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Review

Understanding nuclear mRNA export: Survival under stress

Johanna Franziska Seidler[1] and Katja Sträßer[1,2,*]
[1]Institute of Biochemistry, FB08, Justus Liebig University, 35392 Giessen, Germany
[2]Cardio-Pulmonary Institute (CPI), EXC 2026, 35392 Giessen, Germany
*Correspondence: katja.straesser@chemie.bio.uni-giessen.de
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SUMMARY

Nuclear messenger RNA (mRNA) export is vital for cell survival under both physiological and stress conditions. To cope with stress, cells block bulk mRNA export while selectively exporting stress-specific mRNAs. Under physiological conditions, nuclear adaptor proteins recruit the mRNA exporter to the mRNA for export. By contrast, during stress conditions, the mRNA exporter is likely directly recruited to stress-specific mRNAs at their transcription sites to facilitate selective mRNA export. In this review, we summarize our current understanding of nuclear mRNA export. Importantly, we explore insights into the mechanisms that block bulk mRNA export and facilitate transcript-specific mRNA export under stress, highlighting the gaps that still need to be filled.

INTRODUCTION

When stress strikes, the human body springs into action: the heart races, muscles tense, and hormones surge. Single cells respond in a similar manner, tackling environmental, developmental, or disease-induced stresses by changes in many different processes, one of them being RNA metabolism. Messenger RNA (mRNA) plays a key role as it links genes to their encoded proteins and thus the nucleus and cytoplasm of eukaryotic cells. Consequently, the regulation of nuclear mRNA export is an effective way to change the gene expression profile, especially in response to stress. In a nutshell, nuclear mRNA export under physiological conditions consists of the packaging of the mRNA by RNA-binding proteins (RBPs), called mRNA ribonucleoprotein particle (mRNP) components, to form an mRNP. Several of these mRNP components recruit the mRNA exporter to the mRNP, which transports the mRNP out of the nucleus. Despite the importance of nuclear mRNA export for gene expression, its underlying processes remain unclear. In this review, we will convey our current model of nuclear mRNA export and delve into the changes during stress, both the nuclear retention of bulk mRNA and the selective nuclear export of stress-induced transcripts.

NUCLEAR mRNA EXPORT UNDER PHYSIOLOGICAL CONDITIONS

Nuclear mRNP biogenesis and nuclear mRNP components

Nuclear mRNP biogenesis is a highly interconnected process involving multiple steps. The mRNA is first synthesized by RNA polymerase II (RNAPII), followed by capping at the 5′ end, splicing, and polyadenylation at the 3′ end. Simultaneously, nuclear RBPs package the mRNA into an mRNP in a process known as mRNP assembly.[1–3] These mRNP components function in many processes, such as transcription elongation, mRNA processing, and mRNA stability. Moreover, some mRNP components, known as adaptors, recruit the mRNA exporter to the mRNP, facilitating nuclear mRNA export. The key mRNP components and their functions will be introduced, focusing on mRNP assembly in *Saccharomyces cerevisiae* (*S. cerevisiae*).[1–3] While the major nuclear mRNP components have been identified and are largely conserved, their specific functions often remain unclear.

The 5′-cap structure is bound by the cap-binding complex (CBC). CBC consists of a large and a small subunit, Cbp80 and Cbp20 in *S. cerevisiae* and NCBP1 and NCBP2 in humans (Table 1). CBC protects the mRNA from degradation and enhances transcription elongation, splicing, and nuclear mRNA export.[4]

TREX is a complex coupling transcription to nuclear mRNA export.[5] In *S. cerevisiae*, it consists of the THO subcomplex (Tho2, Hpr1, Mft1, Thp2, and Tex1), the serine/arginine-rich (SR)-like proteins Gbp2 and Hrb1, the ATP-dependent RNA DEAD-box helicase Sub2, and the mRNA export adaptor Yra1. TREX function is necessary for efficient transcription elongation, 3′-end processing, mRNP assembly, and nuclear mRNA export.[2,3,6] TREX is recruited to the site of transcription by its interactions with the nascent mRNA, the C-terminal domain of Rpb1, the largest subunit of RNAPII, as well as the Prp19 complex and Mud2, both of which also function in splicing.[7–9] The components and functions of TREX are well conserved in other organisms, including humans. However, human TREX is recruited in a splicing-dependent manner by the exon junction complex (EJC).[10] The EJC is deposited onto the mRNA during splicing upstream of each exon-exon junction. The EJC regulates splicing, mRNA export, translation, and nonsense-mediated mRNA decay. Nuclear export of human intronless transcripts that are not bound by the EJC instead depends on

Table 1. Nuclear mRNP components

S. cerevisiae	*S. pombe*	*H. sapiens*	*A. thaliana*	Protein complex
Cbc1/Cbp80/Sto1	cbc1	NCBP1	–	CBC
Cbc2/Cbp20	cbc2	NCBP2	–	CBC
Hpr1	tho1	THOC1	HPR1/THO1/EMU	TREX/THO
Tho2	tho2	THOC2	THO2	TREX/THO
Tex1	tho3	THOC3	TEX1	TREX/THO
–	tho5	THOC5	THO5A	TREX/THO
–	–	–	THO5B	TREX/THO
–	–	THOC6	THO6/DWA1	TREX/THO
Mft1	tho7	THOC7	THO7A	TREX/THO
–	–	–	THO7B	TREX/THO
Thp2	–	–	–	TREX/THO
Gbp2	hrb1	–	–	TREX
Hrb1	hrb1	–	–	TREX
Sub2	uap56	UAP56/DDX39B	UAP56A	TREX
–	–	URH49/DDX39A	UAP56B	TREX
Yra1	mlo3, tho4	ALYREF/THOC4	ALY1	TREX
–	–	–	ALY2, ALY3, ALY4	TREX/THO
–	–	UIF	UIEF1	TREX
–	–	–	UIEF2	–
–	–	LUTZP	–	TREX
–	–	CHTOP	–	TREX
–	–	POLDIP3	–	TREX
–	–	ZC3H11A	–	TREX
Tho1	mlo1	CIP29/SARNP	MOS11	–
Npl3	srp2	–	–	–
Nab2	nab2	ZC3H14	–	–
Sac3	sac3, iss9	GANP/MCM3AP	SAC3A, SAC3B, SAC3C	THSC
Thp1	pci2	PCID2	THP1	THSC
Cdc31	cdc31	centrin/CENP/CETN2	CEN1	THSC
–	–	CETN3	CEN2	THSC
Sus1	sus1	ENY2	ENY2	THSC
Sem1	sem1/dss1	DSS1/SEM1	DSS1	THSC
Pab1	Pabp	PABPC1	–	–
–	Pab2	PABPN	–	–
Mex67	mex67	NXF1/TAP	–	mRNA exporter
Mtr2	nxt1	NXT1/p15	–	mRNA exporter

Listed are all known nuclear mRNP components and their homologs in *S. cerevisiae*, *S. pombe*, *H. sapiens*, and *A. thaliana*, indicating the respective protein complex. An empty space indicates no existing or known homolog.

specific RNA sequence elements that are directly bound by TREX.[11]

The conserved THSC or TREX-2 complex consists of Sac3, Thp1, Sus1, Cdc31, and Sem1 in *S. cerevisiae*.[12] By localizing induced genes near the nuclear pore complex (NPC), THSC coordinates transcription activation with nuclear mRNA export.[12]

Tho1 (SARNP in human) is an mRNP component with functions related to THO. However, the function of Tho1/SARNP in nuclear mRNP biogenesis is still unclear.[13]

In *S. cerevisiae* and mammalian cells, several SR (serine/arginine-rich)- and SR-like RBPs function in nuclear mRNP assembly and export.[13,14] In *S. cerevisiae*, the SR-like protein Npl3 functions in transcription elongation, splicing, 3′-end processing, mRNP assembly, and nuclear mRNA export.[13] Nab2 plays a role in poly(A) length control, nuclear mRNP assembly, and nuclear mRNA export.[13] In human cells, the SR-proteins SRSF1–7 are mRNP components and function in mRNP biogenesis. For example, SRSF3 and SRSF7 regulate 3′ UTR length.[14] Although ZC3H14, the human homolog of Nab2, binds to poly(A) tails, it is not known whether ZC3H14 functions in mRNP assembly and export.[15]

As the mRNA exporter is only recruited to correctly processed and packaged mRNPs, several nuclear mRNP components also

function in the quality control (QC) of mRNA. QC ensures that aberrant transcripts are either retained in the nucleus for degradation or downregulated at the transcriptional level, both preventing their translation.[16] Many adaptors, for example, interact with the nuclear basket protein Mlp1, which retains unspliced transcripts in the nucleus.[17,18]

In addition, nuclear mRNP components play a crucial role in maintaining genomic stability by preventing the formation of R-loops—RNA-DNA hybrids formed when the template strand hybridizes with the newly synthesized mRNA.[19] These R-loops expose the single-stranded coding strand to nucleases and genotoxins, making it vulnerable to DNA damage and hyperrecombination. Additionally, R-loops can cause replication stress by stalling or breaking replication forks, leading to genome instability. While R-loops have regulatory functions, such as in immunoglobulin class switching, their dysregulation is linked to neurodegenerative diseases and cancer.[20,21] In cancer, rapid cell division demands efficient nuclear mRNP biogenesis and export.[21] Therefore, nuclear mRNP components that prevent the formation of R-loops as they bind to the nascent mRNA are upregulated in certain cancer types. Moreover, Huntington's disease is associated with CAG trinucleotide repeat instability, where R-loop formation is driven by transcription across the repeats.[22] In Huntington R6/2 mice, Thoc2 (Tho2 in *S. cerevisiae*) mislocalization results in nuclear mRNA retention.[23] Neurodevelopmental disorders, like THOC6 intellectual disability syndrome (TIDS), are associated with mutations in mRNA export-related proteins. Mutations in the human THO complex protein THOC6 disrupt the formation of TREX tetramers and cause severe splicing alterations in long mRNAs and lncRNAs.[24] Furthermore, mRNP components are implicated in aging, as deletion of THO proteins in flies results in decreased lifespan and stress resistance.[25]

Moreover, mRNP components often determine the cytoplasmic localization, translation rate, and half-life of the mRNA they package.[26] Consequently, correct mRNP assembly is crucial for correct gene expression.

Posttranslational modifications of nuclear mRNP components

Various posttranslational modifications play crucial roles in nuclear mRNP biogenesis and export. Among these modifications, ubiquitylation stands out. Notably, three E3 ligases, Tom1, Rsp5, and Mdm30, function in nuclear mRNA export in *S. cerevisiae*. Tom1 ubiquitylates and thus releases Yra1 from nuclear mRNPs before their export, and Rsp5 mediates the interaction between its targets Hpr1 and Mex67, while Mdm30 ubiquitylates Sub2, enhancing Yra1 recruitment.[27–30]

Not surprisingly, phosphorylation of mRNP components controls their interaction with RNA. Dephosphorylated Npl3 binds to mRNA in the nucleus,[31] while its phosphorylation in the cytoplasm leads to the release of Npl3 from the mRNA.[32] Similarly, SR protein activity is governed by posttranslational modifications, particularly phosphorylation of their SR domains.[14] These phosphorylations regulate many processes, such as interaction with the spliceosome, RNA-binding affinity and specificity, cellular localization, as well as alternative splicing and mRNA export.[14]

Nuclear mRNA export

During mRNP assembly, all mRNP components gather on the mRNA in a coordinated manner, resulting in a mature and export-competent mRNP (Figure 1). The mRNP components Hpr1, Yra1, Nab2, and Npl3 in *S. cerevisiae* and several SR proteins in humans, such as 9G8, SRSF3, and SRSF7, function as mRNA export adaptors recruiting the conserved mRNA exporter Mex67-Mtr2 (NXF1-NXT1 in human), which has low intrinsic RNA affinity.[1] Interestingly, these SR proteins interact with NXF1 in their nonphosphorylated form, similar to Npl3. Export adaptors also appear to act in concert as Yra1 enhances the interaction between Nab2 and Mex67.[27] Finally, Mex67-Mtr2 directly interacts with components of the NPC and transports the mRNP to the cytoplasmic side.[33–36]

After nuclear export, the mRNP is disassembled, facilitating unidirectional mRNA export. Here, another DEAD-box helicase comes into play: Dbp5 is already recruited to nuclear mRNPs but mainly localizes to the cytoplasmic side of NPCs by its interaction with the nucleoporin Nup159.[37–39] Here, Dbp5, whose ATPase activity is stimulated by Gle1 and inositol-6-phosphate (IP6), removes Nab2 and Mex67 from the mRNP and releases a "remodeled" mRNP to the cytoplasm.[40]

Nuclear mRNA export, essential due to the spatial separation of transcription and translation, thus offers a vital QC step and the dynamic regulation of gene expression.

mRNA EXPORT BLOCK DURING STRESS

Cells encounter a wide range of stress conditions from environmental changes over infections to diseases. In *S. cerevisiae*, various stress conditions, such as exposure to heat or ethanol, cause nuclear accumulation of poly(A)$^+$ RNA,[41] hereafter referred to as mRNA export block. Interestingly, only "bulk" mRNAs are retained, while stress-specific mRNAs are selectively exported under stress.[41] Although much remains unknown, a few mechanisms contributing to this mRNA export block under different stress conditions in different organisms are known and will be discussed in the following section (Figure 2).

mRNA export block under stress in *S. cerevisiae*

Under stress, posttranslational modifications and kinases of the stress-response pathways modulate the activity of mRNP components.[42–44] For example, the kinase Slt2 is activated under several stress conditions and mediates the mRNA export block in response to heat shock.[42] As phosphorylation of the Slt2 target and export adaptor Nab2 is not sufficient for the export block,[42] additional Slt2 targets must exist. Furthermore, the dissociation of mRNA export adaptors from the mRNA was proposed to cause nuclear retention (Figure 2C).[45] Interestingly, elevated temperature leads to higher compaction of mRNPs,[46,47] a process that could be regulated by posttranslational modifications. Therefore, posttranslational modifications of mRNP components could facilitate the mRNA export block during stress by altering either protein-protein or protein-RNA interactions. Moreover, it is likely that posttranslational

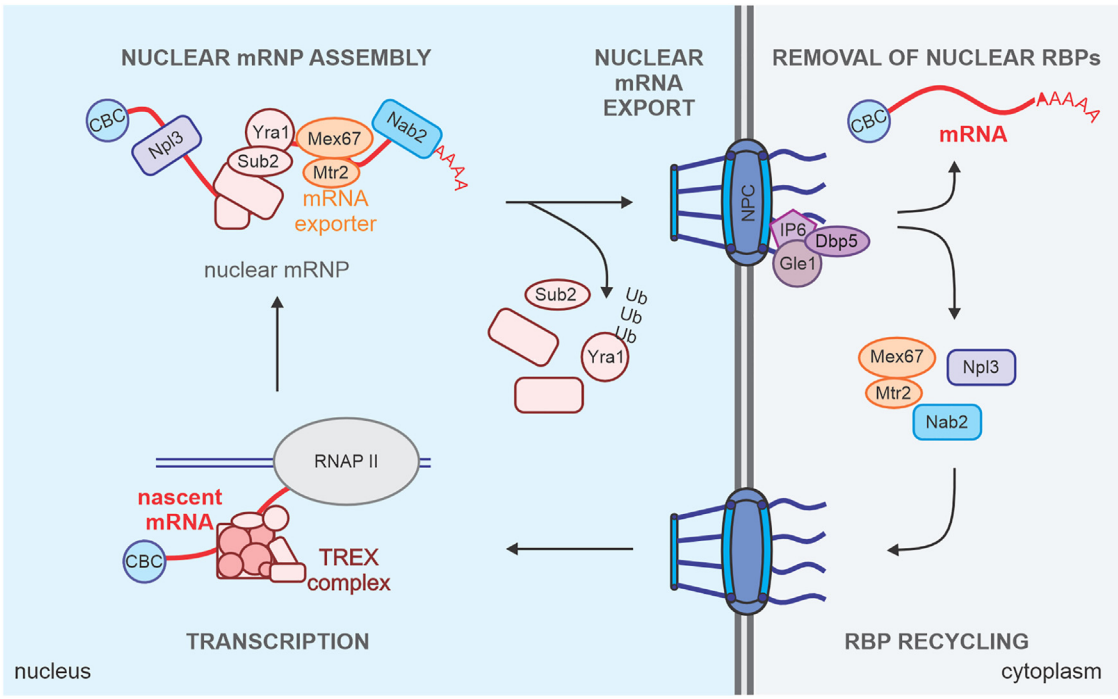

Figure 1. Nuclear mRNA export under physiological conditions

Nuclear RNA-binding proteins (RBPs), such as the cap-binding complex (CBC) and TREX (composed of the THO complex, Yra1, Sub2, Gbp2, and Hrb1), bind co-transcriptionally to the nascent mRNA (red), initiating mRNP assembly in the nucleus (blue). The mRNP is probably remodeled as it moves toward the nuclear pore complex (NPC). The composition and structure of nuclear mRNPs remain unknown. Certain nuclear RBPs are removed from the mRNP before export, e.g., Yra1 upon ubiquitylation (ubiquitin [Ub]). The exporter Mex67-Mtr2 (NXF1-NTF1 in human cells, orange) transports the mRNA through the NPC. On the cytoplasmic side (gray), the DEAD-box helicase Dbp5 (DDX19 in human cells) is stimulated by Gle1 and inositol-6-phosphate (IP6) (purple), removing nuclear RBPs from the mRNA and preventing mRNA re-import. The released RBPs are re-imported to participate in subsequent rounds of nuclear mRNA export.

modifications of multiple proteins act together to mediate the mRNA export block.

Another—not mutually exclusive—mechanism to induce an mRNA export block is the sequestration of proteins essential for mRNA export. Indeed, formation of aggregates or foci has been observed under various stress conditions (Figure 2D).[42,45,48] Under heat stress, Nab2, Yra1, and Mlp1 form foci in the nucleus.[42] During glucose starvation, Nab2-containing condensates form that colocalize with nuclear RNA foci.[48] Furthermore, Dbp5 levels at the nuclear envelope decrease under glucose starvation, which triggers formation of Nab2 condensates.[48] Ethanol stress, in turn, causes nuclear mislocalization of Dbp5, suggesting a role of Dbp5 in the mRNA export block (Figure 2F).[49,50] During heat stress, Dbp5 localization is not changed.[51] However, the interaction between Nab2 and Dbp5 is reduced, which could be a consequence of the sequestration of Nab2 into foci.[50,51] Thus, removal of Dbp5 from the nuclear rim is a major factor in mediating the mRNA export block upon several but not all environmental perturbations. Also, it remains unclear whether reduced Dbp5 levels at the nuclear rim are the cause or the result of the mRNA export block.

Taken together, different mechanisms contribute to the mRNA export block under heat shock, ethanol exposure, or glucose starvation. Even though the mechanisms appear to be distinct for different stress conditions,[42,48,50] the key players seem to be, at least partially, the same. As the mRNA exporter Mex67 is required for the export of stress-specific transcripts,[34,52] Mex67 function is probably not affected. Therefore, the export of bulk mRNA can either be inhibited upstream of NPC passage by preventing the recruitment of the mRNA exporter or downstream by inhibiting the directionality of general mRNA export and mRNA release into the cytoplasm.

Similarities and differences in higher eukaryotes

The regulation of nuclear mRNA export under stress varies in different organisms. Similar to *S. cerevisiae*, human HeLa cells respond to extreme heat stress with a nuclear mRNA export block.[53] Treatment of U2OS cells with Tubercidin, an antineoplastic and antimicrobial ribonucleoside, leads to the accumulation of DDX19 (Dbp5 in *S. cerevisiae*), THOC5, and NXF1 (Mex67 in *S. cerevisiae*) in stress granules, membraneless organelles in the cytoplasm, and to an mRNA export block,[54] whereas ethanol stress in *S. cerevisiae* induces Dbp5 relocalization to the nucleus.[49,50] However, Tubercidin probably interferes with nuclear mRNA export at an early stage as recruitment of ALYREF (Yra1 in *S. cerevisiae*) and EJC proteins to the transcription site is reduced (Figure 2B).[54] The failure to recruit these adaptors, which recruit the nuclear mRNA exporter NXF1-NXT1 (Mex67-Mtr2 in *S. cerevisiae*), could mediate the mRNA export block.[54]

Genotoxic stress results in nuclear retention of, for example, the *histone* mRNAs in *Drosophila* embryos.[55] *Histone* mRNAs

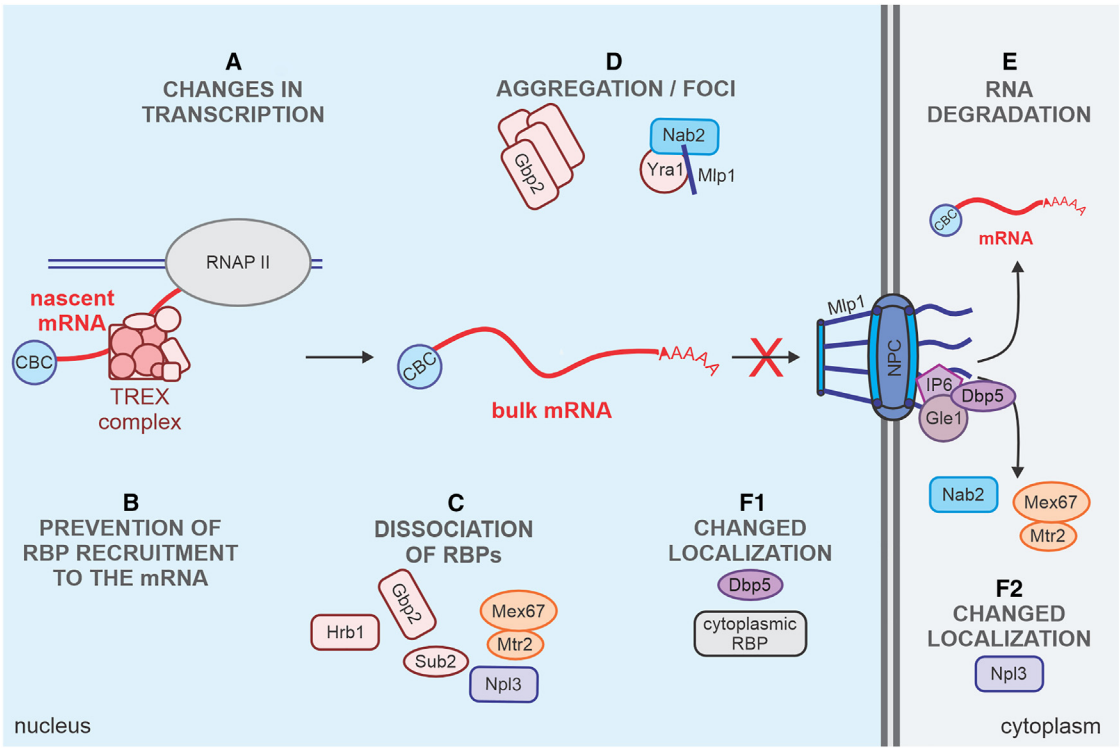

Figure 2. Nuclear mRNA export block in stress conditions

Various stress conditions inhibit nuclear export of bulk mRNA (red). This figure illustrates different proposed mechanisms underlying the mRNA export block. It presents a combination of findings from studies on *S. cerevisiae* (A, D, C, and F2) and virus-infected human cells (B, E, and F1), using the simplified nuclear mRNA export model from *S. cerevisiae* for comparative purposes.

possess a stem loop structure at their 3′ end. During DNA damage, the checkpoint kinase Chk2 (Rad53 in *S. cerevisiae*) phosphorylates the stem loop binding protein (SLBP) reducing its levels. Missing SLBP protein prevents nuclear export of the *histone* mRNAs.[55] This is thought to eliminate damaged cells to guarantee correct developmental progression.[55] A link between RNA metabolism and checkpoint signaling also exists in *S. cerevisiae*, where Rad53 activation upon DNA damage causes nuclear accumulation of unspliced tRNAs.[55]

Manipulation of mRNA export by viruses

Many viruses prevent nuclear export of host mRNAs, which aids their evasion of the host's antiviral response and increases the translation of viral proteins.[56–58] To this end, virus proteins target adaptors, the mRNA exporter, or nucleoporins.[56,57] In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the N7-methyltransferase activity of Nsp14 decreases the binding of CBC to mRNA and, in turn, the recruitment of ALYREF and NXF1 (Figure 2B).[59] Second, ORF6 interacts with the NPC components Rae1 (Gle2 in *S. cerevisiae*) and Nup98 (Nup145, Nup100, and Nup116 in *S. cerevisiae*), competing with mRNA binding to Rae1-Nup98 and thus preventing host mRNA export.[60] Third, Nsp1 inhibits the recruitment of NXF1 to the mRNA, likely by interfering with ALYREF function and the interaction of NXF1 with nucleoporins.[61]

The mRNA export block during viral infection could also be a secondary effect triggered by increased cytoplasmic mRNA decay (Figure 2E).[58] Indeed, increased RNA degradation upon RNase L activation or SARS-CoV-2 infection causes nuclear accumulation of interferon mRNAs.[62,63] Similarly, Kaposi's sarcoma-associated herpesvirus protein SOX induces mRNA degradation.[64] This leads to nuclear enrichment of the cytoplasmic poly(A) binding protein PABPC (Figure 2F) and subsequently hyperadenylation of RNA and an mRNA export block.[64]

In summary, viral proteins interfere directly with the export of host mRNA by binding to adaptors, the exporter, or nucleoporins. In addition, secondary effects have to be considered, since changes in protein localization or alterations in the host mRNA upon virus infections can also influence host mRNA export.

Nuclear mRNA export block in plants

Similar to *S. cerevisiae*, plant cells also display a nuclear mRNA export block in response to various environmental perturbations, such as reduced or elevated temperatures or ethanol.[65,66] Furthermore, hypoxia causes the accumulation of bulk mRNA in nuclear Cajal bodies, while stress-specific mRNAs are exported to the cytoplasm.[67] Posttranslational modifications also play a crucial role in regulating mRNA export in plants. Mutation of the SUMO E3 ligase SIZ1 in *Arabidopsis thaliana*, e.g., leads to an mRNA export block, indicating an important function of sumoylation in plants.[66] Given that SUMO conjugation is significantly elevated during stress, sumoylation may play a role in regulating nuclear mRNA export under these conditions.[66]

SELECTIVE EXPORT OF STRESS-SPECIFIC TRANSCRIPTS

NPCs and the export of stress-specific transcripts

Survival of stress often relies on the induction of stress-specific genes and the production of their corresponding proteins. Thus, the question arises how cells still export stress-specific transcripts while their bulk mRNA accumulates in the nucleus.[13,41] Stress-specific transcripts either escape the export block or are exported by a stress-specific mechanism (Figure 3). Many proteins known to be involved in nuclear mRNA export have been tested for their requirement to export stress-specific transcripts in *S. cerevisiae*. Nucleoporins, including Rip1, Nup84, Nup100, and Nup133, are essential for efficient export of the heat shock mRNA *HSP104*.[68] Of these, the nucleoporin Rip1/Nup42 is essential for export of the stress-specific *SSA4* mRNA both during heat and ethanol stress.[41,69] Rip1 localizes to the cytoplasmic filaments of the NPC together with Dbp5, Gle1, and Nup159, and the latter are also essential for *SSA4* export.[41,49] Dbp5 no longer localizes to the NPC in *Δrip1* cells, which may be a consequence of the requirement of Rip1 for Gle1 stability.[49,70] Accordingly, plant Los4 (Dbp5), IP6, and Gle1 are not only required for nuclear mRNA export under normal growth conditions but also for the export of stress-responsive transcripts at elevated temperature or during salt stress.[71,72]

The remodeling of the exported mRNP by Dbp5 at the cytoplasmic side of the NPC could also be a requirement for the directed export of stress-specific mRNAs.[49] How an mRNA is exported when Dbp5 is relocalized to the nucleoplasm is still unclear. Maybe minor amounts of Dbp5 at the NPC are sufficient, or another protein replaces the function of Dbp5.

Posttranslational modifications not only contribute to the export block, they are also involved in the export of stress-specific mRNAs. For example, during hyperosmotic stress, the stress-activated kinase Hog1 phosphorylates nuclear basket proteins, which is necessary for export of hyperosmotic stress-induced mRNAs.[44]

Taken together, nucleoporins serve important functions for nuclear mRNA export under both favorable and stress conditions.

mRNA export adaptors with roles in the export of stress-specific mRNAs

mRNA export under normal growth conditions requires export adaptors that recruit the mRNA exporter Mex67-Mtr2 to the mRNA.[2,73] To screen for RBPs involved in heat-stress-specific mRNA export, two methods were predominantly employed: fluorescence-activated cell sorting (FACS) to monitor the production of GFP-tagged heat shock proteins and single-molecule fluorescence *in situ* hybridization (smFISH) to directly visualize RNA localization.[34,41,52,68,74] Interestingly, these two techniques yield partially different results. Based on protein production, Rip1, Mex67-Mtr2, Dbp5, Gle1, Nup157, and Sub2 are required for heat-stress mRNA export, as the Ssa4 protein is not produced in the respective deletion or mutation strains.[49,52] By contrast, by smFISH, the *SSA4* and *HSP104* mRNAs show nuclear accumulation in mutants that produce Ssa4 or Hsp104 proteins, such that the respective proteins are considered to be not essential for the export of heat-stress mRNAs. For example, deletion of THO or THSC components or nucleoporins cause accumulation of the *HSP104* mRNA at the site of transcription.[68] Similarly, *SSA4* mRNA accumulates in THO deletion mutants and in the *npl3-1 yra1-ΔC* double mutant.[52] In addition, binding of Yra1, Npl3, and Nab2 to the *SSA4* mRNA was demonstrated by RNA immunoprecipitation further implying a role of these proteins during heat shock mRNA export.[52] During acidic stress, sumoylation of the THO complex protein Hpr1 is necessary for its binding to and stabilization of acidic stress-induced transcripts.[43] In *A. thaliana*, Hpr1 is important for nuclear export of the mRNA encoding the transcription factor STOP1, which regulates the transcriptional response to aluminium.[75]

While these studies pinpoint toward a role of export adaptors in stress mRNA export, Hpr1, Yra1, Mex67, Nab3, Gbp2, Hrb1, and Nab2 dissociate from mRNA upon heat or salt stress, or both.[45] This finding together with the FACS-based studies led to the hypothesis that heat-stress-specific mRNAs are exported through a distinct pathway (Figure 3A) that differs from the mechanism of bulk mRNA export.[52,74] This alternative pathway requires Mex67 and the transcription factor Hsf1, which acts as an adaptor for Mex67 (see below) but does not engage in QC.[45] Relocalization of Mlp1 to nuclear foci[42] could prevent the function of Mlp1 in QC during heat stress and strengthens the hypothesis of QC-free export of stress transcripts.[73] In addition, as splicing is inhibited during severe heat stress in *S. cerevisiae*, it seems logical that splicing surveillance by Gbp2 and Hrb1 is no longer required.[73,76]

However, the hypothesis that QC is omitted during stress-specific export in order to ensure rapid export seems only to be true for some QC pathways. Historically, heat shock transcripts play an important role in studying QC pathways.[77–79] Both the exosome and its activating complex TRAMP play a role in QC of heat-stress transcripts upon deletion of THO proteins. Deletion of THO components leads to reduced *HSP104* mRNA levels and retention at the transcription site. Upon deletion of *RRP6*, which codes for one of two exosome's exoribonuclease, mRNA levels are restored and retention is abolished. A study investigating aberrant mRNPs upon artificial expression of the bacterial helicase Rho identified a potential role of Tho2 in the recruitment of Rrp6 to faulty transcripts independent of the THO complex.[80] Another example for QC of stress transcripts is the retention of heat shock mRNA at the site of transcription when these mRNAs are hypo- or hyperadenylated.[81] Again, deletion of *RRP6* results in the release of the mRNA from the transcription site. However, deletion of *RRP6* alone, which under favorable growth conditions results in the accumulation of faulty transcripts in the nucleus, causes no accumulation of heat shock transcripts.[81]

Taken together, these findings indicate that nuclear mRNA export under stress conditions requires a different set of proteins than under favorable conditions. Some export adaptors may not be involved, but others, such as Yra1 and Hpr1, although not essential for stress mRNA export, are. These probably ensure efficient transcription, QC, and export of stress transcripts and may carry out regulatory functions. Further studies are needed to precisely identify the function of different adaptors in stress-transcript export.

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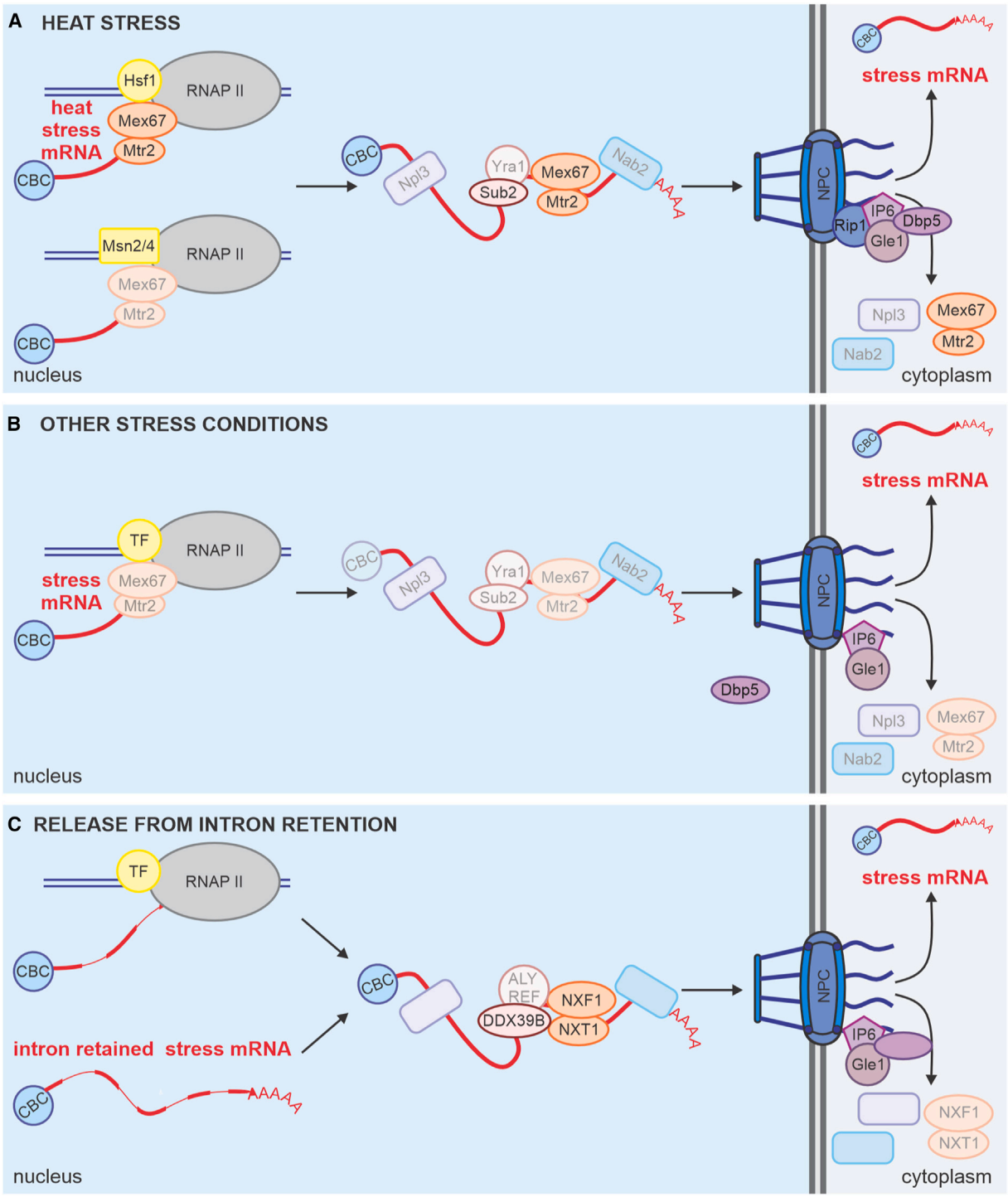

Figure 3. Nuclear export of stress-specific mRNAs

(A) In *S. cerevisiae*, nuclear export during heat stress is facilitated by the transcription factor (TF) Hsf1 (yellow), which recruits the exporter Mex67-Mtr2 (orange) to the heat-stress-induced mRNA (red). The nucleoporin Rip1 and its interaction partners Dbp5, Gle1, and IP6 (purple) are essential for this process. The involvement of other mRNA export adaptors in heat-stress-specific mRNA export is not fully understood (represented by transparent proteins).

(B) The export mechanisms of stress-specific mRNAs under other stress conditions are still unclear. It is uncertain whether a transcription factor is necessary to recruit Mex67-Mtr2 and how mRNP components are removed when Dbp5 is delocalized, such as in ethanol stress.

(C) In higher eukaryotes, mRNAs (red) can be retained in the nucleus due to retention of detained introns (thin red lines). The removal of these detained introns in response to certain stimuli, such as stress, permits export of mature transcripts from the nucleus (light blue) to the cytoplasm (gray).

Intron retention as a mechanism to regulate stress mRNA export

While yeast lacks the EJC, it plays a central role in mRNA biogenesis in higher eukaryotes and provides another layer for regulation.[10] Intron retention often causes nuclear retention of pre-mRNA until a certain stimulus, such as stress or neuronal activation induces maturation, export, and translation of the pre-mRNA (Figure 3C).[82] Although heat stress reduces splicing, the release from intron retention was found to regulate mRNA export of certain transcripts.[83] During heat stress, the lncRNA HSATIII is transcribed and sequesters dephosphorylated SR proteins in nuclear stress bodies (nSBs), suppressing intron retention and allowing maturation of pre-mRNAs and their export.[84] During recovery from stress, the kinase CLK1 phosphorylates the sequestered SR proteins, which likely drives the release of SR proteins and reestablishes intron retention. Interestingly, ribotoxic stress triggers release from intron retention.[85] The inhibition of protein biosynthesis by bacterial or fungal compounds called ribotoxins induces p38 mitogen-activated protein kinase-dependent relocalization of RNAPII, components of the early spliceosome, and the RBP T cell intracellular antigen-1-related protein (TIAR) to nuclear speckles. Subsequently, splicing of pre-mRNAs from immediate early genes (IEGs) is activated.[85,86] These examples highlight that nuclear retention can not only occur upon stress induction but is a general mechanism to facilitate export of certain transcripts required at a distinct time. Release from intron retention allows for the rapid splicing of pre-mRNAs and their subsequent export during stress in a transcription-independent manner.[83,84]

Transcription factors function as alternative export adaptors

The mRNA exporter Mex67 is recruited directly to the transcription site of stress-specific transcripts by interaction with the transcription factor Hsf1, which serves as an alternative export adaptor (Figure 3A).[45] The direct involvement of Hsf1 in the export of stress-responsive transcripts appears to be conserved. In human cells, the interaction of Hsf1 and the NPC component Tpr1 (Mlp1 in *S. cerevisiae*) is important for the export of HSP70 family transcripts.[45] While the *HSP12* promoter is sufficient for nuclear export during heat stress,[45] the *SSA4* promoter is insufficient, and instead, the 3′ or the 5′ end of *SSA4* is required for export during heat stress.[41] In addition to Hsf1, other transcription factors are involved in regulating the heat shock response in *S. cerevisiae*, such as Msn2-Msn4.[87] It remains unknown how Msn2-Msn4-dependent stress transcripts are exported. Whether or not stress-specific transcripts are exported in a transcription factor-dependent manner during other stress conditions (Figure 3B) remains elusive.

CONCLUSIONS AND PERSPECTIVES

Despite intensive investigation of nuclear mRNA export under optimal conditions, many questions remain unanswered. These include the precise timing of RBP recruitment, the composition and structure of a nuclear mRNP, the specific function(s) of each nuclear mRNP component, and the mRNP remodeling steps involved. First data exist, e.g., about the time-resolved recruitment of RBPs in human cells.[88]

Much less is known about the mechanisms blocking general mRNA export and the nuclear export of stress-induced mRNAs. Although first steps have been taken to understand these processes, a comprehensive understanding is still lacking. It is likely that the nuclear export of stress-specific transcripts relies at least on a subset of the proteins that mediate "normal" mRNA export, such as Mex67-Mtr2, TREX, THSC, and certain nucleoporins.[68] Multiple pathways for the export of stress-induced mRNAs could enhance survival chances and explain protein production despite the nuclear accumulation of the corresponding transcripts.[52] Stress-specific export adaptors like Hsf1 and their functions in nuclear mRNA export also require further investigation. Also, it remains unclear how the cell differentiates between bulk and stress-specific mRNAs. One possibility is that only stress-induced mRNAs are exported in *S. cerevisiae* (Figure 2A), a process that might differ from higher eukaryotes where the release from intron retention (Figure 3C) also facilitates the export of stress transcripts.[82] Understanding the similarities and differences between organisms and stress conditions is crucial. Importantly, the signal transduction pathways governing these responses have to be elucidated. Posttranslational modifications are indispensable for rapidly regulating proteins involved in nuclear mRNA export and thus mRNA export itself.[27,28] Consequently, a complex network of posttranslational modifications likely modulates nuclear mRNA export under stress. Identifying the exact modifications and respective proteins as well as uncovering their regulatory functions is important. These studies will be facilitated by advancements in techniques such as smFISH, transcriptome- and proteome-wide analyses, and structural studies.

In addition, understanding the physiological relevance and the regulation of nuclear mRNA export in various disease conditions, including viral infections, is vital. This knowledge will pave the way for the development of novel therapeutic strategies and drugs.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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