. It has been discovered that through binding and changing of chromatins by the nucleoporins (Nups), have potentiality towards altering gene transcription [20-25]. It has been put forward in earlier works that

by direct interacting with FG-Nups after docking, the transport receptors of mRNPs (the transport receptor protein Tap, which creates a heterodimer with cofactor p15 in human cells) enable the complexes' passage across the NPC's selectively permeable barrier and get into the cytoplasm [26-30]. Several sub-steps are probably involved in the export of mRNA from the nucleus to the cytoplasm in eukaryotic cells. The key mRNP export factors Gle1, IP6, and DDX are responsible for directionally dissociating mRNPs into the cytoplasm at Nup214 location [29-35]. According to earlier research, the nuclear basket may serve as the rate-limiting step during mRNP export, which implies that FG-Nups inside the NPC's nuclear basket may be crucial for nuclear mRNP export [4,6,36,37]. The subsequent activities that take place during gene expression following the mRNP's translocation across the NPC have also been well explored, particularly intriguing is the Dbp5 RNA helicase modifies the exported mRNP at the cytoplasmic end of the NPC [38,39].

Therefore, there are plenty of evidence pointing to a close relationship between mRNA export and other stages of gene expression [40]. Here, in order to further develop these relationships, the present work focused on current research published in mRNA export mechanism from nucleus to cytoplasm.

Co-Transcriptional Pathways Regulating mRNP Export and Biogenesis

Investigating the mechanisms that interconnect co-transcriptional processes to mRNA export is an important and focused area of research. Adaptor proteins are placed along developing transcripts when transcription is taking place prior to mRNA export. These mRNA-binding proteins have a variety of roles, from splicing to localizing cytoplasmic RNA, but as a group, they control each transcript's destination, even though export receptors can bind to mRNA transcripts directly [40,41]. Adaptor proteins are expected to significantly increase their recruitment to mature, export-competent mRNA transcripts [42,43]. These adaptor proteins are thought to recognize specific RNA sequences that indicate a particular processing step has ended and the transcript is now ready to be exported to the cytoplasm.

Analyzing the mechanisms that connect co-transcriptional processes to mRNA export is a significant and current focus in the research. Adaptor proteins are placed along developing transcripts when transcription is taking place and prior to mRNA export. Recent research has demonstrated that during transcription, a multi-protein complex known as the transcription and export (TREX) complex is built upon the nascent transcript and plays a crucial role in regulating the effectiveness of mRNA export from the nucleus [44-46]. Components of this complex deposit and then attract adaptor proteins to the freshly produced transcript. The mRNA export adaptor proteins Sub2 and Yra1, as well as the Hpr1, Mft1, Thp2, and Tho2 elements of the THO complex, make up the S. cerevisiae TREX complex [44-47]. The way that THO/TREX components are put together and connected to different levels of gene expression has been clarified by investigations in yeast. It has been suggested that TREX is involved in the co-transcriptional recruitment of the mRNA export adaptor Yra1 [45]. The TREX complex links transcription elongation to 3′ -end formation [26,29] as well as mRNA export [47]. The TREX mutants (tho2 and sub2) cause a defect in the elongation and stalling of RNA polymerase II near to the 3′-end, as shown by research from the Jensen and Libri labs. The polyadenylation cleavage factor dissociates as a result of these alterations, which inhibit polyadenylation and prevent mRNA from being released from the transcription site [48,49]. The TREX complex is conserved, although depending on the species, it may have a varying purpose. While yeast TREX combines transcription with mRNA export without the need for splicing, human TREX often operates in splicing-coupled mRNA export. However, Dunn et al. have proven that in a human TREX factor, the Thoc5 has raised the prospect of a functional connection between TREX and transcription related to export in human cells [50].

The study of TREX's function in higher eukaryotes has drawn a lot of attention from researchers. Many laboratories have recently concentrated on the characterization of novel TREX components. One of them, CIP29 (yTho1), participates in the export of mRNA and, along with Aly, forms the hTREX in an ATP- and UAP56-dependent way. As a result, splicing-coupled mRNA export may now be subject to an additional degree of regulation, hTREX assembly perhaps being dependent on ATP hydrolysis. Hautbergue et al. [51] proposed a new factor named UIF has been discovered by the Wilson lab to interact with TREX in vertebrates. The idea that the TREX function in vertebrates is connected to both splicing and transcription is further supported by these novel export factors taken together. Dunn et al. [50], opined that the higher eukaryotes have a linked polyadenylation and mRNA export pathway, similar to the yeast system [50]. Such a physical link may have the function of ensuring that Pol II transcription correctly ends before the mRNP is processed by the nuclear export machinery. The characterization of a Zn-finger protein, ZC3H3, in addition to TREX components, is a nice example to show how these two things are related [52]. This factor supports the functional linkage between various machinery along the gene expression pathway since it interacts with both polyadenylation and mRNA export components and is necessary for the nuclear export of adenylated transcripts [40]. By interacting with both mRNA transcripts and nucleoporins (Nups), RNA-binding proteins and protein complexes may actively enhance mRNA export from the nucleus [2].

These processes are "coupled" with mRNA export through these adaptor proteins because many of these proteins serve as both adaptors and crucial parts of other processes, such as splicing or 3′-end processing. Similar to an assembly line, each successive step serves as a necessity for the next and, as such,

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is a function. The accuracy of mRNA export from the nucleus is determined in part by the multi-protein complex known as the transcription and export (TREX) complex, which is formed upon the nascent transcript during transcription [44-46].

mRNA Export And 3′ -End Formation Are Coupled

Proudfoot & O'Sullivan opined that there are minor differences in 3′-end creation between yeast and higher eukaryotes, overall cleavage and polyadenylation mechanisms are surprisingly similar [53]. Moreover, they commented that the recognition of particular sequences in the pre-mRNA 3′-untranslated region (3′-UTR) and cleavage of the transcript constitute the first stage of 3′-end creation. It was also revealed by them that 200–250 adenosine nucleotides are added by Poly(A) polymerase (PAP), that make up the poly(A) tail after the transcript has been cleaved. They also validated that a complement of poly(A)-binding proteins (Pabs) binds the poly(A) tail in budding yeast and mammalian cells.

There is extensive debate on the relationship between mRNA export and 3′-end processing in metazoans, 3′-end processing has been more specifically linked to mRNA export from the nucleus in S. cerevisiae. Notably, mutations in a number of yeasts 3′-end processing factors, including Pap1, Pcf11, Rna14, and Rna15, induce an increase of poly(A) RNA in the nucleus [54,55]. Additionally, mutations in several S. cerevisiae mRNA export factors, such as Mex67, Yra1, and the cytoplasmic NPC-associated helicase Dbp5, result in transcripts that are overly polyadenylated [54,56]. mRNA export factors and 3′-end processing machinery components interact genetically [57,58]. Several investigations in S. cerevisiae used reporter transcripts that were shortened by a hammerhead ribozyme instead of processed by the typical 3′-cleavage and polyadenylation machinery to examine the relationship between 3′-end processing and mRNA export [57,58]. Gellatly et al. [59] reported that self-cleaving RNA sequences which is known as hammerhead ribozymes in plant viruses [59]. Dower et al. [57] reported that the ribozyme sequences rather than the typical 3′-UTR seen in RNA polymerase II-produced RNA transcripts prevent them from being polyadenylated and exported from the nucleus effectively. However, deletion of the gene for the cytoplasmic Ribo-exonuclease, XRN1, leads to an increase in cytoplasmic reporter RNA, indicating that some of these reporter transcripts exit the nucleus but are quickly degraded because they lack a polyA tail. This suggests that some of these reporter transcripts are exported from the nucleus [57]. Interestingly, an encoded stretch of adenosines upstream of the self-cleaving ribozyme sequence that mimics a polyA tail saves the export of these reporters [60,61]. This finding implies that although a polyA tail is helpful in facilitating mRNA export from the nucleus, it is not a prerequisite. There is evidence that some of these non-polyadenylated TRP4 transcripts can leave the nucleus and be translated since TRP4 transcripts can partially complement a trp4 deletion mutant when they are terminated at their 3′ ends by a hammerhead ribozyme [60]. It is yet unknown whether Mex67 and the normal mRNA export machinery or parts of another RNA export route are responsible for exporting these ribozyme-terminated transcripts. Although in S. cerevisiae 3′-end creation and mRNA export from the nucleus appear to be related [7,54,56,57] information is meager about the precise physical connection between the elements of the 3′-end processing machinery and the factors involved in mRNA export. The Pabs are a proposed class of proteins. Pabs play a crucial role in the control of transcript polyadenylation, stability, translation, and nuclear export. They are conserved from yeast to higher eukaryotes [61].

Regulatory Function of Nucleoporins (Nups) in Transcription

At several levels, Nups can regulate how a gene expresses itself [62]. For a subgroup of Nups that are not firmly linked with NPCs but can also be found in the nucleoplasm, studies in Drosophila support this theory. These 'free' Nups reportedly interact with particular locations on intranuclear chromatin. According to research done by the Hetzer group, certain Nups bind to the Drosophila genome at particular locations that are not connected to the nucleus' outer shell [63]. Several researches suggest that Nups perform a crucial role in developmentally important gene regulation and transcription activation. It has been found that the knockdown of the Nups prevents the target genes' transcription, indicating that NPC components perform an important role in regulating gene expression in multicellular organisms.

Kalverda et al. [64] reported similar results, where they suggested the active interactions between Nups and cellular cycle and development-related genes in the cellular nuclei. Additionally, it was discovered that megator (Mtor) and Nup153 bind to 25% of the active transcription sites that are included in the drosophila genome. Despite the absence of mechanical understanding of these strange Nup-chromatin interactions, the existence of Nups, and have been shown to carry out additional responsibilities beyond the NPC's use of them for transportation [40].

mRNA Turnover and Translation and are Associated to the Endpoint of mRNA Export

Many distinct proteins associate with the mRNA transcript through the assembly line of mRNA processing that terminates in export from the nucleus. Initial recruitment of mRNA processing proteins to the developing transcript occurs throughout via interactions with RNA polymerase II C-terminal domain transcription. After processing is finished or just before export, certain processing elements are replaced by way of the nucleus. The mature transcripts are subsequently recognized by export factors, who transmit them onto the cytoplasm through the NPC. The export factors are then replaced by other ones that control the transcript's cytoplasmic final destination. These protein cycles Displacement occurs continuously during an mRNA transcript's

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life cycle and aids in coordinating mRNA biogenesis in terms of function. One of the most appropriate illustrations of this cycle of molecular displacement happens right after the mRNP is translocated by route of the NPC. The cytoplasmic side of the NPC is where the mRNP must go through a large remodeling project to add a new complement of nuclear export elements in exchange of proteins that control the transcript's cytoplasmic fate [2].

The modification of the mRNP and the subsequent release of export components following translocation through the NPC is a critical step in providing orientation during mRNA export. The Dbp5 helicase, which sequesters to the NPC's cytoplasmic fibrils, contributes in translocation. Our understanding of Dbp5's function in mRNA export has been strengthened by structural investigations conducted in both yeast and humans. These studies [50,51] focused on the interaction between Dbp5 and Gle1 and Dbp5 and Nab2, respectively. Yeast Dbp5's carboxy-terminal domain facilitates interaction with Gle1, which in turn controls Dbp50's ATPase activity [29]. Without necessity ATP hydrolysis Dbp5 that is coupled with ADP displaces Nab2, which follows mRNA from the nucleus to the cytoplasm [34]. Dbp5 interacts with translation release factors and needs its helicase activity for effective stop-codon recognition, according to further investigations of the mRNA export factor at cytoplasmic face of NPC carried out by Krebber and colleagues [65]. By interacting with the appropriate termination and initiation components, Gle1 and IP6 are necessary for effective translation termination as well as for translation initiation [38]. Together, these findings point to a potential connection between translation and the NPC-driven cessation of mRNA export, a connection that may be mediated by Dbp5 and Gle1 [66]. According to crystal structural studies, the interaction of Nup214 and mRNP-bound Dbp5 may cause the detachment from RNA and ATP. While translocating to the cytoplasmic side of the NPC, Dbp5 is thought to connect to the mRNP that is already present in the nucleus before docking to Nup214. Dbp5 and the mRNP-bound components are then released from the mRNP after Gle1 stimulates Dbp5 ATPase activity [40].

Conclusion

Recent research has greatly increased our understanding of how mRNA transport is integrated into the complex gene expression cascade [40]. There are still a number of significant problems throughout the mRNA assembly, transcription, and translation. The primary molecular role of many of the proteins involved in mRNA export is a crucial one of these unanswered topics.

The nuclear buildup of poly (A) RNA is caused by the disruption of gene product function, not because specific proteins' roles in mRNA export have been identified, despite the fact that several proteins have been implicated in this process. Many of these proteins might serve purposes other than merely serving as adaptors for mRNA export receptors during the synthesis of mRNA. The method by which the cell separates transcripts that are competent for export from those that are not another issue that has not yet been resolved. To eliminate flawed transcripts, the cell has several quality control processes in place [67]. These quality control techniques probably find marker proteins placed upon the transcript after processing rather than looking at the sequence of the mRNA transcript itself. As the transcripts leave the RNA assembly line, these identifiers would be scanned by the quality control equipment similar to shipping labels on freshly produced goods. Future research into these markers' identities will shed light on yet another level of posttranscriptional regulation of gene expression [2].

Future research will need to include structural investigations and potent in vitro reconstitution in order to get additional molecular insights. Such research could aid in figuring out how newly synthesized transcripts are effectively exported through the nuclear export pathway, carried to the cytoplasm, and supplied to the translation machinery [40].

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