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RNA Export

Review

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RNA export from the nucleus can be divided into two general phases. The first involves ribonucleoprotein (RNP) movement from the site of RNA transcription and RNP assembly to the nuclear pore complex (NPC). Proposed mechanisms for this step include diffusion and motor-driven transport along a nuclear skeleton or matrix (reviewed by Rosbash and Singer, 1993), but definitive support for either hypothesis is currently lacking. Intranuclear movement is followed by translocation of the RNP through the NPC. In favorable cases (when the RNP is very large), this can be visualized in the electron microscope (see Figure 1).

The study of RNA export is still at an early stage, and our understanding of the process is fragmentary. This review will therefore mainly summarize the data implicating various factors in the export process. Some nucleoporins (NPC proteins) have roles in RNA export, and the small GTPase Ran, together with its cofactors RCC1 and RNA1, is involved. In addition, a few RNA-binding proteins that may mediate RNP transport have been identified. However, nothing is known about the detailed mode of action of any of these factors in export, nor about how they interact with each other. It is highly likely that translocation through the NPC is associated with alterations in RNP composition, but details of these changes or of their functional significance for export have not been elucidated. Diverse approaches have been used to study RNA export, and we will not attempt to portray the field as an integrated whole. Instead, we will discuss how different aspects of the problem have been tackled and where they may converge in the future.

Experimental Approaches

To date, two radically different strategies have provided much of our insight into RNA export. These are microinjection into Xenopus oocytes and examination of yeast mutants. In the former, export of RNA can be monitored after nuclear injection either of purified or in vitro transcribed RNA or of DNA templates that are transcribed in the oocyte. Similar results are obtained following DNA or RNA injection, with accurate discrimination between substrates for nuclear retention versus export. In addition, similar kinetics of RNA export and susceptibility of export to mutations in the RNA are seen using both approaches (Zasloff, 1983; Jarmolowski et al., 1994; Terns and Dahlberg, 1994). This suggests that, at least in Xenopus oocytes, RNA packaging and export can be uncoupled from transcription and processing events. The first basic observations in the field, for example, that RNA export is energy dependent and saturable and thus a carrier-mediated process, came from such microinjection experiments (Zasloff, 1983).

A genetic approach in Saccharomyces cerevisiae is facilitated by the fact that, in this organism, poly(A) localization probably accurately reflects that of mRNA (discussed by Kadowaki et al., 1994a). Disruption of mRNA export leads to a decline in cytoplasmic poly(A) and concomitant accumulation in the nucleus. Genes whose mutation affects RNA export can therefore be identified by screening strains that are temperature sensitive for growth for those that accumulate poly(A) in their nuclei at the restrictive temperature (Amberg et al., 1992; Kadowaki et al., 1992). While this is only the beginning of the task of finding out how each gene affects RNA export, these methods have already provided interesting and surprising results (see below).

These two in vivo approaches should ideally be complemented by in vitro assay methods, but there are obvious technical difficulties, such as how to make enough fully processed RNA in isolated nuclei to allow export to be detected. One possible approach would be to load isolated nuclei with labeled RNA export substrates if a method could be devised to do this without damaging the nuclear envelope. A biochemical approach to export factor identification would also necessitate a means of manipulating nuclear contents. Existing in vitro systems (see, e.g., Schröder et al., 1987) have not yet established their credentials as faithful reproductions of the export process, and progress in this area is highly desirable.

RNA-Binding Proteins as Export or Retention Factors

Accumulated data, such as analysis of the type of RNPs shown in Figure 1 (reviewed by Mehlin and Daneholt, 1993), make it clear that the substrate for export is not naked RNA, but RNP, implicating RNA-binding proteins as possible mediators of export. Several approaches have led to the identification of the candidate proteins listed in Table 1, although there is as yet no example in which a direct role in export has been proven. Given the size and complexity of nuclear RNPs, it seems likely that several different proteins may combine to determine the rate of export of an RNA.

Among the most abundant nuclear RNA-binding proteins in metazoan cells are the heterogeneous nuclear RNP (hnRNP) proteins. One member of this family, hnRNP A1, shuttles rapidly between the nucleus and cytoplasm and is associated with poly(A)$^+$ RNA in both compartments (Piñol-Roma and Dreyfuss, 1991, 1992). A1 may therefore accompany mRNA to the cytoplasm and could mediate its export. A subset of the hnRNP proteins behave similarly to A1 while others, like hnRNP C, are bound to poly(A)$^+$ RNA in the nucleus, but dissociate before or during mRNA transport and remain in the nucleus (reviewed by Piñol-Roma and Dreyfuss, 1993). The yeast Nop3p/Npl3p protein (Table 2) exhibits considerable sequence and structural similarity to hnRNP proteins from other organisms

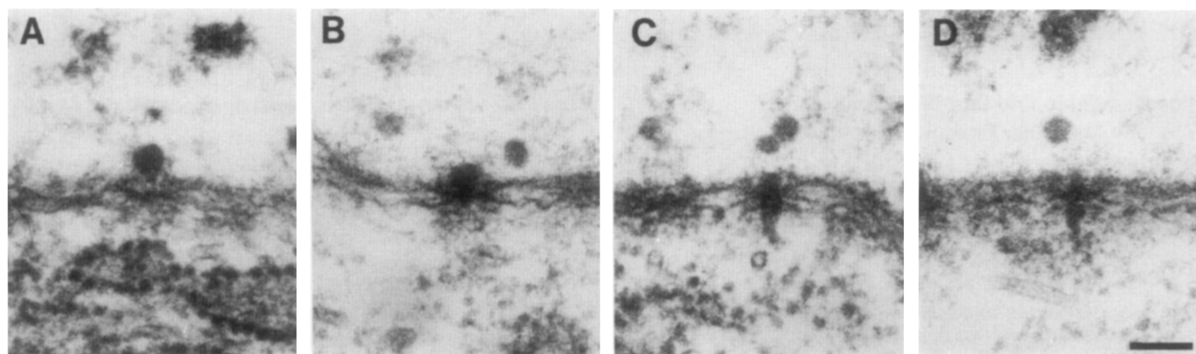

Figure 1. RNP Translocation through the NPC

Chironomus salivary gland cell nuclei synthesize Balbiani ring RNPs. They have a mass of roughly 30 MDa and contain 35–40 kb of RNA. After transcription, the Balbiani ring RNPs adopt a compact folded structure that, after docking at the NPC (A), progressively unfolds during translocation (B–D). The RNP that crosses the NPC is composed of a 7 nm basic filament folded into a structure with a diameter of roughly 25 nm. Since the passive diameter of the NPC for diffusion is roughly 9 nm, this and other examples underline the large conformational changes in the NPC that accompany active transport. Figure reprinted with permission from Mehlin et al. (1992).

and, like A1, shuttles between the nucleus and cytoplasm (Flach et al., 1994). Mutant forms of Nop3p/Npl3p have pleiotropic effects that include both blocking protein import into and mRNA export out of the nucleus (Flach et al., 1994; Wilson et al., 1994; Russell and Tollervey, 1995; Singleton et al., 1995), lending genetic support to the possibility that hnRNP proteins play a role in nucleocytoplasmic transport.

The export of several classes of RNA (transfer RNAs [tRNAs], 5S ribosomal RNA [rRNA], U small nuclear RNAs [snRNAs], and mRNAs) is specifically saturable in the sense that a given tRNA, for example, can competitively inhibit the export of other tRNAs, but does not affect other classes of RNA (Jarmolowski et al., 1994). The export of different RNAs must therefore be mediated by factors that are, at least in part, distinct and class specific. These observations have been further exploited to characterize factors that may be involved in the export of U snRNAs. Earlier work had suggested that U snRNA export might involve recognition of the 5′ cap structures of these RNAs, although there was not complete agreement about the relative magnitude of the direct contribution of the cap to RNA export as compared with other effects such as nuclear RNA stablity (Hamm and Mattaj, 1990; Izaurralde et al., 1992; Terns et al., 1993). By using U1 snRNA derivatives carrying different cap structures as competitors of export, it was possible to demonstrate unequivocally that the export of U snRNAs requires a saturable factor that binds to their 5′ caps (Jarmolowski et al., 1994). This led to the purification of a nuclear cap-binding protein (CBP) complex composed of two proteins, CBP80 and CBP20, whose properties are suggestive of a role in RNA export (Izaurralde et al., 1994). Interestingly, a 5′ cap appears to be less important in mRNA export than in the case of the U

Table 1. RNA-Binding Proteins Implicated in Export

Protein	Involved in Export	Other Functions	Location
hnRNP A1	Of mRNA	RNA packaging and RNA processing	Mainly nuclear
CBP80 and CBP20	Of U snRNA and mRNA	Pre-mRNA splicing	Mainly nuclear
3′-end processing activity[a]	Of histone mRNA		Nuclear
SRP9/SRP14[b]	Of SRP RNA (7SL)	Protein secretion	Mainly cytoplasmic
GAPDH[c]	Of tRNA	Glycolysis	Mainly cytoplasmic
TFIIIA	Of 5S rRNA	Transcription	Mainly nuclear
L5	Of 5S rRNA	Ribosomal protein	Mainly cytoplasmic
Rev	Of HIV mRNA	Pre-mRNA splicing	Mainly nucleolar

[a] Eckner et al., 1991.
[b] He et al., 1994.
[c] Singh and Green, 1993.
For other references see text.

Table 2. Yeast Genes Involved in mRNA Export

Gene	Protein Function	Location	Other Effects of Mutation
RNA1	GAP	Cytoplasmic	Pleiotropic
[*RCC1*] *PRP20*[a]	GEF	Nuclear	Pleiotropic
[*Ran/TC4*] *CNR1/CNR2*[b]	GTPase	Mainly nuclear	Pleiotropic
MTR2 to *MTR16*[c]	Various		
RAT1 to *RAT7*[d]	Various		
NOP3/NPL3	hnRNP protein	Mainly nuclear	Protein import: pre-rRNA processing
MAS3[c]	Heat shock transcription factor	Nuclear	Mitochondrial protein import

[a] The mammalian homolog is *RCC1*.
[b] The mammalian homolog is *Ran/TC4*.
[c] Kadowaki et al., 1994a.
[d] Amberg et al., 1992.
For other references see text. The S. pombe homologs of *RCC1* and *Ran* are *PIM1* and *SPI1*, respectively. Alternative names for *PRP20* are *MTR1* and *SRM1* and for *CNR1* and *CNR2*, *GSP1* and *GSP2*. *NOP3/NPL3* has also been called *MTS1*, *MTR13*, and *NAB3*.

snRNAs (Jarmolowski et al., 1994). This approach, consisting of the identification of the features of an RNA required for its export followed by a search for nuclear factors that recognize these features, could in principle also be applied to other RNAs.

A complementary approach has been to make use of RNA mutants that are defective in nuclear export and to correlate this change in transport activity with a difference in protein binding between the mutant and wild-type RNAs. For example, a number of mutants in human initiator methionyl tRNA or in 5S rRNA that are not exported have been characterized (Zasloff et al., 1982; Tobian et al., 1985; Guddat et al., 1990). For 5S rRNA, it was shown that mutants that could bind neither to ribosomal protein L5 nor to transcription factor IIIA in vivo were not exported from the nucleus, suggesting that interaction with either of these proteins might be sufficient for export (Guddat et al., 1990). Whether these or the other proteins identified in a similar way (glyceraldehyde-3-phosphate dehydrogenase and SRP9/SRP14; see Table 1) are genuine export factors remains to be seen, since the absence of export of a mutant RNA could result not only from the loss of interaction with an export factor but also from the gain of a novel interaction with some nuclear component that leads to its retention. That particular RNAs are retained in the nucleus via binding was shown by Legrain and Rosbash (1989), who demonstrated that interaction with components of the splicing machinery prevented pre-mRNA export. More recently, Terns and Dahlberg (1994) provided an example of a mature nuclear RNA, the U3 small nucleolar RNA, that seems to be retained in the nucleus by interaction with a saturable factor.

Regulation of RNA Export

One example of regulation of cellular RNA export involves maternal histone mRNAs that are stored in the nucleus of the oocytes of certain sea urchin species and released during oocyte maturation (Showman et al., 1982; De Leon et al., 1983). A second but less well-established case is that of some Drosophila mRNAs that are produced at the cellular blastoderm stage of embryonic development. These RNAs are confined to particular regions of the cytoplasm, on one side or the other of the nucleus, and it has been suggested that vectorial export from the nucleus may be the mechanism by which they are localized (reviewed by St Johnston, 1995 [this issue of *Cell*]).

Currently, there is no detailed information on the mechanism of these examples of regulation. However, several viral proteins have been implicated in either positive or negative regulation of RNA export (Krug, 1993; Fortes et al., 1994). The best studied of these proteins is Rev, a human immunodeficieny virus (HIV) protein that is required for the nuclear export of the partially spliced or unspliced viral RNAs that are essential for completion of the HIV life cycle. Rev only affects RNAs to which it binds via a specific site, the Rev response element (RRE). Consistent with a role in RNA export, Rev has been shown to shuttle between nucleus and cytoplasm, although shuttling occurs even in the absence of RRE-containing RNAs (Meyer and Malim, 1994; Kalland et al., 1994). There has been a long-standing controversy as to whether the action of Rev is best explained by a direct, positive effect on RNA export or by its ability to dissociate pre-mRNA splicing factors and thus prevent nuclear retention of incompletely processed RNAs (reviewed by Cullen and Malim, 1991). It was therefore of interest when Fischer et al. (1994) showed, using RNA and Rev microinjection into Xenopus oocytes, that Rev can stimulate the export of RNA from the nucleus in these cells in the complete absence of RNA processing events. This required both the presence of an RRE in the RNA and an intact "activation" domain in the Rev protein. Mutation of the latter eliminates Rev activity in HIV infection and also prevents Rev shuttling between the nucleus and cytoplasm in somatic cells (Meyer and Malim, 1994). The requirement for both an RRE and the Rev activation domain provide an argument that Rev functions similarly in oocytes and in somatic cells. Even if this is not the case, study of Rev action in oocytes may provide much-needed insight into the general problem of how RNA-binding proteins might stimulate RNP export. The discovery that Rev can work in yeast may also allow a genetic approach to the problem, although currently the

Table 3. Yeast Nucleoporins Implicated in RNA Export

Nucleoporin	Genetic or Physical Interactions	Other Effects of Mutation
Nup49p[a]	Nsp1p, Nup133p	Protein import
Nup133p/Rat3p	Nup49p, Nup159p, Nup1p, Nsp1p	Protein import, NPC clustering
Nup159p/Rat7p	Nup133p	NPC clustering
Nup145p[b]	Nsp1p, Nup100p, Nup116p	Protein import, NPC clustering, nuclear envelope defects
Nup116p[a,c]	Nsp1p, Nup145p, Nup100p	Nuclear envelope defects
Nup100p[d]	Nup116p, Nup145p	None
Nup1p	Rna1p, Srp1p, Nup2p, Nup133p, Nsp1p	Protein import, nuclear envelope defects

[a] Wimmer et al., 1992.
[b] Wente and Blobel, 1994.
[c] Wente and Blobel, 1993.
[d] Wente et al., 1992.
For additional references see text.

evidence is consistent with the action of Rev here involving inhibition of splicing (Stutz and Rosbash, 1994). In summary, there are several strong candidates for factors that directly affect RNA binding export, and further investigation of how they function should be rewarding.

Genes Encoding Export Factors

A genetic screen for yeast mutants that accumulate poly(A)$^+$ RNA in their nuclei led to the identification of the *rat* (ribonucleic acid trafficking) (Amberg et al., 1992) and *mtr* (mRNA transport) mutants (reviewed by Kadowaki et al., 1994a). Study of the phenotypes of the mutants (Tables 2 and 3) revealed that they accumulate nuclear poly(A) in distinct patterns, suggesting that they might affect, directly or indirectly, different aspects of RNA export. Examples are mutants (e.g., *mtr2*) that accumulate poly(A) in a few large granular structures and others (e.g., *mtr12*) in which poly(A) is concentrated at the nuclear periphery (Kadowaki et al., 1994a, 1994b). Unexpectedly, among the genes whose mutation results in nuclear poly(A) accumulation are several that encode nucleolar proteins. Indeed, several *mtr* mutant strains have defects in rRNA processing, and some exhibit nucleolar fragmentation or enlargement at the restrictive temperature. In these strains, poly(A) colocalizes with nucleolar proteins (Kadowaki et al., 1994a, 1994b). This might suggest that nucleolar components function in mRNA export, although it is also possible that nucleolar disintegration would allow many nucleolar RNA-binding proteins that are normally masked to associate nonspecifically with poly(A)$^+$ RNA.

It was more predictable that mutations in components of the NPC would cause nuclear poly(A) accumulation. Previous work had shown that both monoclonal antibodies directed against NPC components and wheat germ agglutinin, a lectin whose target is thought to be NPC glycoproteins, inhibit the export of various classes of RNA when injected into Xenopus oocytes (Featherstone et al., 1988; Bataillé et al., 1990; Neuman de Vegvar and Dahlberg, 1990; Terns and Dahlberg, 1994). Two NPC proteins or nucleoporins, Rat7p/Nup159p and Rat3p/Nup133p, were identified in one of the yeast mutant screens (Table 3). The *NUP133* gene interacts genetically with both *NUP159* and another nucleoporin gene, *NUP49* (Doye et al., 1994; Gorsch et al., 1995; Li et al., 1995). Certain alleles of *NUP159*, *NUP133*, and *NUP49* specifically affect RNA export but not protein import. (There is also an allele of *NUP49* that preferentially affects protein import [Doye et al., 1994].) This suggests that these mutations do not simply cause a general structural disruption of the NPC. It may be that all three nucleoporins are part of a subdomain of the NPC necessary for RNA export or, alternatively, that they interact with mRNPs during export.

The suggestion that nucleoporins might directly interact with exported RNPs received some support from the study of *NUP145*, *NUP116*, and *NUP100* (Table 3). The products of these three genes share a common motif, the nucleoporin RNA-binding motif (NRM), that is capable of binding homopolymeric RNA in vitro. Deletion of the NRMs showed that all three participate in a redundant but essential function (Fabre et al., 1994). The suggestion was therefore made that the NRMs either might be involved directly in RNA export or might bind to a (hypothetical) RNA component of the NPC (Fabre et al., 1994).

The nucleoporin mutants with specific effects on RNA export offer a way to identify additional components of the export machinery, by screening for suppressors or enhancers of their effects. This approach has already been used by several groups to reveal extensive genetic interactions among nucleoporins (Table 3). In the case of *NUP1*, genetic interactions with other genes whose products are of particular interest have been reported. *NUP1* interacts genetically with both *RNA1* and *SRP1* (Belanger et al., 1994). *RNA1* encodes a protein whose Schizosaccharomyces pombe and human homologs have recently been shown to activate the RanGTPase (see below). On the other hand, a Xenopus protein that is related in sequence to yeast Srp1p is essential for the import of proteins into the nucleus (Görlich et al., 1994). Although it is not yet clear whether yeast Srp1p has a similar function (see, e.g., Belanger et al., 1994), detection of these interactions underlines the promise of genetic methods both in identifi-

cation of transport factors and its potential to reveal cross-talk between different components of the transport machinery.

The RanGTPase Cycle

Ran is a GTPase that resembles other small GTPases like Ras and the Rabs (reviewed by Moore and Blobel, 1994). Guanine nucleotide binding or GTP hydrolysis by these GTPases is accompanied by a change in conformation. They then act, through conformation-specific binding, as bifunctional effectors that influence the behavior of proteins with which they interact. GTPases act in concert with two types of partner, GTPase-activating proteins (GAPs) that stimulate their GTP hydrolysis and guanine nucleotide exchange factors (GEFs) that stimulate dissociation of bound GTP or GDP. Since cellular GTP concentration exceeds that of GDP, this results in the net replacement of bound GDP by GTP.

A battery of studies have shown both in yeasts and vertebrates that homologs of Ran, RCC1 (a nuclear RanGEF), and RNA1 (a cytoplasmic RanGAP) are involved in both protein import into and RNP export out of the nucleus (Shiokawa and Pogo, 1974; Forrester et al., 1992; Kadowaki et al., 1992, 1993; Amberg et al., 1993; Belhumeur et al., 1993; Melchior et al., 1993a; Moore and Blobel, 1993; Bischoff et al., 1995; Cheng et al., 1995). For example, loss of RCC1 protein from the Chinese hamster tsBN2 cell line, whose mutant RCC1 is unstable at 40°C, results in accumulation of poly(A)$^+$ RNA in the nucleus (Kadowaki et al., 1993) and inhibition of nuclear export of spliceosomal U snRNAs (Cheng et al., 1995). Interestingly, tRNA export continues in tsBN2 cells at the nonpermissive temperature (Cheng et al., 1995), indicating that lack of RCC1, and thus of the only detectable RanGEF in tsBN2 cells (Bischoff et al., 1995), does not block all transport through the NPC. RCC1 is also necessary for the accumulation in the nucleolus of U3 snRNA (Cheng et al., 1995). Since the latter process can occur without U3 ever leaving the nucleus (Terns and Dahlberg, 1994), it is possible that RCC1 (and thus likely Ran) may also be required either for intranuclear RNP movement, as proposed by Cheng et al. (1995), or for nucleolar integrity.

How does the Ran cycle affect RNA export and protein import? RCC1 is nuclear, Ran is 80%–90% nuclear, and RNA1 is cytoplasmic (Ohtsubo et al., 1989; Hopper et al., 1990; Melchior et al., 1993b; Bischoff et al., 1995, and references therein). Studies in yeast show that mutation of either RCC1 or RNA1 has pleiotropic and, to a large extent, overlapping effects (Forrester et al., 1992). This strongly suggests that many of the consequences of mutation of either of these proteins results from the same primary defect, that in the RanGTPase cycle. There are problems with this, however. For example, there is evidence that both RNA export and protein import may need RanGTPase activity (Melchior et al., 1993a; Moore and Blobel, 1993; Schlenstedt et al., 1995). The predominant locations of the major GEF and GAP activities (i.e., RCC1 and RNA1, respectively) would, however, suggest that Ran-mediated GTP hydrolysis would only be favored in the cytoplasm and GDP/GTP exchange only in the nucleus. Thus, Ran would have to cross the nuclear envelope once in each direction to progress once through a complete GTPase cycle and to exhibit functional activity. An alternative hypothesis would be that Ran's cytoplasmic function in protein import depends on GTP hydrolysis, but its nuclear role in RNA export requires either GDP dissociation or GDP/GTP exchange. It is at this stage also possible to imagine that there might be sufficient RCC1 in the cytoplasm and RNA1 in the nucleus to allow for RanGTPase activity at both locations, even if their concentrations in these compartments are below the level of current detection methods. In the future, a better understanding of the role of Ran in transport will be obtained with the identification of other factors with which it interacts and whose activity it modulates.

In summary, the different sections of this review can be considered as parts in a puzzle. Progress in the field now depends on connecting the isolated fragments of information into a more complete picture. Success will require defining export in relation to the structure and function of the NPC, and here, as in other aspects, studies of nuclear protein import and RNA export will be of mutual benefit. Finally, study of RNA export may lead to—and will likely profit from—advances in understanding the functions of nuclear subcompartments.

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