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Review

Nuclear export of RNA: Different sizes, shapes and functions

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ABSTRACT

Export of protein-coding and non-coding RNA molecules from the nucleus to the cytoplasm is critical for gene expression. This necessitates the continuous transport of RNA species of different size, shape and function through nuclear pore complexes via export receptors and adaptor proteins. Here, we provide an overview of the major RNA export pathways in humans, highlighting the similarities and differences between each. Its importance is underscored by the growing appreciation that deregulation of RNA export pathways is associated with human diseases like cancer.

Contents

1. Introduction

The central dogma of molecular biology states that the flow of biological information is from DNA to RNA to protein. However, this flow of information encounters a physical barrier, the nuclear envelope, which encapsulates the genome and physically separates transcription within the nucleus from translation in the cytoplasm. This necessitates the continuous transport of RNA through the inner channel of nuclear pore complexes (NPCs). Cellular functions depend on accurate expression of both protein-coding and non-coding RNAs, which have important functions both in the nucleus and the cytoplasm. Non-coding RNAs are diverse in shapes and sizes and participate in RNA processing [e.g small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs)] as well as translation [e.g. ribosomal RNA (rRNA), transfer RNA (tRNA) and microRNA (miRNA)]. Protein and certain RNA cargoes, including rRNAs and snRNAs, are actively transported out of the nucleus by a family of conserved nuclear transport receptors that recognize leucine-rich

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nuclear export signals (NES) and bind directly with nucleoporins that line the central channel of the NPC [1]. In contrast, export of messenger RNA (mRNA) requires export adaptors such as the TREX (TRanscription-EXport) [2,3] and TREX-2 [4–6] complexes, which recognise mRNAs during early stages of their biogenesis. Cargo mRNAs from both TREX and TREX-2 are then transferred to transport factors such as the NXF1–p15 dimer for transit through nuclear pores by directly interacting with the nucleoporins that line it [7–10].

In this review, we provide an overview of the major RNA export pathways in humans, highlighting the similarities and differences between each (Fig. 1). We discuss current understanding of the more mechanistically complex mRNA export machinery and highlight the increasing evidence linking deregulation of RNA export pathways with human disease.

2. Export of mRNA

Efficient export of mature mRNPs is achieved by coupling the upstream processes in the gene expression pathway to mRNA export. Once export competent mRNPs have been generated in the nucleoplasm, they travel through zones of heterochromatin exclusion to NPCs [11–20]. One factor involved in the maintenance of these zones of heterochromatin exclusion is the nucleoporin TPR [21]. Once mRNPs reach NPCs, NXF1 facilitates their export through its interactions with the phenylalanine-glycine (FG) repeats of nucleoporins that line the central NPC transport channel [22–25]. Analysis of the kinetics of transport of individual mRNPs has revealed that there is a rate-limiting step at the nuclear basket, which is consistent with the complexity involved in recruitment, docking and release of cargo mRNPs prior to their transport through NPCs [13,14,16,17]. During and after translocation through NPCs, several mRNP binding components disassemble from the mRNP, exposing binding domains for cytoplasmic translation adaptors to bind and facilitate translation [26].

2.1. TREX

TREX is a highly conserved multi protein complex that plays a key role in the effective export of mRNA. It achieves this by integrating multiple steps of the gene expression pathway, namely transcription and splicing, with mRNA export [27,28]. In humans, TREX is recruited predominantly by the splicing machinery [29], is assembled in an ATP-dependent manner [30] and it binds the 5′ end of mRNA [2]. TREX consists of conserved core subunits such as ALY, UAP56 and the THO sub complex [3,29–46] (Fig. 1). ALY has also been recently shown to be recruited to the 3′ end of mRNA *in vivo* [47]. During splicing, UAP56 is recruited to the mRNP (messenger ribonucleoprotein) where it is involved in the ATP-dependent recruitment of ALY and CIP29 to the mRNP [30]. UAP56 mediates the association between these proteins and the THO sub complex, thus forming TREX [30]. The nuclear export activity of ALY is regulated by inositol polyphosphate multi-kinase (IPMK) and its catalytic product, phosphatidylinositol (3,4,5)-trisphosphate (PIP_3) [48]. Recent evidence has also implicated a post-transcriptional modification of RNA, 5-methylcytosine (m^5C), in the regulation of mRNA export. ALY specifically recognises m^5C, whose formation in mRNA is catalyzed by the RNA methyltransferase NSUN2 [49]. Interestingly, NSUN2 also modulates the nuclear-cytoplasmic shuttling and RNA-binding affinity of ALY [49]. Binding of ALY and UAP56 to mRNPs is mediated by the cap-binding complex (CBC), which couples transcription to maturation of mRNA [2,50,51]. The canonical CBC consists of NCBP1 and 2 subunits, however an alternate CBC has been identified consisting of NCBP1 and NCBP3 that functions in export of mRNA, with NCBP3 being pivotal for export under stress conditions [52]. A number of TREX adaptors can bind directly to mRNA to promote their export. These include ALY and THOC5, whose binding is crucial for the recruitment of NXF1 in a proposed two part mechanism. NXF1 exhibits an interdomain interaction between its RNA binding (RBD) and NTF2L domains that blocks the RBD from binding RNA [53]. It has been suggested that ALY partially destabilizes this interaction, which in turn allows the binding of THOC5 and full displacement of the RBD from the NTF2L domain allowing binding of RNA by NXF1 [53].

2.2. TREX-2 (also known as THSC in yeast)

Another conserved complex that links transcription to export is TREX-2. In humans, it is based around the scaffold of GANP (Germinal-centre Associated Nuclear Protein), to which other components including PCID2, DSS1, ENY2 and CETN2/3 bind [4,9]. In yeast, TREX-2 can bind nucleic acids, through the Sac3 homology domain of GANP (yeast Sac3), PCID2 (yeast Thp1) and DSS1 (yeast Sem1) [5]. A number of studies have demonstrated that TREX-2 is also associated with transcription. Thus, ENY2 and GANP interact with RNA polymerase II [4] and facilitate its recruitment to specific subsets of genes [54]. Moreover, in yeast, TREX-2 associates with the Mediator complex, an essential regulator of RNA polymerase II, to regulate transcription [55]. TREX-2 is located primarily at the NPC [4,9,56], however a fraction of GANP is also located within the nuclear interior [9]. Like TREX, mRNAs are transferred from TREX-2 to NXF1, however the mechanism is not well characterized (Fig. 1). NXF1 interacts directly with the N-terminal domain of GANP, which contains a cluster of 6 nucleoporin-like FG repeats, thus the higher concentration of FG repeats at NPCs may displace GANP and TREX-2 from NXF1, allowing its associated cargo mRNAs to pass through NPCs into the cytoplasm for translation [9]. Whether TREX and TREX-2 mediate alternative export routes or if they co-operate to export the same transcripts remains an important, unanswered question.

2.3. CRM1

Although a large proportion of mRNAs use TREX, TREX-2 and NXF1 receptors to transit through NPCs, a subset of mRNAs instead uses CRM1, the major protein-export receptor. A number of different types of RNA such as snRNA and rRNA also use CRM1 for their efficient export, which will be discussed extensively in the next section (Fig. 1). CRM1 itself does not bind RNA. Instead, CRM1 is recruited via NES-containing adaptor proteins that bind directly to RNA or to other RNA-binding proteins in a mechanism analogous to protein export [57–61]. One of these factors is eukaryotic translation initiation factor 4E (eIF4E), which along with CRM1, preferentially export a subset of mRNAs required for proliferation, survival, metastasis, and invasion [58–61]. Analysis of these mRNPs has shown that they do not contain NXF1 or ALY [61], suggesting that CRM1 performs a broadly similar function to NXF1 for these particular cargo mRNAs.

2.4. mRNA export competence and selectivity

Following maturation of mRNA, involving the addition of a m^7G cap at the 5′ end, splicing, and addition of poly(A) tails at the 3′ end, NXF1 is recruited to mature mRNPs by TREX and/or TREX-2 in the nucleus. How mRNPs acquire export competence remains an area of active study. Clues have come from a number of recent yeast studies. For example, the ISW1 chromatin remodelling complex was shown to be an mRNP nuclear export surveillance factor that retains export-incompetent transcripts near their transcription site [62]. Furthermore, stress-responsive transcripts can be exported by

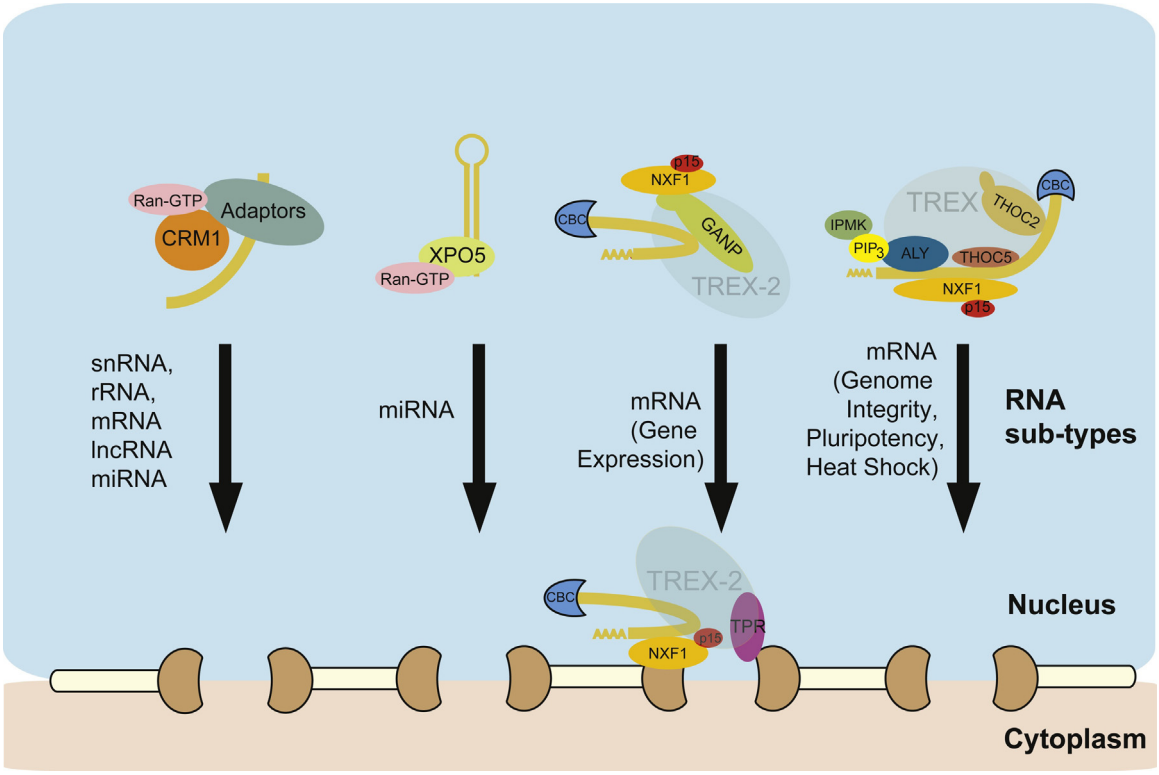

Fig. 1. Nuclear export of different RNA subtypes.
This figure outlines the different nuclear export pathways used by snRNA, rRNA, lncRNA, and different subsets of miRNA and mRNAs. CRM1 is recruited by a variety of NES-containing adaptor proteins (labelled Adaptors) that bind directly to specific subtypes of RNA or to other RNA-binding proteins to export different RNA subtypes. miRNAs are predominantly exported by Exportin-5 and RanGTP, while a family of pre-miRNAs bearing a m^7G-cap at their 5′-end is exported by CRM1 and PHAX. The major mRNA export complexes (TREX and TREX-2) and the functional subsets of transcripts that they export are also indicated. The cap binding complex (CBC) is indicated. The proteins highlighted are those that have been shown to function in selective mRNA export. Although the majority of mRNAs use TREX, TREX-2 and NXF1 export receptors to transit through NPCs, a subset of mRNAs involved in proliferation, survival and metastasis use CRM1.

yeast NXF1 independent of adaptor proteins, whose bound mRNAs normally undergo quality control [63]. This finding provides key insights into export competence, and how stress-responsive transcripts can be rapidly exported at the cost of error-free mRNA formation to ensure that cells can respond quickly to external stimuli [63]. Another potential mechanism involves the SR (Serine-Arginine rich) proteins, which promote recruitment of splicing factors to 5′ and 3′ splice sites and couple splicing to mRNA export [64–67]. Indeed, SRSF3 and SRSF7 couple alternative splicing and polyadenylation to NXF1-mediated mRNA export by recruiting NXF1 to the 3′ UTR of target transcripts [68].

Recent work has demonstrated that specific biological pathways can be regulated by selective mRNA export, giving priority to some sets of mRNA over others [69]. Selective mRNA export can modulate the efficiency of DNA repair, gene expression, stress responses and proliferation, as well as developmental processes such as pluripotency and haematopoiesis [36,38,48,60,61,70–73]. In most of these cases, selectivity is mediated by components of the TREX and TREX-2 complexes as well as CRM1 [69]. Indeed, a number of TREX components including THOC5 preferentially regulate the nuclear export of mRNAs encoding factors required for haematopoietic development [38]. THOC2 and THOC5 can regulate the nuclear export of mRNAs encoding proteins required for pluripotency establishment [71]. TREX component ALY, along with IPMK and its catalytic product, PIP_3 function to preserve genome integrity by controlling the nuclear export of transcripts that encode proteins essential for accurate genome duplication and repair [48] (Fig. 1). TREX-2, through GANP, also promotes the nuclear export of specific classes of mRNA required for gene expression itself, such as RNA processing, splicing, mRNP and ribosome biogenesis [70]. Lastly, CRM1 and eukaryotic translation initiation factor 4E (eIF4E) preferentially export a subset of mRNAs that encode proteins involved in proliferation, survival, metastasis, and invasion [58–61]. How these selective mRNA export pathways are activated and regulated remain poorly understood. One potential mechanism may be through m^5C modification of mRNA. As previously discussed, ALY specifically recognises m^5C, whose formation in mRNA is catalyzed by the RNA methyltransferase NSUN2 [49]. Presumably only a subset of mRNA is modified by m^5C, raising the attractive possibility that m^5C and ALY may regulate pathways of selective mRNA export. Strikingly, a nuclear virus can also modulate selective mRNA export. Thus, herpesvirus protein ORF10 can selectively inhibit cellular mRNA export to restrict host gene expression for optimal replication [74]. This indicates that selective mRNA export is a crucial mechanism for regulating patterns of gene expression from the human transcriptome.

It remains possible that cell-type specific TREX complexes may exist and regulate selectivity. In support of this, ALY and UAP56 were not required for embryonic stem cell (ESC) maintenance, whereas THOC2 and THOC5 expression correlated with the pluripotent state of ESCs [71]. Adding to complexity, multiple TREX components and mRNA export components in general have been shown to exhibit redundancy. For example, a paralogue of UAP56 – DDX39 has been shown to bind ALY and CIP29, and both RBM15 and RBM15B have also been shown to bind NXF1 [53]. However, DDX39 has been proposed to target a separate set of transcripts [75]. Interestingly, a recent study found that a number of novel short linear peptide motifs are shared between a variety of mRNA export adap-

tors including TREX components [26]. The combination of different motifs may determine the specificity of a given export adaptor for certain mRNA targets and provide an explanation for the observed plasticity of mRNA export factors [26].

3. Export of other types of RNA

Non-coding RNAs have been shown to be important regulators of gene expression and can affect a plethora of biological processes through different mechanisms. They display different cellular localization patterns, with some concentrated in the cytoplasm and others in the nucleus. While some RNAs can use similar pathways to those used for mRNA export, others such as rRNAs and snRNAs use CRM1, while miRNAs predominantly use Exportin-5 for their efficient export (Fig. 1). Specific export mechanisms for non-coding RNAs are discussed below.

3.1. Long-non-coding RNA

Long-non-coding RNA (lncRNA) is an interesting class of RNAs that have attracted much research interest in the past decade due to their diversity in origin and especially their versatility in function at both transcriptional and post-transcriptional levels. LncRNAs are able to interact with DNAs, RNAs, and proteins to carry out their roles, which include histone modification, transcriptional activation or repression via recruitment and formation of gene regulatory complexes, titration of miRNAs and proteins, as well as modulating protein translation and function [76,77].

Traditionally, lncRNAs are defined as non-protein-coding transcripts that exceed 200nt in length. Similar to mRNAs, lncRNAs are transcribed by RNA Pol II and have to be processed to be fully functional. This includes 5′-cap addition and polyadenylation, and many lncRNAs are also alternatively spliced [78]. Depending on their physical locations within the genome, lncRNAs can be divided in four groups: (i) large intergenic non-coding RNAs (lincRNAs) involving transcripts with an average length of 1 kb that lie in regions between coding genes; (ii) natural antisense transcripts arising from transcription of the antisense strand, forming a sense-antisense (SAS) pair with the mRNA on the opposite sense strand (up to 70% of mRNA transcripts may have equivalent anti-sense transcripts); (iii) pseudogenes, whose coding potential is lost due to mutations and may acquire new functions through epigenetic modifications; and (iv) long intronic ncRNAs nested within introns flanking protein coding exons [76].

The discrepancy in the cellular localization of lncRNAs is an intriguing feature that deserves further investigation. While the nuclear export mechanisms for lncRNAs still remain elusive, lncRNAs appear to be more concentrated in the nucleus compared to their mRNA counterparts. Given that both lncRNAs and mRNAs possess a methyl-guanosine cap and poly(A) tail, features that are critical for mRNA export, the nuclear accumulation of lncRNAs suggests a potential retention mechanism being in place to prevent lncRNAs from being exported. Indeed, in yeast, comparison of the maturation pathways of mRNAs and lncRNAs suggested that transcript fate is largely determined during 3′ end formation, with the length of the poly(A) tail a determinant for this process [79]. Most of these lncRNAs are targeted for nuclear surveillance [79]. Furthermore, a recent study in yeast has implicated transcription elongation factor Paf1 in control of differential nuclear export of mRNAs and nuclear retention of the majority of lncRNAs [80]. Since lncRNAs resemble mRNAs in structure, lncRNAs and mRNA may share the same export pathways, but with different sets of adaptor proteins. Interestingly, a recent study identified CRM1 and human antigen R (HuR) as the nuclear export mediators of lncRNA *RMRP*, the RNA component of the RNA processing endoribonuclease (RNase MRP) [81]. CRM1 is recruited via HuR, a known nuclear export adaptor for some mRNAs [57,82], to both the 3′ and 5′ ends of RMRP to mediate its export into the cytoplasm [81]. It will be important to determine the potential overlap between the export machinery for lncRNAs and mRNAs. Moreover, if lncRNAs undergo the same nuclear export route as mRNAs, the underlying mechanisms for selective retention of lncRNAs rather than mRNAs in the nucleus remain to be elucidated in humans.

3.2. Ribosomal RNA

Ribosomes are multi ribonucleoprotein complexes that are fundamental to effective gene expression [83]. Ribosome biogenesis is a highly regulated, energy intensive process that takes place in both the nucleus and the cytoplasm. Ribosomal RNA (rRNA) is exported following assembly with ribosomal proteins into pre-60S and pre-40S subunits. Pre-60S and pre-40S subunits are formed in the nucleolus from ribosomal proteins (translated from RNA transcribed by RNA Pol II) and rRNA (transcribed by RNA Pol I and RNA Pol III) [84]. Following formation, pre-40S and pre-60S subunits are exported to the cytoplasm where they are processed and combined to form the mature 80S ribosome [83,85]. Hence, formation of the 80S ribosome is compartmentalised, involves 3 different RNA polymerases and is highly complex. Indeed, around 300 factors have been implicated in human ribosome biogenesis [83,84,86,87].

The machinery involved in the nuclear export of ribosomal subunits is diverse and exhibits differences between yeast and humans. In yeast, ribosomal subunits can be exported using pathways normally used for mRNA export (through Mex67, the yeast homolog of NXF1) or protein export (CRM1) [88–90]. In contrast, NXF1 was not identified in a screen for human 60S export factors, and did not co-purify with the 60S subunit [86]. While this suggests that NXF1 may not be essential in export of the 60S subunit in humans, it remains possible that it plays a redundant/backup role. Export of the human pre-60S subunit depends on both CRM1 and Exportin-5 in a RanGTP dependent manner [86,91]. NMD3 acts as an adaptor for CRM1–RanGTP mediated 60S subunit export, by a mechanism that is conserved from humans to yeast [91]. Given the size of the ribosomal subunits (>2 MDa), it is not surprising that the large pre-60S complex requires more than one transport adaptor; indeed it is highly likely that other unidentified adaptors may also facilitate the export of the pre-60S complex. CRM1, along with RPS15, also functions in the nuclear export of the pre-40S subunit in humans, with RPS15 implicated in CRM1's pre-40S export function [92]. Due to the lower complexity and smaller size of the 40S subunit, it is possible that fewer adaptors of the pre-40 s subunit exist [93].

3.3. miRNA

MicroRNAs (miRNAs) play a critical role in gene regulation at the post-transcriptional level in mammals through mRNA degradation and translational repression [94]. miRNAs guide the RNA-induced silencing complex (RISC) to the targeted mRNAs to be degraded through RNA enzymatic cleavage, hence modulating the level of mRNA available for translation within cells [95]. The canonical export pathway for miRNAs involves Exportin-5 (XPO5) [96–98], while CRM1 acts as an alternative export route for a subset of miRNAs [99].

The maturation of miRNAs involves several steps, commencing in the nucleus with transcription of miRNA coding genes nested within introns or residing at separate genomic loci to produce primary miRNAs (pri-miRNA), which are then subjected to sequential enzymatic cleavage in both the nucleus and cytoplasm. Traditionally, the pri-miRNAs are first processed by the nuclear RNase III DROSHA and DGCR8 to produce 60–80nt long precursor miRNAs

(pre-miRNAs) which contain a loop at the top connecting to a double-stranded-RNA (dsRNA) stem at the base with a 2 nucleotide (2nt) overhang at the 3′-end [100]. Pre-miRNAs are subsequently exported to the cytoplasm by Exportin-5 in a RanGTP-dependent manner [96–98] (Fig. 1). In the cytoplasm, DICER further excises the RNA loop to isolate a ∼22nt RNA duplex, from which one strand, either 3′ or 5′, is selected by Argonaute (AGO) and assembles with other proteins to form a functional RISC complex [101]. However, alternative pathways for pre-miRNA processing have been identified which bypass selected nuclear enzymatic cleavage reactions and also employ distinct nuclear export factors such as CRM1 [99].

The crystal structure of the Exportin-5 complex bound to pre-miRNA reveals that the two nucleotide 3′ overhang of pre-miRNAs functions as a RNA recognition signal allowing its interaction with Exportin-5 through strong ionic and hydrogen bonds, while a baseball mitt-like structure of Exportin-5 stabilises the dsRNA stem, protecting pre-miRNAs from degradation [102]. Since export of pre-miRNA is a rate-limiting step in the miRNA maturation process, efficient binding of Exportin-5 to pre-miRNA is critical for regulating miRNA biogenesis. It has recently been shown that nuclear export of pre-miRNA can be suppressed by phosphorylation of Exportin-5 following ERK activation [103]. Furthermore, ERK also phosphorylates nucleoporin NUP153 to inhibit translocation of Exportin-5 into the cytoplasm, resulting in Exportin-5 and pre-miRNA being retained in the nucleus [103].

Interestingly, CRM1 can also function in the nuclear export of a family of pre-miRNAs bearing a m^7G-cap at their 5′-end [99]. This involves the recruitment of PHAX as an adaptor to anchor pre-miRNA to CRM1 [99]. How PHAX binds to pre-miRNA is unclear, however it may involve the cap-binding-complex (CBC) deposited at the 5′-end of capped pre-miRNA, given that the interaction between PHAX and CBC is required for nuclear export of snRNA via the CRM1 pathway [104,105]. Overall, cross-talk between different export pathways may exist to ensure that no RNA subtype is completely deprived should its primary export route be compromised. It is important to note that different export pathways are selective for specific subtypes of RNAs, except in the case of CRM1, which can export a variety of RNA subtypes. This raises an interesting question about which factors determine the preferential export pathway of each RNA subtype, and why.

4. RNA export and human disease

4.1. mRNA export

Given the importance of the nuclear export machinery in gene expression and the maintenance of genome integrity [106], it is unsurprising that multiple TREX and TREX-2 components have been implicated in human diseases, including cancer. For example, the expression patterns of THOC1, ALY and other TREX components differ among several tumours [107] and have been implicated in tumour metastasis and tumourigenesis [108–110]. Furthermore, Luzp4, an mRNA export adaptor that interacts with TREX component UAP56, is upregulated in a range of tumours including melanomas [111]. TREX-2 component GANP is upregulated in lymphomas [112]. Lastly, the selective mRNA export function of eIF4E, which uses CRM1 to export transcripts required for cell proliferation, also contributes to its oncogenic potential [72]. Thus, cancer cells may sustain proliferation by altering pathways that regulate selective mRNA export, raising the possibility that mRNA export might be an attractive therapeutic target. mRNA export derangements may also contribute to other diseases. Indeed, recent work has implicated mutations in THOC2 and THOC6 in intellectual disability [113,114], mutations in GANP in Charcot-Marie-Tooth neuropathy [115], while mutations in mRNA export factor GLE1 are implicated in both autosomal recessive motor neuron disease [116] and in amyotrophic lateral sclerosis (ALS) [117].

4.2. Non-coding RNA

The activity and levels of non-coding RNAs are altered in a myriad of diseases. We will focus here on a few recent examples in cancer, encompassing ribosomal RNA, miRNA, long non-coding RNA and the proteins that export them. Increased rRNA transcription by RNA Polymerase I is a common feature of cancer and has been therapeutically targeted to selectively kill B-Lymphoma cells [118]. Given that the THO complex has been shown to be involved in transcription initiation and elongation by RNA Polymerase I in yeast [119], it is possible that altered ribosomal RNA export may play a role in neoplastic disease. Interestingly, CRM1 inhibitors have shown great promise in treating a variety of cancers including leukaemias [120–122]. While at least part of their effect may be due to inhibiting nuclear transport of proteins such as IκBα in the case of oncogenic KRAS lung cancer cells [122], it is likely that export of rRNAs and snRNAs will also be preferentially affected. This may explain why leukaemias are especially sensitive to CRM1 inhibitors, given their heavy reliance on altered RNA processing [123–125].

Given the important role of miRNAs in modulating gene expression, it is not surprising that alterations in miRNA expression are a common feature of many cancer subtypes [126]. As miRNA biogenesis involves multiple steps, abnormalities arising at any stage of miRNA processing could hinder effective miRNA maturation. In particular, nuclear export of pre-miRNA is a critical step whose impairment has important implications in tumourigenesis. For example, mutations in Exportin-5 were found to be prevalent in tumours with microsatellite instability, and human colorectal cancer cells harboring a frameshift mutation which disrupts the C-terminal domain of Exportin-5 were unable to form an export competent complex with pre-miRNA and RanGTP [127]. This resulted in nuclear retention of many tumour-suppressor miRNAs, concomitant with increased expression of oncoproteins such as MYC and K-RAS [127]. Importantly, re-introduction of wild-type Exportin-5 reduced cell viability and decreased tumourigenicity [127]. Another study demonstrated that increased phosphorylation of Exportin-5 by ERK resulted in nuclear retention of many miRNAs, which promoted tumor growth and drug resistance [103]. Together, these findings suggest that factors involved in miRNA export may be important therapeutic targets in cancer.

5. Perspectives

A number of studies have revealed in remarkable detail how different subtypes of RNA are exported from the nucleus to the cytoplasm in humans. Given the differences in size, shape and function of these protein coding and non-coding RNAs, it is unsurprising that a variety of different export pathways are employed. Nevertheless, one common nuclear export receptor used by rRNA, snRNA and subsets of miRNA, lncRNA and even mRNA is the general protein exporter, CRM1. In a mechanism analogous to protein export, CRM1 is recruited by a variety of NES-containing adaptor proteins that bind directly to specific subtypes of RNA or to other RNA-binding proteins. In contrast, efficient export of mRNA requires a number of conserved multi-protein complexes such as TREX, TREX-2 and the NXF1-p15 dimer. With the recent identification of selective mRNA export as a potentially significant mechanism for the control of patterns of gene expression from the human transcriptome, future research will provide key insights into how selective mRNA export pathways are regulated and how they are altered in disease.

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