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Review

Review

Nuclear mRNA export

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Abstract

In eukaryotic cells, gene expression begins with transcription in the nucleus, followed by the maturation of messenger RNAs (mRNAs). These mRNA molecules are then exported to the cytoplasm through the nuclear pore complex (NPC), a process that serves as a critical regulatory phase of gene expression. The export of mRNA is intricately linked to precursor mRNA (pre-mRNA) processing, ensuring that only properly processed mRNA reaches the cytoplasm. This coordination is essential, as recent studies have revealed that mRNA export factors not only assist in transport but also influence upstream processing steps, adding a layer of complexity to gene regulation. Furthermore, the export process competes with RNA processing and degradation pathways, maintaining a delicate balance vital for accurate gene expression. While these mechanisms are generally conserved across eukaryotes, significant differences exist between yeast and higher eukaryotic cells, particularly due to the more genome complexity of the latter. This review delves into the current research on mRNA export in higher eukaryotic cells, focusing on its role in the broader context of gene expression regulation and highlighting how it interacts with other gene expression processes to ensure precise and efficient gene functionality in complex organisms.

Key words mRNA export, mRNA processing, orchestrate regulation, gene expression

Introduction

Eukaryotic cells contain all kinds of organelles that serve as sites of different cellular activities to maintain a variety of functions. The largest among them is the cell nucleus, which stores genetic information in the form of chromosomal DNA. A series of biological events, such as DNA replication, gene transcription and RNA processing, occur in the nucleus. However, protein translation and synthesis take place exclusively in the cytoplasm. The nuclear envelope that surrounds the nucleus separates these different activities. Owing to this physical separation, messenger RNAs (mRNAs) harboring genetic information must be exported to the cytoplasm for protein translation. Thus, the process of mRNA export is a key step for accurate expression of genetic information.

To be efficiently exported, nascent pre-mRNA needs to undergo a series of co- and post-transcriptional processing steps, including capping at the 5′ end, splicing to remove introns, 3′ end formation and RNA modifications. Then, the mature mRNA must cross the nuclear envelope through the NPC. This involves docking onto the nuclear basket, passing through the central channel of the nuclear envelope and being released from the cytoplasmic fibrils. All of these steps are highly regulated and coordinate with each other [1]. Correctly processed mRNAs are targeted for export by the formation of messenger ribonucleoprotein (mRNP) particles, with mRNA export factors recruited to the nascent mRNA co-transcriptionally. The mRNP with defects is eventually eliminated by mRNA surveillance systems.

The subsequent sections of this review will focus primarily on summarizing current research regarding mRNA export in higher eukaryotic cells. We explore its role within the broader context of gene expression regulation and highlight its interactions with other gene expression processes, ensuring precise and efficient gene functionality in complex organisms.

mRNA Export Machinery

Upon maturation, mRNAs form mRNP and navigate through the NPC with the assistance of specific export receptors. Export

receptors are essential for guiding mRNP to the cytoplasm, where the mRNA can be translated into proteins [2]. This process involves two main receptors for the nuclear export of mRNA: NXF1-NXT1 (referred to as Mex67-Mtr2 in yeast) and CRM1, with selected groups of mRNAs preferentially transported by different receptors [1,3,4] (Figure 1).

While mRNA export mechanisms are conserved from yeast to humans, significant variations are noted due to the complex regulatory landscapes of higher eukaryotes. In *Saccharomyces cerevisiae*, the primary mRNA export receptor is the Mex67-Mtr2 complex, which is analogous to the NXF1-NXT1 complex in higher eukaryotes. Both utilize associated proteins such as Yra1 (equivalent to ALYREF) and Sub2 (similar to UAP56) to facilitate the formation of export-competent mRNPs [5,6]. However, in metazoans, transcribed RNA molecules undergo extensive and intricate processing, including widespread alternative splicing, necessitating multiple adaptor proteins for regulating and modifying the export complex. Additionally, sophisticated surveillance systems such as the exon junction complex (EJC) monitor mRNA processing and integrity before being exported through the nuclear pore complex (NPC) [7]. These advanced systems, which are embedded within a complex nuclear architecture and regulated by diverse signaling pathways, enable refined gene expression regulation in response to various stimuli, reflecting evolutionary enhancements in mRNA export to support increased cellular complexity and functional demands.

Exporting receptors

NXF1-NXT1 has emerged as the primary receptor for mRNA nuclear export and uniquely binds to RNA without the need for specific sequence recognition [4,5,8,9]. This receptor complex is crucial for the export of most cellular mRNAs, with disruptions leading to mRNA accumulation within the nucleus [10]. NXF1, a component of this receptor, typically adopts a closed conformation with minimal affinity for RNA. The interaction with NXT1 enables NXF1 to effectively interact with and export mRNAs [11] (Figure 1A). While NXF1 is pivotal for the export of the majority of mRNAs, not all transcripts utilize this pathway. Certain mRNAs are transported from the nucleus to the cytoplasm through the karyopherin CRM1, also known as Exportin 1 (XPO1). This essential protein is responsible for the nuclear export of a diverse array of molecules, including both RNAs and proteins. Unlike NXF1, CRM1 does not interact directly with RNA; instead, it relies on NES-bearing protein cofactors to mediate the export of a specific subset of mature mRNAs in a RanGTP-dependent manner. Notably, CRM1 also facilitates the nuclear export of small non-coding RNAs such as rRNA, snRNA, and some miRNAs, which are not typically exported by NXF1 [12–14] (Figure 1B and Table 1).

Given that NXF1-NXT1 has only a modest inherent affinity for RNA and that CRM1 lacks direct RNA binding, both receptors rely on adaptor proteins to facilitate their interaction with RNA targets. This necessity underscores the complexity and specificity of the mRNA export process, ensuring that transcripts navigate from the nucleus to the cytoplasm efficiently and accurately.

Export adaptors

The transcription-export (TREX) complex, which is crucial for mRNA export and is universally conserved, acts as an indispensable NXF1 adaptor [2,11,15]. The THO subcomplex, together with the RNA helicases UAP56 (Sub2 in yeast) and ALYREF (Yra1 in yeast), forms the TREX complex, which facilitates the initiation of mRNA export in human cells [10,16]. ALYREF is recruited to mRNA by UAP56 and connects with the cap-binding complex (CBC) at the 5′ end of the mRNA. When ALYREF and THOC5 interact with NXF1, they induce a conformational change that opens NXF1, exposing its RNA-binding domain and enabling RNA binding by overcoming NXF1's intramolecular inhibition of its RNA-binding activity [11,17–19]. Consequently, this increases the efficiency of transporting various cellular mRNAs through the NPC, utilizing NXF1's interaction with the NPC's FG repeats [20]. CHTOP, a new component of the TREX complex, activates the ATPase and RNA helicase activities of UAP56. Co-knockdown of *ALYREF* and *CHTOP* results in potent mRNA export block [21]. In addition to TREX, SR proteins, which are essential for NXF1-dependent mRNA export and pre-mRNA splicing regulation, influence export dynamics by challenging ALYREF for NXF1 association. SR proteins such as SRSF3 and SRSF7, by identifying specific mRNA motifs, directly recruit NXF1 to promote mRNA export [22,23]. Moreover, recent studies highlighted the roles of SRSF3 and SRSF7 in enhancing NXF1 mRNA recruitment, revealing a detailed network of interactions facilitating mRNA export [24,25]. Furthermore, CFI-68, a key component of the CFI complex, acts as a novel adaptor for NXF1, promoting the export of both reporter mRNAs and endogenous mRNAs. Depletion of CFI-68 results in the accumulation of mRNAs in the nucleus [26] (Figure 1A and Table 1).

CRM1, although not directly associated with mRNAs, requires the involvement of RNA export adaptor proteins that bind to RNA molecules. These adaptors, equipped with nuclear export signals (NESs), are recognized by CRM1, facilitating RNA export through the NPC in the presence of RanGTP [12,13]. Among these, HuR, NXF3, and eIF4E stand out for their roles in CRM1-mediated mRNA export, orchestrating the selective export of distinct mRNA subsets [27,28]. HuR targets mRNAs containing the AU-rich element (ARE) within their 3′ UTR, increasing mRNA stability and facilitating the export of ARE-containing transcripts in conjunction with CRM1 [29,30]. NXF3, a member of the nuclear RNA export factor family yet uniquely dependent on CRM1 for NPC traversal, highlights a tailored export route for certain transcripts, the details of which are still not fully understood [31]. eIF4E, which is traditionally associated with cap-dependent translation, is pivotal for the nuclear export of mRNAs harboring a 4E-sensitivity element (4ESE) in their 3′ UTR [32,33]. This export is mediated by the adaptor LRPPRC, which acts as a link between eIF4E and CRM1, ensuring the targeted export of these transcripts [32,34] (Figure 1B).

Nuclear pore complexes

In eukaryotic cells, the NPC serves as a crucial gateway for the export of RNAs, proteins, and ribonucleoprotein (RNP) particles through its extensive aqueous channels [35–37]. The mammalian NPC, characterized by its composition of approximately 30 distinct protein components, exhibits a remarkable degree of conservation across species from yeast to mammals. Each of these complexes has a mass of approximately 125 MDa and a diameter of 125 nm, highlighting their substantial size and complex architecture. NPCs, which are embedded within the double-layered nuclear envelope, play essential roles in regulating nucleocytoplasmic transport. The architecture of the NPC is dynamically and multimerically constructed, with 500–1000 nucleoporins (Nups) [38]. These are

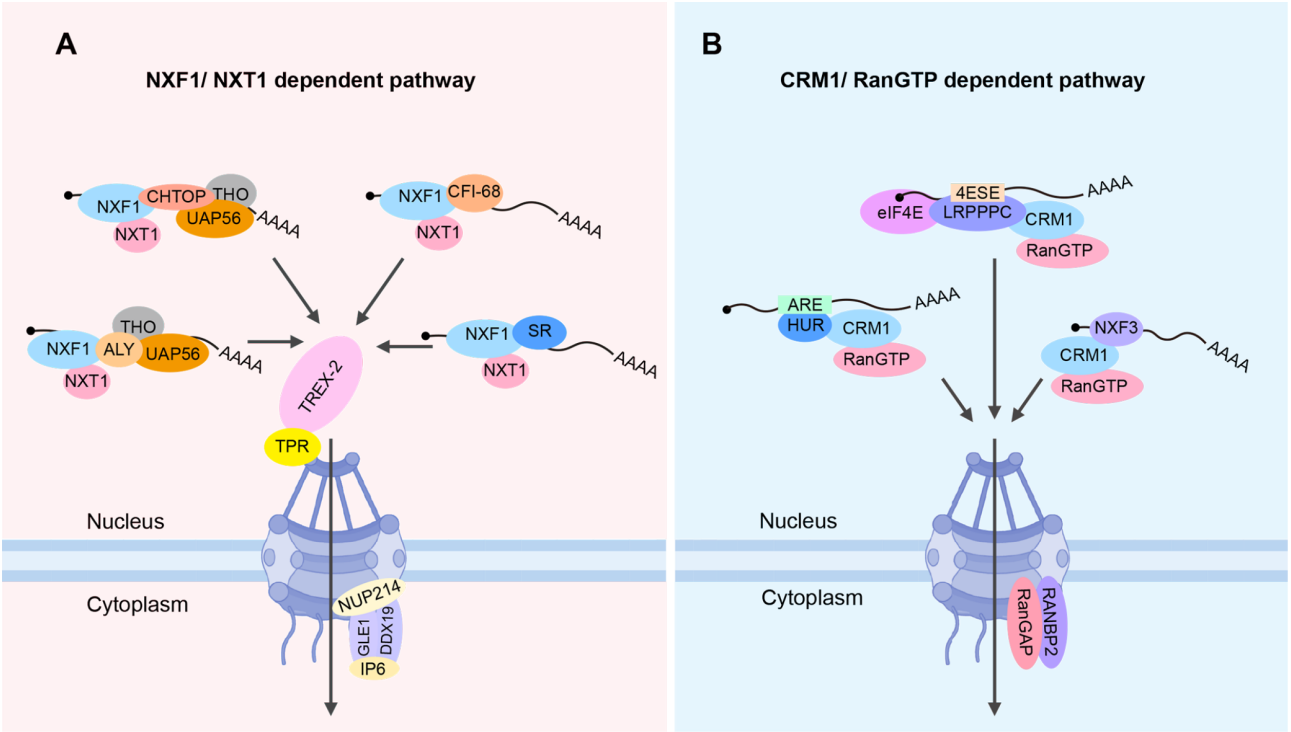

Figure 1. Schematic of mRNA export pathways mediated by NXF1 and CRM1 (A) NXF1, with a limited affinity for RNA on its own, binds to various adaptor proteins, including TREX, SR proteins, and CFI-68. The mRNP complex approaches the NPC via TPR and TREX-2 and is transported through the central channel. In cytoplasmic fibrils, proteins such as NUP214, DDX19, and GLE1 assist in the release of bulk mRNA into the cytoplasm. (B) CRM1, which lacks the ability to directly bind to RNA, depends on interactions with diverse adaptor proteins, including NXF3, HuR, and eIF4E, in the presence of RanGTP to traverse the NPC and reach the cytoplasmic fibrils. Upon such arrival, the complex undergoes dissociation facilitated by RANBP2 and RanGAP, wherein RanGTP is hydrolyzed to RanGDP.

Table 1. Key factors of mRNA export machinery

Export factors		Function
Metazoan	Yeast	
NXF1-NXT1	Mex67-Mtr2	mRNA export receptors facilitating various mRNA transports through NPCs
CRM1	Xpo1	mRNA and protein export receptor in the export of a subset of mRNAs via adaptors
THO complex	THO complex	TREX components facilitating the formation of export-competent mRNP
ALYREF	Yra1	Recruiting NXF1-NXT1 to mRNP
UAP56	Sub2	Recruiting ALYREF and involved in the assembly of export-competent mRNP
TREX-2	TREX-2	Guiding mRNP to the NPC's nuclear basket
EJC	EJC	Recruiting THO complex in metazoans
CHTOP	-	Activating the ATPase and RNA helicase activities of UAP56
TPR	Mlp1	Assisting the mRNP's export through the NPC with TREX-2
NUP214	Nup159	Nucleoporin present on the cytoplasmic face binding DDX19
DDX19	Dbp5	Docking at NPC via NUP214 and involved in the disassembly of the mRNP export complex at NPC cytoplasmic face
GLE1	Gle1	Enhancing DDX19 activity
IP6	IP6	Binding GLE1, facilitating the ATPase activity of DDX19
SR proteins	Hrp1/Nab4 family	Recruiting NXF1 to mRNP
CFI-68	Ysh1	Export adaptor facilitating the export of mRNAs with long 3′UTR

organized into six distinct subcomplexes: the inner and outer pore rings, the transmembrane ring, the nuclear basket, the cytoplasmic filaments, and the central channel. Each subcomplex contributes uniquely to the NPC's functions, facilitating the selective and efficient transport of molecules between the nucleus and the cytoplasm [35,39–41]. Nups can be further categorized into three functional groups: pore membrane Nups, which secure the NPC to the nuclear envelope; FG Nups, characterized by hydrophobic

sequences rich in phenylalanine (F) and glycine (G); and structural Nups, which provide robust folded protein domains [42–44]. The interactions between NPCs and cargo receptors, especially those with transport receptors or karyopherins, are crucial for the translocation of molecules through the channel. Evidence of such interactions has been provided by the crystal structures of FG peptides in complex with multiple transport receptors. Following these FG interactions between Nups and mRNPs, cargo is exported to the cytoplasm through the NPC channel [45].

Other export factors

After mRNA processing, an NXF1-mRNP complex forms in the nucleoplasm and is destined for the nuclear periphery to connect with the nuclear basket for transport. However, the direct interaction between NXF1 and the NPC is impossible without auxiliary factors. The TREX-2 complex serves as a conduit for mRNPs, guiding them from the sites of transcription and processing to the NPC's nuclear basket [46–48]. In humans, the TREX-2 complex is composed of GANP, ENY2, CETN2/CETN3, PCID2, and DSS1. GANP provides structural support and directly interacts with NXF1, facilitating the engagement of mRNPs with the NPC via the TPR protein [49].

On the cytoplasmic side, the release and subsequent translation of mRNA are supported by additional factors, including three key components: Nup214, GLE1, and the DEAD-box helicase DDX19 (also known as DBP5) [50–52]. The release process begins with the ATP-induced activation of DDX19 by GLE1, enabling the ATP/DDX19/GLE1 complex to attach to the mRNP. When stimulated by GLE1 and IP6 (inositol hexakisphosphate), DDX19 undergoes a conformational shift from the ATP state to the ADP state. This shift is speculated to drive an RNA-protein remodeling event that ejects NXF1 from the mRNP, releasing the mRNA into the cytoplasm and marking the completion of mRNA export. DDX19-ADP is then recycled via interaction with Nup214 [53–55] (Figure 1A and Table 1).

Regulation of mRNA Export

The orchestrated generation of mRNPs, which are ready for nuclear export, is controlled by a complex network of epigenetic mechanisms, such as chromatin remodeling and histone modification, which coordinate with transcription regulation to ensure that genes are properly positioned and accessible in the nucleus, facilitating the recruitment of the TREX complex to active transcription sites and linking transcription to mRNA export. Additionally, the interaction between mRNA and its export machinery is refined through pre-mRNA processing, RNA modifications such as m^6A, and post-translational changes such as ubiquitination and acetylation, emphasizing the system's complexity and crucial role in gene expression.

Chromatin structure and histone modification

Recent research has shed light on the complex ways in which chromatin structure and histone modifications orchestrate mRNA export. This regulatory mechanism, which operates independently of DNA sequence alterations, is often referred to as "epigenetic" regulation. It encompasses a multifaceted approach that includes modulating chromatin accessibility, recruiting transcription and mRNA processing machinery, and strategically positioning genes within the nucleus.

Although direct connections between chromatin structure and mRNA export are largely unknown, the tight coupling of gene expression steps suggests that chromatin structure, which influences the assembly and activity of the transcription complex, may affect mRNA maturation and export. The structural organization of chromatin, with heterochromatin anchored near the inner nuclear membrane while euchromatin extends toward the NPC, plays a significant role in determining its localization and transcriptional activity in higher eukaryotes. Proteins such as the TPR, which is integral to the nuclear basket, are essential for maintaining this configuration [56–58] (Figure 2A). Additionally, chromatin remodelers such as ISW1 and SWI/SNF in *Saccharomyces cerevisiae* play a pivotal role in chromatin structure and mRNA export. ISW1 selectively retains immature mRNPs at transcription sites, ensuring that only processed mRNPs are exported [59]. Moreover, SWI/SNF adjusts chromatin accessibility for transcription factor binding and RNA polymerase II (RNAP II) recruitment, which are crucial for activating genes with unique promoter characteristics vital for signal transduction, development, and cell identity [60,61] (Figure 2).

Histone modifications constitute a key aspect of epigenetic regulation that influences mRNA export through changes in chromatin structure or by organizing chromatin remodeling complexes and regulatory factors [62,63]. Inhibition of histone deacetylases (HDACs) leads to significant genome reorganization in mammals, moving promoters and active regions closer to nuclear pores, indicating the relationship between chromatin architecture and gene regulation [64]. Histone H2B ubiquitination facilitates the ubiquitylation of the Swd2 protein, which is necessary for the proper recruitment of the mRNA export receptor Mex67 and its Yra1/Nab2 adaptor complex to mature mRNPs [65] (Figure 2A). In yeast, Mog1 plays a crucial role in maintaining H2B ubiquitination and H3K4 methylation, which are essential for transcription and mRNA export, by recruiting ubiquitination factors and interacting with mRNA biogenesis components [66]. Similarly, Sgf73, the yeast ortholog of human Ataxin-7, acts as a molecular scaffold to integrate the regulation of H2B ubiquitin levels, anchoring a gene to the NPC and exporting mRNA [67]. Histone chaperones such as Spt6 and FACT also facilitate this process by facilitating the recruitment of mRNA export factors to chromatin [68–70].

Transcription

Transcription regulation is essential for mRNA processing and export. Sträßer and colleagues demonstrated that the TREX complex is specifically recruited to actively transcribed genes and travels the entire length of the gene with RNA polymerase II. This recruitment ensures a direct link between transcription and mRNA export, which is crucial for efficient protein synthesis across different species [15]. Intriguingly, the rate of transcription has been found to impact how mRNAs are packaged by the THO/TREX complex, thereby affecting the susceptibility of the mRNP complex to degradation by the nuclear exosome [71,72].

The TREX-2 complex provides another fascinating example of how transcription regulation is intricately linked with mRNA nuclear export. It physically and functionally interacts with the Spt-Ada-Gcn5 acetyltransferase (SAGA) transcription coactivator complex and the NPC, creating a seamless link between transcription, mRNA export, and the targeting of active genes to the NPC [46,47,73–75]. Within this framework, Sus1 emerges as a vital component shared by both SAGA and TREX-2 complexes and interacts with key proteins such as phosphorylated RNAP II, Yra1,

and Mex67 to coordinate gene transcription and mRNA export [76,77]. In addition, Sus1 is instrumental in maintaining nuclear integrity by promoting the nuclear rim association of Mex67 and Dbp5, which are crucial for preventing abnormal nuclear RNA accumulation [78].

In addition to the TREX and TREX-2 complexes, other factors facilitate the connection between transcription regulation and mRNA export, highlighting the complexity of the regulatory network. Among these proteins, Spt6, a transcription elongation factor, interacts with Ser2-phosphorylated RNAP II, which is crucial for precise mRNA processing and nuclear export. Additionally, depletion of IWS1, a human spt6-interacting protein, results in mRNA processing defects and nuclear retention of bulk polyA RNA *in vivo* [79]. WNK1, initially recognized as a critical regulator of ion homeostasis in the cytoplasm, has emerged as a significant player in the mammalian mRNA export pathway. It phosphorylates the termination factor PCF11 on its RNAPII C-terminal domain (CTD)-interacting domain (CID), weakening its interaction with RNAPII. This potentially facilitates the release of mRNPs from transcription loci, thereby improving mRNA export to the cytoplasm [80] (Figure 2B).

Pre-mRNA processing

The transport of fully processed mRNA from the nucleus to the cytoplasm is widely acknowledged [81], emphasizing the essential role that processing plays in regulating mRNA export. The maturation of an mRNA transcript involves three core processing events: 5′ capping, splicing, and 3′ end cleavage accompanied by polyadenylation. A large body of research has shown that RNA processing enhances the efficiency of mRNA export [5]. The assembly of mRNP complexes is accomplished by recruiting specific protein factors essential for guiding the mRNA translocation process, ensuring that only fully processed mRNAs are exported. Those mRNAs that fail to undergo correct processing are actively retained within the nucleus or are prone to degradation [5,82,83].

The initial step in the processing of newly transcribed mRNA is the addition of a 5′ m^7G cap, which occurs co-transcriptionally immediately after the synthesis of the first 25–30 nucleotides. This process is facilitated by capping enzymes recruited to the transcription start site, which are partly signaled by serine 5 phosphorylation of the RNAP II C-terminal domain (CTD) [84,85]. Following this modification, the heterodimeric nuclear cap-binding complex (CBC), consisting of Cbp20 and Cbp80 (CBP20/CBP80 or NCBP1/NCBP2 in metazoans), binds to the cap structure, protecting the transcript from degradation. CBP20 directly interacts with the m^7G cap, whereas CBP80 provides a platform for binding regulatory factors that influence various pathways, including transcription, splicing, export, and translation. Additionally, the CBC complex facilitates nuclear export by co-transcriptionally recruiting the Yra1/ALYREF subunit of the TREX complex to the 5′ end of the mRNA [17,86,87]. The alternative CBC complex, formed by NCBP3 and NCBP1, is involved in mRNA processing and polyA RNA export in higher eukaryotes, as demonstrated by Gebhardt and colleagues [88]. In yeast, CBC promotes co-transcriptional recruitment of Npl3 and Yra1 and enhances mRNA export [87] (Figure 2C). Additionally, arsenite resistance protein 2 (ARS2) acts as a crucial adapter, connecting CBC-capped RNA complexes with RNA maturation pathways, such as 3′ end processing, RNA transport, and nuclear exosomal degradation. This finding underscores the importance of capping in regulating mRNA export [89–91].

Pre-mRNAs harboring introns are subject to both co-transcriptional and post-transcriptional splicing, a process initiated by the association of the U1 small nuclear RNA complex with the 5′ splice site, followed sequentially by the engagement of the U2, U4, U5 and U6 snRNP complexes [92]. The exon-junction complex (EJC) is subsequently strategically assembled at exon-exon junction sites, facilitating the integration of TREX subunits and the involvement of its crucial component UAP56 in spliceosome assembly [93–95]. The THO/TREX complex preferentially associates with spliced mRNAs. Moreover, the speed and efficiency of mRNA export are enhanced 6- to 10-fold for spliced mRNAs relative to their cDNA counterparts [17,96]. The study by Hohmann and colleagues highlights how the export factors ALYREF and UAP56, which are recruited postspliciningly, are crucial for efficiently directing mRNPs to TREX complexes and facilitating mRNA export [97]. The importance of this interplay is further exemplified by the involvement of SR proteins, whose phosphorylation status is pivotal in conferring mRNP complexes with export competence [98,99]. SRSF3 and SRSF7 emerge as critical NXF1 adaptors that not only facilitate NXF1 recruitment but also control the cytoplasmic abundance of transcripts, thereby coupling pre-mRNA processing with mRNA export [25] (Figure 2C). This conclusive evidence strengthens the intricate and functional connection between splicing and mRNA export, reinforcing its role in maintaining fidelity, a fundamental aspect of gene expression in higher eukaryotes.

The 3′ end cleavage and polyadenylation represent the final step in pre-mRNA processing, with the regulatory carboxy-terminal domain (CTD) of RNAP II coordinated by a suite of approximately 20 core proteins. This assembly encompasses four primary protein complexes—cleavage and polyadenylation specificity factor (CPSF), cleavage stimulatory factor (CSTF), and cleavage factors I and II (CFI and CFII)—along with several individual proteins, such as symplekin, RBBP6, PABPN1, PAP, and the RNAP II regulatory carboxy-terminal domain (CTD) [100]. The assembly of these factors into nascent pre-mRNAs is guided primarily by the consensus polyadenylation signal sequence (PAS) AAUAAA and its variants, which are located upstream of the cleavage site, alongside G/U-rich downstream and U-rich upstream elements that aid in polyA site recognition [101]. Influenza A virus selectively inhibits the export of cellular mRNAs by targeting CPSF30 and PABPN2 [102]. In yeast, the link between 3′ end processing and mRNA export is well established, as mutations in CFII subunits (RNA14, RNA15, PCF11) and PAP have been shown to affect mRNA export [103]. Moreover, such coordination is further supported by the interaction between 3′ end processing factors and export factors, including NXF1, ALYREF, and THOC5. For example, CFI-68, a crucial component of the CFI complex, is directly involved in mRNA export through its interaction with the export adaptor NXF1 [26]. PCF11, a component of the CFII complex, interacts with the mRNA export adaptor Yra1 to increase its recruitment, underscoring the functional connection between 3′ end processing and mRNA export [104] (Figure 2C). Additionally, the length of polyA tails can significantly affect mRNA export, as alterations in polyA tail length can disrupt normal mRNA export, leading to the accumulation of mRNAs in the nucleus [105]. This effect is emphasized by the depletion of NAB2, a protein required for polyA length control, leading to hyperadenylation and nuclear retention of polyA RNAs [106]. The above studies collectively highlight the critical coordination between 3′ end processing and mRNA export, which is

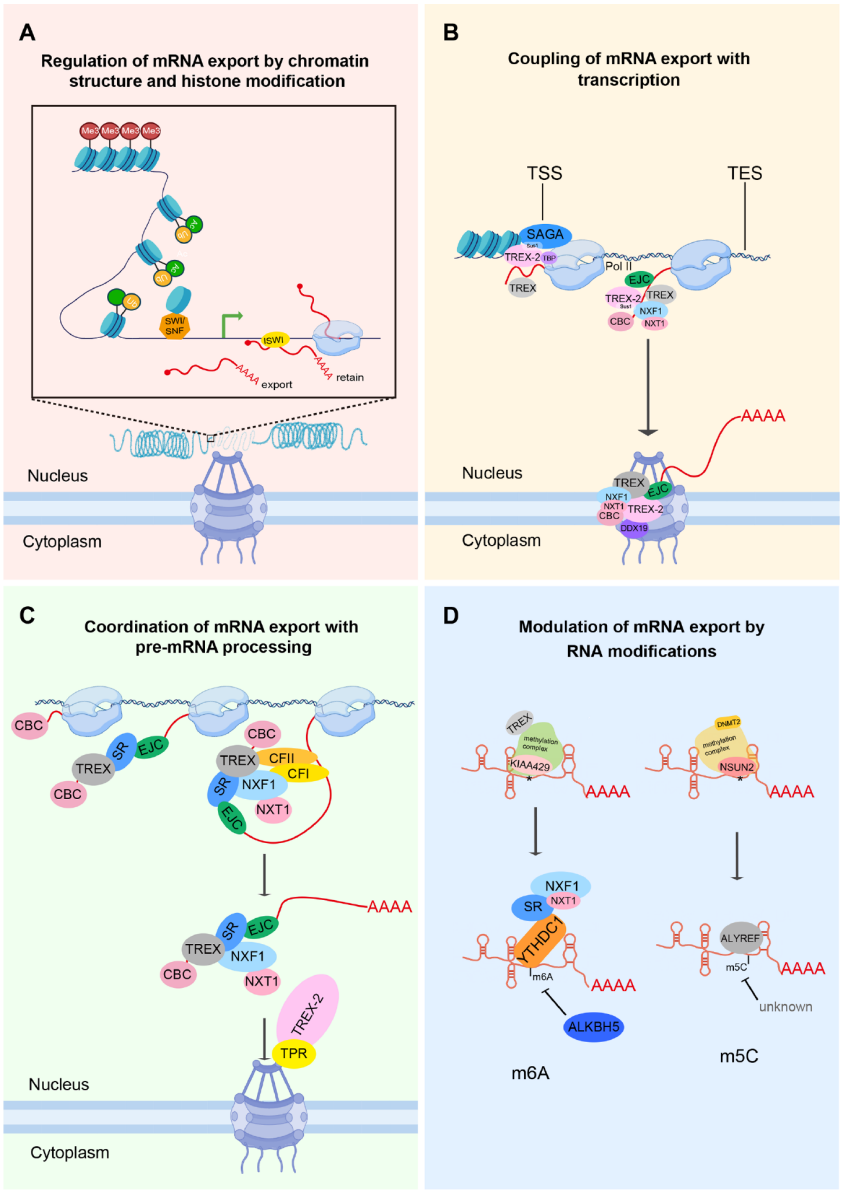

Figure 2. Regulation of mRNA export by upstream processes (A) Chromatin structure and histone modifications significantly regulate gene expression and consequently mRNA export. Euchromatin, which is typically characterized by histone acetylation and ubiquitination, extends toward the NPC, indicating regions of active transcription. Conversely, heterochromatin, which is often associated with the inner nuclear membrane, is usually transcriptionally inactive. In yeast, chromatin remodelers such as ISW1 and SWI/SNF are vital for transcription and mRNA export. SWI/SNF is globally and continuously required for chromatin accessibility and transcription initiation. ISW1, in particular, selectively retains immature mRNPs at transcription sites, ensuring that only fully processed mRNPs are exported. (B) Coupling of mRNA export with transcription. At the transcription start site (TSS), the transcription coactivator complex SAGA modulates initial RNA production with other transcription factor binding proteins. TREX-2 interacts with SAGA via factor Sus1, which is shared by both complexes, and further coordinates with the phosphorylated polymerase, together with co-transcriptional loading of other RBPs and complexes, including CBC, TREX, EJCs, and NXF1. The assembly of mRNPs is well maintained throughout the entire transcription process to the transcription end site (TES), and thus carrying great regulatory potential. mRNP components, once released from active transcription, can facilitate efficient transcript export by interacting with Nups and other export factors. For example, Sus1 of TREX-2 can bind Dbp5 on the cytoplasmic site of NPC, pushing the mRNP out to the cytoplasm. (C) Coordination of mRNA export with pre-mRNA processing. CBC initially binds to the 5′ cap of nascent pre-mRNA post-transcriptionally, facilitating the recruitment of the TREX complex, which includes components such as ALYREF and the RNA helicase UAP56, to the 5′ end of the mRNA. ALYREF and THOC5 interact with the NXF1/NXT1 dimer, which is crucial for the formation of the NXF1-mRNA complex. The TPR and TREX-2 complexes then assist in mRNA export through the NPC. Additionally, the interactions of CFI and CFII with NXF1 emphasize the importance of 3′ end processing in augmenting mRNA export, ensuring that only fully processed transcripts are released into the cytoplasm. (D) Modulation of mRNA export by RNA modifications. Left: the most common RNA modification, m^6A, is produced by a methylation complex composed of multiple methyltransferase-like proteins, such as METTL3 and METTL16, as well as the zinc finger protein ZCCHC4 and the transferase KIAA1429. This complex recruits the TREX complex, which further promotes the binding of m^6A readers such as YTHDC1, YTHDC2, and SR proteins and NXF1 to mRNA. In contrast, the m^6A eraser ALKBH5 removes such modifications to suppress mRNA export. Right: m^5C is designated by its corresponding complex, which includes DNMT2 and NOL1/NOP2/sun domain (NSUN) RNA methyltransferase family proteins from NSUN1 to NSUN7. The specific eraser(s) involved are still unknown, but m^5C is recognized by ALYREF to modulate subsequent export.

fundamental to the regulation of gene expression.

RNA modification

Within the intricate landscape of gene expression, mRNAs undergo extensive processing and a variety of modifications, including but not limited to m^6A, m^5C, m^6Am, and pseudouridylation (Ψ). These RNA modifications play a fundamental role in the regulation of RNA biogenesis and functionality, influencing aspects such as mRNA splicing, stability, localization, export, and translational efficiency [107]. Among these, m^6A modification stands out as a crucial signal for export, enabling the efficient translocation of mRNA from the nucleus to the cytoplasm. The associations between m^6A regulators, KIAA1429, WTAP, YTHDC1 and ALKBH5, and the TREX complex underscore the importance of this modification in mRNA export dynamics [108]. YTHDC1, which serves as a m^6A reader, is instrumental in the nuclear export of methylated mRNAs. It interacts with splicing factors and the nuclear export adaptor SRSF3 and facilitates RNA binding to both SRSF3 and NXF1 [109]. Recent findings demonstrated that the m^6A methylation complex recruits the TREX complex to m^6A-modified mRNAs, whereas TREX stimulates the recruitment of YTHDC1 to mRNPs, underscoring the key role of TREX in the export of m^6A-modified mRNAs [110]. Additionally, the demethylation activity of ALKBH5 has been identified as crucial for mRNA export. Depletion of ALKBH5 leads to abnormally increased cytoplasmic RNA levels due to accelerated nuclear RNA export [111]. Similarly, the inhibition of m^6A RNA methylation, as demonstrated by *Mettl3* knockdown, is associated with RNA nuclear retention, highlighting the essential role of m^6A in mRNA export [112] (Figure 2D).

Moreover, the m^5C modification serves as an additional instance of how RNA modifications can regulate export. m^5C is primarily catalyzed by NSUN2 and recognized by the mRNA export adaptor ALYREF. NSUN2 modulates mRNA export by regulating ALYREF shuttling between the nucleus and cytoplasm and RNA-binding affinity. More importantly, m^5C and its associated proteins participate in the dynamic regulation of selective mRNA export in mammalian cells [113] (Figure 2D). Furthermore, modifications such as Ψ, adenosine to inosine (A to I) editing, and 2'-O-methylation (Nm), which are also implicated in splicing, indirectly contribute to the regulation of mRNA export, establishing a connection between RNA modification and mRNA export [114–117]. These insights into RNA modifications not only highlight their critical role in mRNA export but also contribute to our understanding of the sophisticated regulatory mechanisms governing gene expression.

Far more regulatory mechanisms

In addition to the regulatory factors mentioned above, mRNA export from the nucleus is governed by a complex network of additional mechanisms, including ubiquitination and acetylation. These post-translational modifications play crucial roles in fine-tuning the interaction between mRNA and its export machinery, ensuring precise control over gene expression. Ubiquitination of RNAP II, especially the Rpb1 subunit and associated factors, profoundly impacts its interaction with both transcriptional and mRNA processing factors [118,119]. A notable example is the ubiquitination of the Ser5-phosphorylated CTD by Asr1, which alters the association of RNAP II with the Rpb4/7 heterodimer, affecting transcription initiation, polyadenylation, and mRNA export, especially under stress conditions [120–122]. The regulatory complexity is further enhanced by the involvement of the THO complex, which is recruited to actively transcribe RNAP II and is mediated by the Prp19 complex, a process integral to both splicing and transcription elongation. The ubiquitin ligase function of Prp19 potentially influences THO complex operation [123], and polyubiquitination of the THO component THOC5 is crucial for recruiting the mRNA export receptor NXF1, safeguarding THOC5 from premature degradation and facilitating efficient mRNA export [65,124,125]. Furthermore, the ubiquitination status of NXF1, which is regulated by Ubp15, is critical for recruiting the THO complex component THOC5 and facilitating mRNA nuclear export [126].

In addition to ubiquitination, acetylation has also been shown to regulate mRNA export. Gomar-Alba and colleagues revealed that acetylation of the NPC component Nup60 by Esa1, a lysine acetyltransferase (KATs) subunit of the yeast NuA4 complex, plays a crucial role in promoting mRNA export. Acetylation of Nup60 recruits the mRNA export factor Sac3, the scaffolding subunit of the TREX-2 complex, to the nuclear basket and enhances mRNA export [127].

The process of mRNA export from the nucleus is an intricately complex and sophisticated step in gene expression, suggesting that the regulatory mechanisms governing this process extend well beyond our current understanding. The interplay of various factors underscores the complexity of this critical cellular function. As such, the full breadth of regulatory pathways and their implications for cellular physiology and gene expression regulation remain rich fields for future exploration and discovery.

Export Factors as Regulators of Upstream Steps

A wide range of studies have revealed a bidirectional relationship, wherein the intricate stages preceding mRNA export, specifically transcription and pre-mRNA processing, not only influence the export mechanism but are also profoundly shaped by it.

Transcription

The TREX complex is indispensable for regulating the interdependence between transcription and mRNA export, illustrating its essential role in interactions where transcription dynamics not only influence mRNA export but are also affected by it. The critical function of the TREX complex in increasing RNAP II efficiency, thereby mitigating transcriptional delays at gene termini, is well documented [128]. The THO subcomplex of the TREX complex has been identified as a key player in preventing the formation of RNA:DNA hybrids, which can impede transcription elongation. This role is thought to facilitate the packaging of newly synthesized mRNA by safeguarding it from hybrid formation [129,130]. Additionally, the ubiquitous presence of THO along the entirety of actively transcribed RNA molecules underscores its significant contribution to transcriptional elongation, with ALYREF enhancing the efficacy of selected transcription factors, broadening its regulatory scope beyond mere transcriptional facilitation [131,132]. Viphakone and colleagues reported that the mRNA export receptor NXF1 and two TREX components, ALYREF and CHTOP, are recruited to mRNAs co-transcriptionally, influencing the human transcriptome [95]. Furthermore, the TREX-2 complex adds another layer to the intricate relationship between transcription and mRNA export. In *Drosophila*, the two components of TREX-2 ENY2 and Xmas-2, in collaboration with SAGA, play a crucial role in tethering a subset of

transcription sites to the NPC to achieve efficient transcription and mRNA export [73,76,133]. The engagement of Sus1 within TREX-2 in both the initiation and progression of transcription suggests its strategic recruitment to gene regions [48,134].

The regulatory capacity of NPCs, which oscillates between enhancing and inhibiting gene expression, introduces a new dimension to the complexity of genomic regulation. In contrast to their initial characterization as primarily gene silencers, recent discoveries have redefined NPCs as facilitators of gene activation for specific sequences, with certain nucleoporins localized at the promoters of actively transcribed genes [135]. The deliberate repositioning of genes to NPCs upon activation highlights the indispensable role of NPCs in achieving precise gene expression and preserving transcriptional fidelity [136]. Recent research further substantiates that NPCs selectively influence the activity of distinct gene groups, meticulously outlining their critical function in segregating transcriptionally active domains from repressive domains [136,137].

Processing

Multiple lines of evidence indicate that nuclear export can regulate alternative polyadenylation (APA). ALYREF is recruited via interaction with the 3′ end processing factor PCF11 and can thus regulate APA. In addition, the TREX component THOC5 controls polyadenylation site choice by recruiting the mammalian cleavage factor CFI-68 [138]. Furthermore, THOC5 controls 3′ end-processing of immediate early genes (IEG) via interaction with the polyadenylation-specific factor CPSF100 [139]. Notably, SR proteins, which are mRNA export adaptors, also couple alternative polyadenylation to NXF1-mediated mRNA export and impact the nuclear export of APA isoforms [25]. A recent study reported that mRNA export factors generally influence APA. The TREX components THOC2, UAP56, ALYREF, and NXF1 promote the usage of distal PASs, resulting in increased long 3′ UTR isoform expression. NXF1 interacts with RNAP II and promotes RNAP II elongation, leading to preferential usage of distal PASs [140]. Additionally, mRNA export factors can also reversely regulate replication-dependent histone mRNAs, which are non-polyadenylated mRNAs. The TREX component ALYREF not only promotes histone mRNA export by enhancing NXF1 recruitment but also stimulates proper histone mRNA 3′ end formation by facilitating efficient U7-snRNP recruitment [105]. Taken together, these findings indicate that the nuclear export of mRNA is coupled with its processing steps and reciprocally regulates upstream events for mRNAs.

Competition between mRNA Export and RNA Processing

The complex interplay among mRNA processing, export, and degradation is crucial for gene expression. A delicate balance ensures that mRNAs are properly processed and exported for translation, whereas those that are incorrectly processed are earmarked for degradation. This equilibrium involves competitive interactions among various nuclear factors, such as the competition between U2 snRNPs and nuclear export factors for the SF3B complex, which is considered a key component of U2 snRNPs [141]. Effective gene expression relies on this carefully coordinated competition, emphasizing the complexity of managing the mRNA lifecycle within the cell.

A rich body of literature has demonstrated the necessity of maintaining a balance between mRNA processing and nuclear export for accurate gene expression. When few splicing factors and excessive export factors exist in the cell, even unspliced pre-mRNAs are leaked into the cytoplasm [142,143]. In contrast, many fully processed mRNAs are degraded when nuclear export factors are downregulated [144–146]. Given the inefficiency and wastefulness of producing many mature mRNAs that are ultimately degraded, maintaining the balance between pre-mRNA processing and mRNA export is clearly highly important.

The U2 small nuclear ribonucleoprotein (snRNP), which consists of U2 snRNA, SF3A and the SF3B complex, is a core component of the spliceosome [147,148]. SF3B is engaged in recognizing the branch point sequence and promoting spliceosome assembly and activation [149,150]. In addition to splicing, U2 snRNPs physically interact with CPSF and contribute to the coupling of splicing and 3′ end formation on polyadenylated mRNAs [151]. In addition, SF3B155, the largest SF3B subunit, together with Prp43, directly recognizes and binds with a seven-nt element present in the coding region to facilitate the 3′ processing of nonpolyadenylated histone mRNAs [152]. Although these studies have shown that the main function of SF3B is executed in the context of U2 snRNPs, a recent work revealed an important role of SF3B in promoting mRNA export in a U2 snRNP-independent way.

Wang and colleagues reported that SF3B binds to mature mRNAs to promote export by recruiting the key mRNA export adaptor THO via direct interaction. Disruption of U2 snRNPs enhances the interaction between SF3B and THO and their recruitment to mature mRNAs. Therefore, the role of SF3B in mRNA export is not dependent on but rather competes with that of U2 snRNP. The competition between U2 snRNPs and mature mRNPs for SF3B impacts the balance between mRNA processing and export [141] (Figure 3A). This SF3B-mediated balance is crucial for ensuring that the majority of fully processed mRNAs are transported to the cytoplasm under normal conditions. When SF3B is released from mature mRNAs, it can enter the next cycle for pre-mRNA processing as a component of the U2 snRNP.

Competition between mRNA Export and Nuclear RNA Degradation

For efficient export, nascent mRNAs undergo a series of processing events, including the addition of a 5′ cap, removal of introns and 3′ cleavage and polyadenylation. The mature mRNA is then exported from the nucleus to the cytoplasm for protein translation. The whole process is subject to surveillance by the nuclear RNA degradation machinery to ensure that RNAs with defects in processing or export are detected and degraded rapidly. RNAs with the potential to be exported enter nuclear speckles to gain export competence, whereas those for degradation are removed in the nucleoplasm [153]. The balance between RNA export and degradation has emerged as a novel regulatory layer of gene expression. Although nuclear export or degradation pathways have been studied separately in depth, the interplay between these two pathways remains to be fully investigated.

A central component of nuclear surveillance is the essential RNA exosome complex, which is involved in both RNA processing and degradation of the majority of cellular transcripts [154–156]. For the exosome to function effectively, it requires association with many cofactors. The RNA helicase MTR4 plays a central role by interacting with multiple proteins to form different adaptor complexes. These include the mammalian-specific Nuclear EXo-

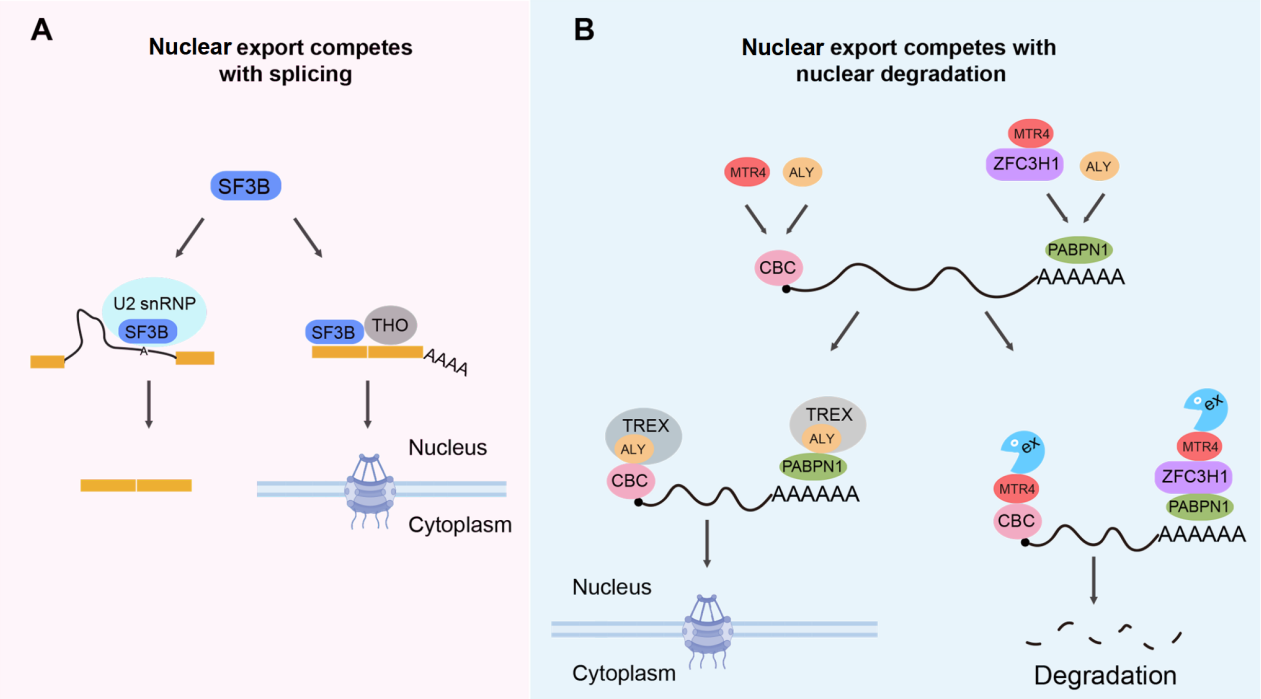

Figure 3. Competition model of mRNA export with RNA processing and degradation (A) Competition between U2 snRNPs and mature mRNPs for SF3B helps maintain a balance between pre-mRNA processing and mRNA export. (B) Competition between the nuclear export and degradation of mRNAs. RNA export factors, such as ALYREF, which bind to key factors at RNA ends, compete with degradation factors such as MTR4 and ZFC3H1. If ALYREF is swiftly recruited, the mRNA is set for export; otherwise, MTR4 or ZFC3H1 takes over, leading to decay via exosome recruitment.

some Targeting (NEXT) complex, the PolyA eXosome Targeting (PAXT) connection, the TRAMP complex, and the MTR4-NRDE2 complex [157–160]. NEXT functions primarily in the degradation of short ncRNAs, such as promoter upstream transcripts (PROMPTs), enhancer RNAs (eRNAs) and 3′ end extended snRNAs and snoRNAs [158,161]. On the other hand, PAXT is involved in the decay of longer polyadenylated transcripts, such as snoRNA host gene transcripts [157,159].

Accumulating evidence has shown that the competition between exosome cofactors and RNA export factors functions in the nuclear sorting of RNAs into decay or export pathways. For most polyadenylated RNAs, such as mRNAs and lncRNAs, MTR4 competes with the mRNA export adaptor ALYREF for association with CBC-bound RNAs at the 5′ end [146]. If an mRNA molecule can rapidly and efficiently recruit ALYREF, it has a good chance of being exported. However, if ALYREF cannot be recruited in time, MTR4 gains access to CBC and consequently recruits the exosome for degradation. Similar competition between the export and degradation machinery for CBC also occurs with other types of RNAs, such as snRNAs. The snRNA export adaptors PHAX and ZC3H18 compete for binding to CBC, resulting in opposite effects on the fate of the snRNA [90]. Additionally, at the 3′ end of mRNA, ALYREF also functionally counteracts the PAXT component ZFC3H1. In the absence of ZFC3H1, exosome targets are exported to the cytoplasm in an ALYREF-dependent manner [162] (Figure 3B). Consistent with this concept, recent research has shown that the depletion of MTR4 and ZFC3H1 causes their target to leak into the cytoplasm and compete with functional mRNAs for translation machinery [159]. The competition between export and degradation factors ensures the preferential binding of export or exosome factors to RNAs, thus determining RNA fate for export and degradation. These competitions mainly occur in the nucleoplasm before mRNAs enter nuclear speckles, where export-competent messenger RNAs are assembled [153,163].

These competitions not only function in distinguishing aberrant RNAs from normal ones but also provide cells with a new level of regulation of gene expression, regulating the balance of nuclear RNA pools for export and degradation. This regulation might be critical in particular tissue and growth stages when the RNA pool needs to be strictly controlled. Despite many new insights, the understanding of the mechanism underlying the interaction between the nuclear export pathway and the degradation pathway is still in its infancy.

mRNA Export-Related Biological Processes

Given the fundamental role of mRNA export in gene expression, its dysregulation is linked to various physiological and pathological processes. Mutations that inhibit the proper export of transcripts can disrupt normal cellular processes. Abnormalities in mRNA export mechanisms can arise from mutations in genes encoding export factors or mRNA-binding proteins, leading to compromised cellular function and ultimately disease. Furthermore, viruses can hijack the host's mRNA export machinery, either by turning down RNA export in general or by repurposing such machinery for the export of viral genes, facilitating viral replication and pathogenesis.

Physiological processes

Cell proliferation and differentiation are under fine-tuned regulation. Several studies have shown the important roles of the mRNA export machinery in this process. Emerging research underscores

the importance of both the TREX complex and Nups in this regulatory process. Components of the TREX complex, such as ALYREF, are critical for the nuclear export of specific transcripts essential for DNA repair and cellular differentiation processes. ALYREF facilitates the export of RAD51 transcripts, which are essential for ensuring DNA repair via homologous recombination and are regulated by IPMK-catalyzed PIP3 synthesis [164,165]. Furthermore, THOC5, a member of the THO complex, which is a subcomplex of TREX, plays a pivotal role in regulating mRNA export in response to growth factors and cytokines. Although it affects less than 1% of total mRNA export under steady-state conditions, THOC5 depletion significantly impacts the expression of more than 90% of growth factor/cytokine-induced genes, influencing cell growth and differentiation [139,166]. Depletion of THOC1 not only disrupts gene expression essential for proper testicular development in mice but also leads to embryonic lethality and pathological changes in small intestinal stem cells [167–169]. Additionally, the significance of THOC extends to nervous system development, regulating mRNA export in dopamine (DA) neurons. THOC mutations cause presynaptic transcript retention in the nucleus of *C. elegans* DA neurons, reducing mRNA cytoplasmic levels and impairing protein synthesis, which is essential for neuronal health. THOC5 deletion in mouse DA neurons precipitates synapse loss, DA neurodegeneration, and subsequent animal death, and this mechanism is conserved from worms to mice [170] (Figure 4).

In parallel, which is crucial for mRNA export, Nups directly impact cell cycle progression and differentiation. The expression of certain Nups, such as Nup153, Nup133, and Nup358/RanBP2, is suggested to be cell cycle dependent [171–174]. Nup133 deficiency in mouse ESCs leads to impaired neural lineage differentiation and the retention of pluripotency characteristics, highlighting its necessity in neural development [175]. Additionally, the role of Nup358/RanBP2 in muscle cell differentiation emphasizes the importance of Nups in specific lineage commitments, with its depletion inhibiting myotube formation [176,177]. Moreover, alterations in NPC structure and Nup expression, such as changes in Nup214, Nup358, and Nup153, have been shown to facilitate differentiation into cardiac lineages of stem cell-derived cardiomyocytes [178–180]. The interaction between Nup153 and polycomb repressor complex 1 (PRC1) at the transcriptional start sites of developmental genes highlights the multifaceted role of Nups in regulating gene expression during differentiation [181] (Figure 4).

Pathology processes

The process of mRNA export from the nucleus to the cytoplasm is a critical step in gene expression and has been increasingly linked to various pathological conditions, including cancer development, neurodegenerative diseases, and viral infections. This connection underscores the importance of understanding the mechanisms underlying mRNA nuclear export and its dysregulation in disease.

Alterations in mRNA export pathways have been shown to contribute to genome instability and the development of various cancer types [182] (Figure 4). Since 1994, research has demonstrated the carcinogenic involvement of components of the NPC, such as Nup214 and Nup88 [183,184]. Elevated levels of these components have been observed in several cancers, with oncogenic chimeric nucleoporins produced from chromosomal translocations in genes such as TPR, Nup98, and Nup214. These alterations upregulate proto-oncogene expression, particularly in leukemia [185]. Dysregulation of nucleoporins such as Rae1 in breast cancer indicates their role in tumorigenesis [186]. Furthermore, the p53 signaling pathway, which is essential for cancer suppression, is influenced by Nup98-mediated protection of p21 mRNA from degradation [187,188]. Alterations in the TREX complex are associated with increased tumor size and metastasis in breast cancer, whereas elevated ALYREF protein levels in oral squamous cell carcinoma suggest the involvement in oncogene transcript export [189–192]. Additionally, changes in components such as GANP of the TREX-2 complex and mutations affecting the eIF4E mRNA export function highlight their contributions to cancer development [27,190]. These findings illustrate the complex and crucial roles of dysregulation of mRNA export in tumorigenesis.

In neurodegenerative diseases such as Huntington's disease, Alzheimer's disease, frontotemporal dementia and amyotrophic lateral sclerosis (ALS), abnormalities in mRNA export mechanisms have been recognized as contributing factors [193] (Figure 4). The TREX complex is linked to neuronal development and differentiation, with mutations in its components associated with neurological disorders and intellectual disabilities [194]. In ALS, which is characterized by the loss of motor neurons, dysfunctions in RNA metabolism marked by the presence of RNA-binding protein aggregates and mutations in mRNA export-related proteins underscore the importance of RNA processing in the disease [195,196]. The GGGGCC repeat expansion in the C9orf72 gene, a common cause of ALS and frontotemporal dementia, illustrates how RNA processing disruptions can lead to neurodegeneration, highlighting a novel mechanism involving compromised mRNA export [197–200].

During viral infections, the nuclear export of mRNA is crucial for cellular responses, including the production of antiviral proteins. However, viruses have also evolved strategies to manipulate the host's mRNA export machinery to promote viral transcript export and replication while inhibiting the host's antiviral response [201–203] (Figure 4). Examples include the matrix (M) protein of the vesicular stomatitis virus, which disrupts the Nup98-Rae1 interaction, and the HSV-1 protein ICP27, which hijacks the cellular RNA export adaptor ALYREF [204–208]. These viral strategies demonstrate sophisticated manipulation of host gene expression, offering insights into the regulation of mRNA export and potential therapeutic targets for antiviral strategies.

Therapeutic Potential of Targeting mRNA Export Mechanisms

Recent studies have made significant progress in the development of therapies that target mRNA export, which is crucial for cancer treatment. ALYREF, an mRNA m^5C-binding protein, is overexpressed in various cancers and is associated with poor prognosis. It promotes tumor progression in stomach adenocarcinoma, and reducing ALYREF expression suppresses gastric cancer cell growth, indicating that ALYREF is a promising therapeutic target [209]. Nup155, a component of the nuclear pore complex, influences p53-dependent repression and cancer signaling in hepatocellular carcinoma by regulating p21 mRNA translation [210]. Selective inhibitors of nuclear export (SINE), such as KPT-335 and KPT-185, inhibit the nuclear exporter CRM1 to reduce respiratory syncytial virus replication and increase the efficacy of antineoplastic agents in hematological cancers [211,212]. Additionally, THOC3, which is highly expressed in lung squamous cell carcinoma (LUSC), enhances cell growth, migration, and glycolysis by regulating the

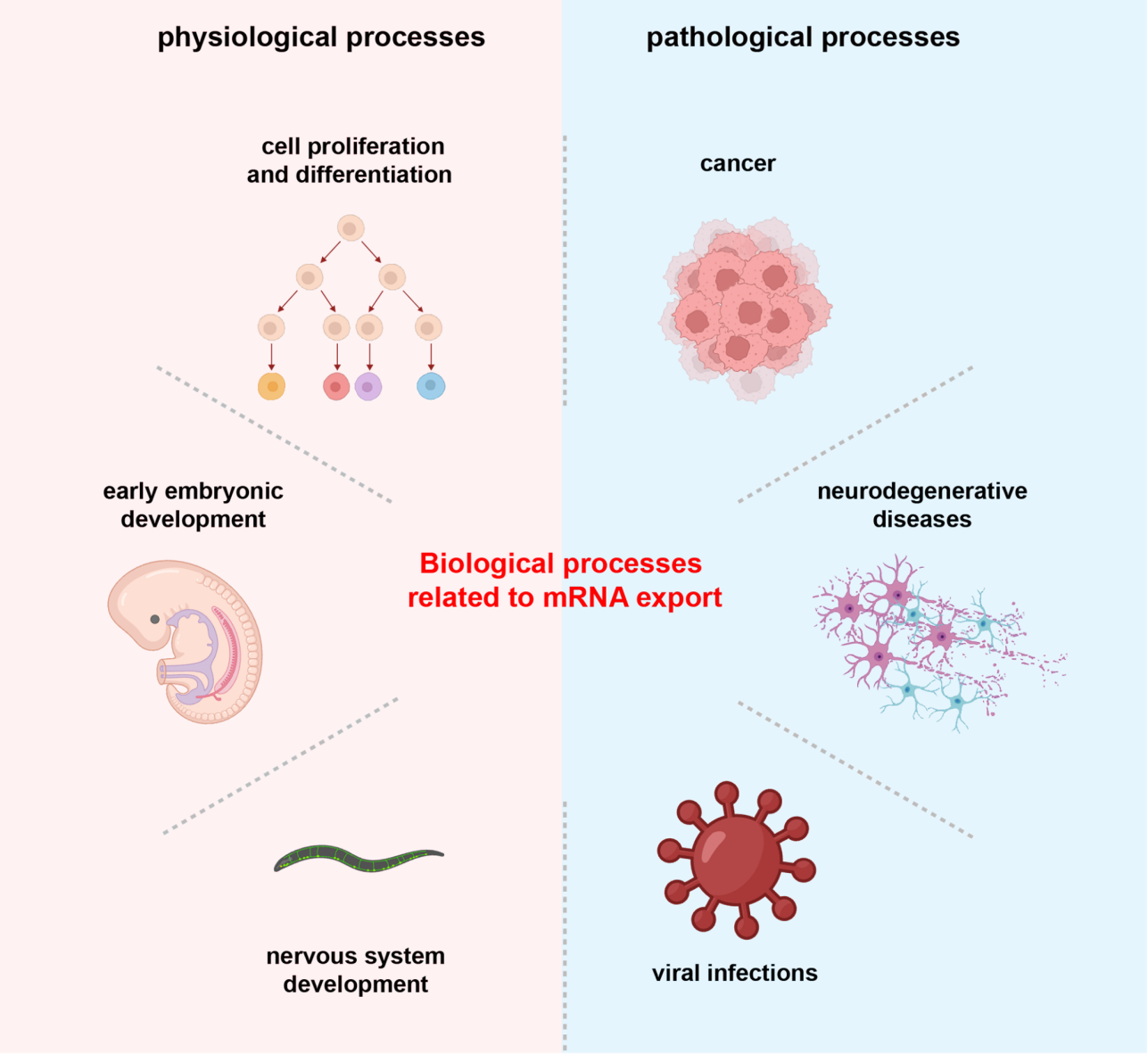

Figure 4. Biological processes related to mRNA export mRNA export factors are crucial for various physiological functions, including cell proliferation, differentiation, early embryonic development, and nervous system development. Mutations or alterations in the expression of these factors can contribute to a range of diseases, such as cancer and neurodegenerative disorders. Additionally, these export factors are commonly exploited by viruses during infection, potentially leading to disease progression.

transcription and export of PFKFB4 mRNA, making it a potential therapeutic target [213]. SF3B4, which is crucial for pre-mRNA splicing and mRNA export, is significantly elevated in clear cell renal cell carcinoma (ccRCC). It promotes cell migration and invasion by facilitating KLF16 mRNA export and activating Twist1 transcription, which triggers epithelial-to-mesenchymal transition (EMT) and ccRCC progression. Thus, targeting the SF3B4-KLF16-Twist1 pathway represents a novel therapeutic strategy [214]. These findings underscore the therapeutic potential of targeting mRNA export mechanisms in various diseases, providing new avenues for treatment development.

Perspective

Recent advancements in mRNA export research have significantly improved our understanding of the molecular mechanisms and regulatory frameworks that govern the nuclear export of genetic information. Despite these insights, several critical questions remain. First, the role and timing of NXF1 in RNA binding are still unclear. Originally thought to bind to RNA after ALYREF and THO within the nuclear matrix and facilitate transport to the NPC, NXF1 might act as a nucleoporin-like protein that directly binds RNAs at the NPC, as recent studies suggest [215,216]. Other studies have indicated that NXF1 binds to RNAs earlier than the TREX complex during the initial stages of RNA synthesis [140,217]. An interesting question thus arises as what is the the precise role of NXF1 in these processes and how it impacts mRNA export and gene expression. Second, while mature mRNAs are typically exported to the cytoplasm for translation, some are targeted for degradation within

the nucleus by the exosome complex, specifically through the PAXT connection [218,219]. What criteria distinguish mRNAs destined for degradation from those slated for export and translation? Additionally, nuclear speckles (NSs) are recognized as crucial sites for the assembly of export-competent mRNPs, especially for intronless mRNAs [163]. How do NSs interact with other nuclear bodies, and how does this interaction influence mRNA export and gene expression? Addressing these questions in future studies will enhance our understanding of the complexities of mRNA export and its regulatory mechanisms.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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