Minireview

Nuclear RNA export in yeast

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Abstract Eukaryotic cells massively exchange macromolecules (proteins and RNAs) between the nucleus and cytoplasm through the nuclear pore complexes. Whereas a mechanistic picture emerges of how proteins are imported into and exported from the nucleus, less is known about nuclear exit of the different classes of RNAs. However, the yeast *Saccharomyces cerevisiae* offers an experimental system to study nuclear RNA export in vivo and thus to genetically dissect the different RNA export machineries. In this review, we summarize our current knowledge and recent progress in identifying components involved in nuclear RNA export in yeast.

Key words: Nuclear pore complex; Nuclear export; Yeast; mRNA; rRNA; tRNA

1. Introduction

In eukaryotic cells, the nuclear membrane creates a barrier for exchange of molecules between the nucleus and the cytoplasm. Accordingly, karyophilic proteins, which are synthesized in the cytoplasm, are imported into the nucleus, and RNAs, which are transcribed inside the nucleus, are exported to the cytoplasm. All transport processes are facilitated by the nuclear pore complexes (NPCs). NPCs consist of about 50 different proteins called nucleoporins (Nups), of which more than 30 have already been identified [1]. Transport through a nuclear pore can occur in both directions and one distinguishes between free diffusion and active transport. Although it was estimated that diffusion through the nuclear pores is possible for small molecules (up to 20 kDa), both small and large macromolecules (>60 kDa) are actively transported.

Active transport through the nuclear pores requires the concerted action between nuclear pore proteins forming the stationary phase and soluble transport factors, which shuttle between the nucleus and the cytoplasm. One of the key factors of the soluble nucleocytoplasmic transport machinery is the small GTPase Ran [2]. Ran provides directionality to the various transport processes by a steep RanGTP/RanGDP gradient across the nuclear membrane. The concentration of RanGTP is high in the nucleus, whereas the RanGDP concentration is high in the cytoplasm due to the cytoplasmically located RanGAP and the nuclear RanGEF [3]. A key role of Ran during nucleocytoplasmic transport is its transient interaction with the various nuclear import and export receptors, which are members of the importin/karyopherin β family [4,5].

For nuclear uptake, an import complex consisting of an NLS (nuclear localization sequence)-containing import cargo and its cognate importin β receptor forms in the cytoplasm, followed by docking to the nuclear pores. The successive translocation through the pore channel is not yet understood, but could involve multiple cycles of binding to and release from FXFG/GLFG/FG repeat sequences containing nucleoporins. Alternatively, nucleoporins may be more dynamic than initially anticipated and migrate with bound receptor/cargo complexes through the nuclear pore channel. Upon arrival at the nuclear site of the NPC, the import complex dissociates upon binding of nuclear RanGTP. An opposite mechanism is true for nuclear protein export (for review see [6,7]).

2. Export of RNAs

Nuclear export of RNAs is one of the major routes through the nuclear pores. However, in most cases naked RNAs are not transport substrates since proteins are generally bound to RNAs forming RNP particles. Accordingly, signals in either the RNA or protein moiety or both may contribute to the nuclear export of RNPs. In this respect, elementary insights came from the analysis of how the HIV protein Rev mediates export of the viral mRNA. Rev specifically binds to the RRE (Rev response element) of viral pre-mRNAs and with its short leucine-rich NES (nuclear export sequence) to a specific exportin, which was shown to be Crm1 (Xpo1p in yeast; for review see [8]). Crm1 belongs to the group of importin/karyopherin β transport receptors (see above). Yet, whether cellular mRNAs and other classes of RNAs are exported in a similar way is still under debate. In this review, we focus on the nuclear export of RNAs with an emphasis on yeast, which serves as a model organism amenable to genetic approaches. Microinjection of RNAs or proteins into *Xenopus* oocytes is a complementary approach to analyze the mechanisms and components of the different RNA export machineries.

2.1. mRNA

Cis-acting signals in mRNA such as the monomethyl cap structure or the poly(A) tail have been suggested to facilitate mRNA export [9,10]. Since hnRNP proteins associate with mRNA during or shortly after transcription and some of them shuttle between nucleus and cytoplasm, they were thought to mediate nuclear mRNA export *in trans*, i.e. that they provide NES signals for mRNA export [11,12]. Indeed, nuclear export signals have been identified in hnRNP proteins such as the M9 sequence in vertebrate hnRNP A1 [13].

In yeast, a major shuttling hnRNP protein is Npl3p, which is likely to play an important role in the assembly of hnRNPs [14,15]. Since Npl3p not only shuttles between the nucleus and cytoplasm, but npl3 mutants are also impaired in mRNA

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export (*NPL3* was also found in a genetic screen for poly(A)$^+$ RNA export mutants; *MTR11* = *NPL3*, see below), it was suggested to be involved in mRNP export (similar to hnRNP A1 in the vertebrate system). However, to this date no NES has been found in the Npl3p sequence. On the other hand, an extended NLS was identified within the 'RGG' box domain of Npl3p, which binds to its specific importin β-like import receptor Mtr10p (Kap111p) [16,17]. After import into the nucleus, Npl3p dissociates from Mtr10p only efficiently in the presence of RanGTP and RNA [17]. This suggests a mechanism for vectorial intranuclear delivery of the Npl3p/Mtr10p complex to the sites of mRNA/Npl3p assembly. The identification of *MTR10* as the import receptor of Npl3p also explains the initial identification of *MTR10* in a screen for poly(A)$^+$ RNA export mutants (see below).

Through various genetic approaches, it was possible to identify many genes of the mRNA export machinery. In one genetic approach, randomly generated temperature-sensitive mutants were screened for nuclear poly(A)$^+$ RNA accumulation. Identified mRNA export mutants were called either *mtr* (for **m**RNA **tr**ansport) [18] or *rat* (**r**ibonucleic **a**cid **t**ransport) [19]. Several of the *RAT*/*MTR* genes have been cloned and analyzed. They fall into several categories: (i) components of the Ran system, (ii) nucleoporins, (iii) factors involved in RNA metabolism such as RNA helicases or nucleases, and (iv) components involved in membrane biogenesis. Since Ran and its modulating factors are expected to participate in mRNA export (either directly or indirectly), we will discuss the components that fall into categories ii–iv.

In addition to the *rat*/*mtr* mutants, a vast number of nucleoporins were found in synthetic lethal screens and by biochemical approaches. However, only a limited number of the identified nucleoporins participate in mRNA export [1,20]. To this group belong members of two different NPC subcomplexes: Nup85p (Rat9p), Nup120p (Rat2p), and Nup145p-C (Rat10p) within the Nup84p subcomplex, and Nup159p (Rat7p), Nup82p, and a fraction of Nsp1p within the Nup82p subcomplex [21–26]. Interestingly, both subcomplexes are located at the cytoplasmic site of the nuclear pores, as revealed by immunoelectron microscopy [26–28] (B. Fahrenkrog and N. Panté, unpublished data). Accordingly, both subcomplexes may function at late or terminal stages during translocation through the NPC by a mechanism that could involve direct and consecutive interaction of the export cargo/receptor complex with nucleoporins of these subcomplexes.

In this context, Gle1p should be mentioned, which could be another (but perhaps not stably attached) component of the Nup82p complex. This is suggested on the basis that *GLE1* is strongly linked to the Nup82p complex, since overexpression can complement *nup159* and *nup82* mutants [26,29]. *GLE1* was initially found in a synthetic lethal with the *NUP100* null allele, a GLFG repeat sequence-containing nucleoporin, and shown to be an essential, NES-containing RNA export factor interacting with Nup100p and Rip1p/Nup42p [30]. Finally, Gle2p belongs to this group of nuclear pore-associated proteins with a role in RNA export. It was found in the same synthetic lethal screen as *GLE1* [31]. Gle2p localizes to nuclear pores by binding directly to a short sequence within Nup116p called GLEBS [32]. Gle2p is homologous to Rae1, an essential mRNA export factor in *Schizosaccharomyces pombe* [33], and to human mrnp 41 [34].

It is conceivable that some nucleoporins or nuclear pore-associated transport factors gain direct physical contact with the RNA moiety of the RNP. Nup145p-N and Nup116p contain an 'NRM' (nucleoporin RNA binding motif) and were found to interact with RNA in vitro [35]. In the vertebrate system, Nup153p was recently shown to have a high affinity for homopolymeric RNA [36]. In this respect, Mex67p (**m**RNA **ex**port factor of **67** kDa) should be mentioned, since it also binds to poly(A)$^+$ RNA in vivo. *MEX67* was found as a synthetic lethal mutant of the *nup85*Δ allele [37]. Temperature-sensitive mex67 mutants exhibit an extremely fast onset of inhibition of poly(A)$^+$ RNA export after shift to the restrictive temperature (within the 5 min range) suggesting that Mex67p is at the heart of the mRNA export machinery. Mex67p forms a tight complex with Mtr2p [38]. Since the Mex67p/Mtr2p complex can bind directly to mRNA (via the Mex67p subunit) and interact with nuclear pores (e.g. with Nup85p via Mtr2p, or FG nucleoporins via Mex67p), it fulfills two important requirements for an mRNA export receptor complex, which could function independently of an importin β-like export factor such as Xpo1p. In yeast, the possible involvement of Xpo1p in mRNA export is being discussed since xpo1-1 mutants are impaired not only in NES-mediated export, but also in mRNA export [39]. TAP, the human homologue of Mex67p [37,40], was shown to be the cellular co-factor necessary for nuclear export of the CTE-containing RNA of simple type D retroviruses [41]. These RNAs are exported through an mRNA export pathway, since injection of CTE RNA blocks mRNA export in *Xenopus* oocytes [41,42]. TAP shuttles between the nucleus and the cytoplasm and can directly bind to poly(A)$^+$ RNA, FG repeat sequences of nucleoporins such as CAN/Nup214, and a novel human 15 kDa protein (p15), which shows homology to NTF2 (a nuclear transport factor which associates with RanGDP). Co-expression of TAP and p15 restores growth of the otherwise lethal mex67/mtr2 double disruption mutant. Accordingly, the Mex67p/Mtr2p-mediated mRNA export pathway is conserved from yeast to human [40].

Interestingly, some of the *mtr*/*rat* mutants of category iii are mutated in enzymes involved in RNA folding or turnover. *MTR4*/*DOB1* encodes an essential nuclear DEAD-box RNA helicase [43] required for 3′ end formation of 5.8S rRNA [44]. *RAT1 (XRN2)* is an essential exoribonuclease required for the degradation of excised pre-rRNA spacer fragments and the synthesis of the 5′ ends of several snoRNAs, but is not involved in mRNA turnover [45]. It thus appears that disturbing the metabolism of different classes of RNA may cause a feedback inhibition on mRNA export.

Recently, the characterization of the *rat8* mutant gave us an idea of how mRNA export could be terminated at the cytoplasmic site of the nuclear pore complex. *RAT8*, which is identical to *DBP5*, encodes a cytoplasmically located, but NPC-associated RNA helicase [46,47]. Thus, Rat8p/Dbp5p may play a role in unwinding mRNP export complexes upon arrival at the cytoplasmic site of NPC which may trigger release of shuttling hnRNP proteins from the mRNA.

The role of nuclear mRNA export mutants falling into category iv is still obscure. For example, the *mtr7* mutant is affected in mRNA export. Unexpectedly, *MTR7* is allelic to *ACC1* which encodes the yeast acetyl-CoA carboxylase required for the generation of very long chain fatty acids. It was suggested that this type of lipid is crucial for the correct insertion of nuclear pores into the nuclear membrane, which is

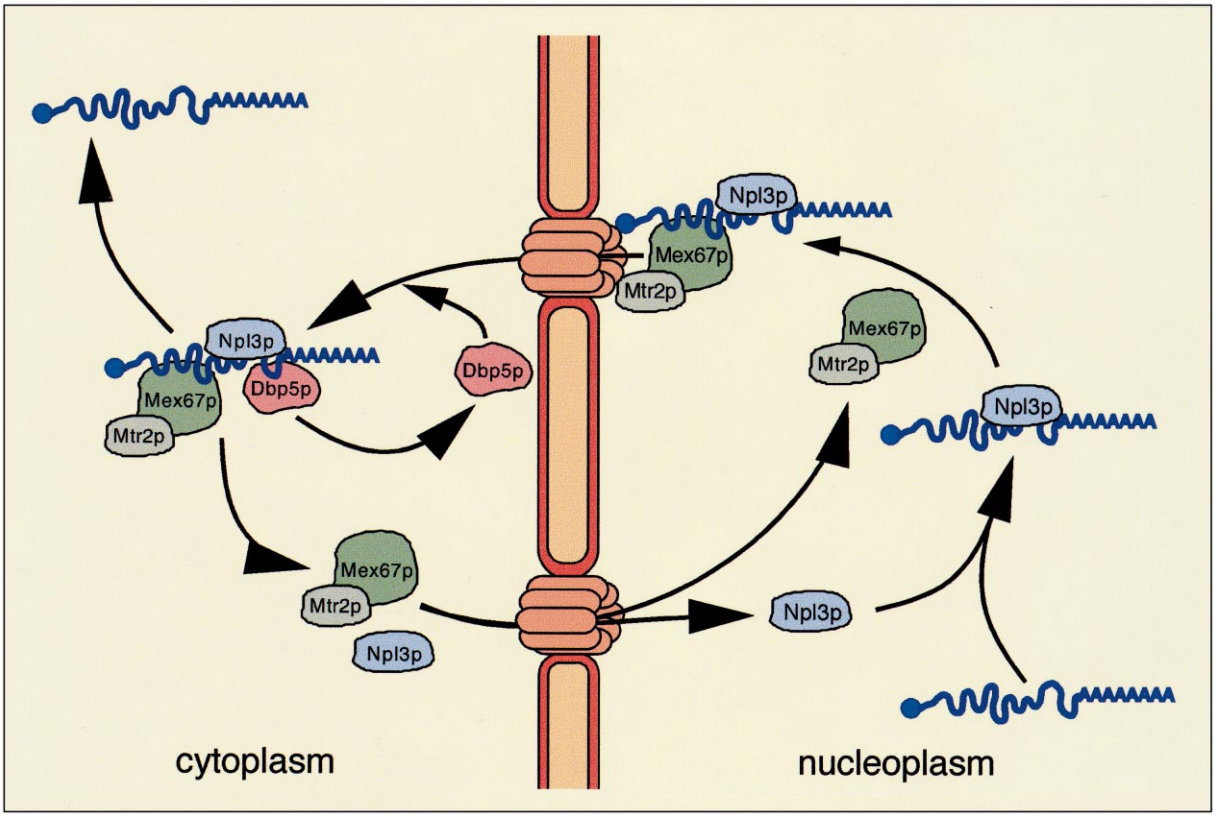

Fig. 1. A model of mRNA export in yeast. Binding of hnRNP proteins such as Npl3p, capping, and polyadenylation of the newly transcribed mRNA results in an export-competent hnRNP particle. This particle is recognized by mRNA export factors (e.g. Mex67p/Mtr2p complex). After translocation through the nuclear pore, Dbp5p triggers the dissociation of the mRNP export complex. The hnRNP proteins and Mex67p/Mtr2p are recycled to the nucleus, whereas the mRNA is delivered to the ribosomes for translation.

consistent with the finding that *mtr7/acc1* mutants also exhibit an abnormal nuclear envelope structure [48]. A similar phenotype was found for the *nup84* null mutant that exhibits a moderate impairment in mRNA export, but strong defects in nuclear membrane/nuclear pore organization [21]. Since *NUP84* is genetically linked to two nuclear envelope/endoplasmic reticulum membrane proteins involved in membrane biogenesis and morphology [49], the mRNA export defect could be indirect. Finally, it should be mentioned that *NUP116* and *GLE2* mutants (which reveal mRNA export defects) exhibit striking NPC herniations and sealed nuclear pores [31,32]. In contrast *mex67*, *mtr2*, and *gle1* mutants do not exhibit structural abnormalities of the nuclear envelope. Although an intimate link between nuclear membrane/NPC organization and mRNA export is evident in the above mentioned mutants, the mechanistic aspects of this crosstalk remain obscure.

In summary, more and more companions escorting an mRNA during nuclear export become known. hnRNP proteins are likely to be the first players to generate transportable hnRNPs. Next, binding of export receptors to the export-competent hnRNPs followed by NPC targeting may occur. During translocation through the pore the export complex may gain direct contact with certain nucleoporins, e.g. Nup85p, Nup159p and possibly others. The final release of the hnRNP from the nuclear pores is probably facilitated by helicases such as Dbp5p (Fig. 1). The mRNA is then delivered to the ribosomes, whereas hnRNP proteins are re-imported into the nucleus. Whether intranuclear RanGTP or cytoplasmic RanGDP play a direct role in nuclear mRNA export remains to be shown.

2.2. tRNAs

In contrast to mRNA, it was shown that tRNA binds directly to its importin β-like export receptor Los1p (exportin-t in higher eukaryotes) cooperatively with RanGTP [50–52]. However, since *LOS1* is not essential in yeast, there has to exist an additional export route for the export of tRNAs [53]. Recently, an in situ hybridization assay for tRNAs was developed by Hopper and co-workers [54] and in our lab (Grosshans et al., unpublished data). With this assay, it was possible to demonstrate that mutations in nucleoporins, Rna1p, and Los1p cause accumulation of tRNA. From the *Xenopus* oocyte system it is known that tRNAs with immature 5′ and 3′ ends are not efficiently exported from the nucleus. Surprisingly, tRNAs are also aminoacylated inside the nucleus, which is a trigger for efficient tRNA export [55,56]. Intranuclear aminoacylation of tRNA is therefore suggested to be a proofreading mechanism to ensure that only correctly matured and aminoacylated tRNAs will be exported. Whether this is also true for yeast remains to be shown.

2.3. snRNAs

Very little is known about the biogenesis of snRNAs in yeast [57]. In higher eukaryotes, snRNAs are monomethylated at the 5′ end, which is a signal for nuclear export. Both the CBP80/20 complex, which binds to the 5′ monomethyl cap,

and Crm1 (snRNA export is inhibited by Rev NES peptides) appear to be involved in the export process [58–60]. After arrival in the cytoplasm, the snRNA is hypermethylated and the Sm proteins assemble. This creates a bipartite nuclear import signal. Recently, one of the import factors that binds to the trimethyl cap has been identified and named snurportin [61]. As importin α, snurportin acts as an adapter by binding to the hypermethylated 5′ cap structure and to importin β. In yeast, no evidence has been obtained that snRNAs leave the nucleus. Thus, yeast snRNPs may assemble inside the nucleus without export and re-import steps [57].

2.4. rRNAs

The nucleolus is the site of ribosomal assembly. Similar to mRNA, rRNA leaves the nucleus only in association with proteins, i.e. as ribosomal particles [62,63]. Until recently, little was known about nuclear export of ribosomal particles since reliable rRNA export assays (e.g. by in situ hybridization of rRNA) were not available. First clues come from an in vivo assay developed to monitor nuclear export of ribosomes by following the GFP-tagged ribosomal protein L25 [64]. With this assay it was shown that mutants defective in the Ran cycle (Gsp1p, Rna1p, Prp20p) and certain nucleoporin mutants (such as Nsp1p, Nup49p, and Nic96p) cause defects in the export of ribosomes. Other nucleoporin mutants (such as Nup85p which is involved in mRNA export), pse1-1 (ribosomal protein import), xpo1-1 (export of NES-containing proteins), and *los1*$^{-}$ mutants (tRNA export) export ribosomes normally. Thus, Ran and its modulating factors, as well as some nucleoporins, are involved in the export of ribosomes. Employing this in vivo export assay, it should be possible to identify the ribosomal export receptor(s).

3. Discussion

Although several components involved in the export of mRNA, tRNA, and rRNA have been identified, the mechanism of RNA export (in particular for mRNA and rRNA) is not understood and many questions remain open. How is an RNA recognized as fully processed and therefore made export-competent? How do nuclear export factors interact with transport-competent hnRNPs and what are the nuclear export signals (on the RNA, the proteins, or both)? Which components are involved directly in RNA export and which ones play a role in RNA folding and RNP assembly? How does transport occur within the NPC environment and are there delivery routes from the pores to the sites of translation? Thus, it is evident that many questions still remain open in the field of nuclear RNA export through the nuclear pores.

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