Control of mammalian gene expression by selective mRNA export

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Abstract | Nuclear export of mRNAs is a crucial step in the regulation of gene expression, linking transcription in the nucleus to translation in the cytoplasm. Although important components of the mRNA export machinery are well characterized, such as transcription-export complexes TREX and TREX-2, recent work has shown that, in some instances, mammalian mRNA export can be selective and can regulate crucial biological processes such as DNA repair, gene expression, maintenance of pluripotency, haematopoiesis, proliferation and cell survival. Such findings show that mRNA export is an unexpected, yet potentially important, mechanism for the control of gene expression and of the mammalian transcriptome.

Messenger ribonucleoprotein particles (mRNPs). Complexes that are formed by coating of cellular mRNAs with RNA-binding proteins, ensuring correct packaging of mRNA for nuclear export.

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Before mRNA can be translated into protein, it must be processed and spliced into a mature transcript and then exported from sites of transcription and processing in the nucleus to the cytoplasm. Extensive detail has emerged on general mRNA export processes and their links to mRNA synthesis and processing. Although mRNA export was originally thought to be one of the few constitutive steps in the gene expression pathway, evidence is accumulating that mRNA export in mammalian cells can be highly selective, giving priority to some mRNAs over others.

Nuclear export of mature mRNAs to the cytoplasm occurs through nuclear pore complexes (NPCs) (BOX 1) and is mediated by transport factors such as the conserved nuclear RNA export factor 1 (NXF1) and its cofactor p15 (also known as NXT1) that bind and export mature, spliced mRNAs. Most mRNAs use the NXF1–p15 dimer to transit through NPCs, although a subset of endogenous mRNAs and viral RNAs use chromosome region maintenance 1 protein homologue (CRM1; also known as exportin 1), which is the main protein export receptor. Transport through an NPC is achieved by overcoming the permeability barrier that is generated by nuclear pore proteins known as FG-nucleoporins. These line the NPC transport channel and have regions that are rich in phenylalanine–glycine (FG) repeats. In addition to factors such as NXF1 and CRM1, which interact with FG-nucleoporins at NPCs, mRNA export involves adaptors that recognize mRNAs during early stages of their biogenesis. Two conserved complexes have key roles in the nuclear export of mRNA during early stages of biogenesis: transcription-export complex (TREX)[1–4] and TREX-2 (also known as the THSC complex in yeast) (REFS 5–9). Cargo mRNAs from both TREX and TREX-2 are transferred to NXF1–p15, which interacts directly with the FG-nucleoporins that line the channel to mediate transit through the NPC[10–13].

Although it is possible that a large proportion of mRNAs are exported through bulk export pathways, recent findings have shown that mRNA export can also be selective. In this Review, we first introduce the mechanisms of nuclear mRNA export in mammalian cells and then discuss the evidence for selective mRNA export in mammalian cells, and how it can regulate specific biological processes[14–22]. We also discuss the potential implications for selective mRNA export in the development of human cancers and genetic disorders.

Although there have been pioneering studies on mRNA export in yeast and in *Drosophila melanogaster*, there is an urgent need for a revision of nomenclature to adopt a consensus, and the use of different names for conserved factors in different phyla makes an integrated review difficult to write or understand. We therefore focus on mammalian cells in the interests of clarity and because of several clear differences between yeast and metazoa. Other excellent reviews discuss mRNA export in other organisms[23–29].

From nuclear transcription to the cytoplasm

Efficient export of mature messenger ribonucleoprotein particles (mRNPs) that originate from sites of transcription is achieved by coupling the upstream processes in the gene expression pathway — that is, transcription, splicing and polyadenylation — to mRNA export (FIG. 1).

Box 1 | **Transport through nuclear pore complexes**

A primary characteristic of eukaryotic cells is the physical separation of transcription in the nucleus and translation in the cytoplasm. The evolution of this nuclear–cytoplasmic compartmentalization requires the continuous transport of proteins and RNA molecules through nuclear pore complexes (NPCs), which is carried out by distinct nucleocytoplasmic transport machineries. NPCs are ~110 MDa macromolecular complexes[145] with an overall octagonal symmetry, which consist of several copies of ~30 proteins termed nucleoporins. These form a central structure, which is surrounded by cytoplasmic pore filaments and the nuclear basket, thus extending the reach of the NPC into the cytoplasm and nuclear interior, respectively (FIG. 2). As well as their well-defined role in protein import and export, NPCs also function in the export of mRNA, as depletion of nucleoporins results in defects in mRNA export[146,147]. During the export process, mRNA export factors interact with specific components of NPCs. For example, the conserved protein nuclear mRNA export factor 1 (NXF1) interacts directly with repeats of phenylalanine–glycine residues that are present in a subset of nucleoporins[10,58,59] that line the central NPC transport channel. This promotes transport of its cargo mRNA into the cytoplasm by overcoming the sieve-like permeability barrier[60] within the central channel. Transcription-export complex (TREX) components such as ALY (also known as THOC4) shuttle between the nucleus and the cytoplasm[4], in contrast to TREX-2 components such as germinal centre-associated nuclear protein (GANP), which preferentially interact with nucleoporins that form the nuclear basket and are not found on the cytoplasmic face of the NPC[12,56], although *Drosophila melanogaster* PCI domain-containing protein 2 (a TREX-2 component) has been reported to shuttle between the nucleus and cytoplasm[77]. An alternative route for export of large messenger ribonucleoprotein particles during synaptic Wnt signalling in *D. melanogaster* has also recently been characterized[148]. The export of these synaptic protein transcripts involves nuclear envelope budding, although its precise mechanism remains to be determined.

Actively transcribed genes localize in discrete nuclear foci that are marked by RNA polymerase II (Pol II) and are known as 'transcription factories'. Nascent transcripts need to be processed into mature transcripts that are competent for export. Processing of mRNA occurs primarily co-transcriptionally and has been reviewed extensively elsewhere[30–33].

Generation of export-competent mRNPs. Splicing factors, TREX components and poly(A)$^+$ RNA localize in nuclear domains that are distinct from transcription factories and are known as 'nuclear speckles' (REFS 4,15,34–37). Whether mRNA processing events take place in nuclear speckle domains remains controversial[35–37]. As transcription occurs throughout the nucleus, it is unlikely that all transcripts undergo processing and maturation in nuclear speckle domains; however, there is evidence suggesting that some transcripts may be processed and matured in these domains.

In support of a role for nuclear speckle domains in generating export-competent mRNPs, TREX components have been implicated in the release of spliced mRNA from nuclear speckle domains[34]. Indeed, depletion of some export factors, including the TREX component ALY (also known as THOC4)[4] and inositol polyphosphate multikinase (IPMK)[15] (which we discuss later) result in nuclear accumulation of poly(A)$^+$ RNA in nuclear speckle domains. Conversely, depletion of other export factors, such as the TREX-2 scaffold protein germinal centre-associated nuclear protein (GANP) and NXF1, leads to accumulation of poly(A)$^+$ RNA in more punctate foci, which is reminiscent of transcription factories[12,15] and consistent with processing occurring co-transcriptionally.

Inositol polyphosphate multikinase
(IPMK). A kinase that is implicated in the synthesis of both inositol phosphates (inositol-1,3,4,5-tetrakisphosphate ($Ins(1,3,4,5)P_4$), $InsP_5$ and $InsP_6$) and phosphatidylinositol-3,4,5-trisphosphate.

There is conflicting evidence as to whether active genes cluster at pre-formed transcription factories with multiple active RNA polymerases, and whether these are the main location for processing. Using super-resolution photoactivation localization microscopy in living cells, one study observed transiently forming clusters of Pol II[38]. By contrast, another study using reflected light-sheet super-resolution microscopy in fixed cells found no evidence for clustering of Pol II[39].

Recent studies have provided evidence that nuclear phosphoinositides such as phosphatidylinositol-4,5-bisphosphate ($PtdIns(4,5)P_2$), which is a physiological substrate of IPMK that localizes to nuclear speckles[40,41], can also regulate mRNA export[15,42,43] (BOX 2). The localization of ALY to nuclear speckle domains and its mRNA export activity can be regulated through binding to $PtdIns(4,5)P_2$ and $PtdIns(3,4,5)P_3$ (REF. 43). Furthermore, sequence-based selection of transcripts for nuclear export by ALY is regulated by IPMK-catalysed synthesis of $PtdIns(3,4,5)P_3$(REF. 15) (see below). Some active genes are present around nuclear speckles[44], raising the possibility that certain subsets of transcripts, such as those regulated by ALY and IPMK, may transit through nuclear speckles as part of their maturation process.

Transport of mRNPs to the nuclear periphery. After export-competent mRNPs are generated in the nucleoplasm, they must be moved to the nuclear periphery (FIG. 1). Recent studies have provided insight into the kinetics of nucleocytoplasmic transport of specific mRNPs in living mammalian cells[29,45–50].

Transport of mRNPs from transcription and processing sites to NPCs is a rate-limiting step in the pathway from the nucleus to the cytoplasm, as it can take several minutes, whereas the transit through NPCs themselves is comparatively rapid (less than 500 ms)[45,46,49]. In mammalian cells, mRNPs diffuse throughout interchromatin space or zones of heterochromatin exclusion in the nucleoplasm to reach NPCs[51–53]. Analysis of single-mRNP translocation in living cells showed that mRNPs may travel from sites of transcription to NPCs through these nucleoplasmic-channelled pathways, as mRNPs undergo one-dimensional rather than three-dimensional diffusion[49].

How are these zones of heterochromatin exclusion established and maintained? Nucleoprotein TPR, which is a filamentous NPC-associated protein that is required for mRNA export[54], is known to be involved, as depletion of TPR results in NPCs being covered by heterochromatin[55], presumably blocking transport through NPCs. Thus, a TPR-mediated scaffold might confine the diffusive movement of exported cargos[55]. Interestingly, targeting of TREX-2 components to NPCs requires TPR[14,56], suggesting that it may be advantageous for TREX-2-associated mRNPs to interact with TPR-mediated scaffolds, as this could potentially increase the efficiency of their diffusion to NPCs.

Translocation of mRNPs through nuclear pores. The last step in the mRNA export pathway involves transfer of cargo mRNAs from TREX and/or TREX-2 to NXF1–p15

for transit through nuclear pores. NXF1 itself has weak binding affinity for RNA[11], but binding to TREX components drives NXF1 into an open conformation, exposing its RNA-binding domain, increasing its affinity for RNA[13] and allowing it to have direct contact with mRNA cargoes during export[57]. To push its cargo mRNAs through NPCs into the cytoplasm for translation, NXF1 interacts directly with FG repeats that are present in the nucleoporins[10,58,59] that line the central NPC transport channel and form a sieve-like permeability barrier[60] (BOX 1; FIG. 1).

Examination of the kinetics of translocation of endogenous β-actin mRNAs through NPCs in mammalian cells shows that most of the transport time of ~180 ms is spent between docking and release at the nuclear basket and at cytoplasmic filaments (BOX 1), in contrast to translocation through the central channel, which takes ~20 ms[50]. Although a recent study has suggested that NPC transport time is in the order of 20 ms instead of 180 ms[48], the studies agree that most of this transport time is spent at the nuclear basket and at cytoplasmic filaments. Comparison of three-dimensional reconstructed transport routes for mRNPs and NXF1–p15 through NPCs shows that there is substantial overlap at the nucleoplasmic side and in the central region of NPCs[48], where FG-nucleoporins that interact with NXF1 are concentrated[10,58,59]. Interestingly, most mRNPs probe NPCs at their nuclear face but then return to the nucleoplasm, which is reflected by the fact that only 15–36% of all nuclear mRNP export events are successful[47,48,50]. This suggests that there is a rate-limiting step at the nuclear basket[47–50], consistent with the complexity that is involved in recruitment, docking and subsequent release of cargo mRNPs in preparation for their transport through NPCs. This may involve transfer of mRNPs from TREX-2 to NXF1, for example. Docking at NPCs is associated with quality control of exported mRNPs, in a process involving TPR[61,62]. It has been proposed that this TPR-dependent quality-control step contributes to developmentally regulated gene expression[63].

Cytoplasmic remodelling of mRNPs. After mRNPs have transited through NPCs, they are extensively remodelled at its cytoplasmic face to remove the receptors from cargo mRNAs, thus ensuring that the mRNPs do not re-enter the nucleus (FIG. 1). One crucial factor that imposes mRNA export directionality is the ATP-dependent RNA helicase DBP5 (also known as DDX19B). The ATPase activity of DBP5 catalyses the release of RNA-binding proteins (RBPs) from mRNAs. This process is regulated by three DBP5-interaction partners: mRNA export factor nucleoporin GLE1, small signalling molecule inositol hexakisphosphate ($InsP_6$) and cytoplasmic nuclear pore complex protein NUP214 (Nup159 in yeast)[64–70] (BOX 2). DBP5 binding to RNA and to NUP214 are mutually exclusive events, suggesting that they are two separate and consecutive steps in the mRNA export pathway[64]. Studies in yeast have shown that activation of the ATPase function of Dbp5 is mediated by interaction with Gle1-bound $InsP_6$ (REFS 66,70), and recent crystallographic studies have suggested that $InsP_6$ may function as a small-molecule tether for the Gle1–Dbp5 interaction[65].

Two models have been proposed to explain how the ATPase cycle of DBP5 remodels the mRNP by facilitating release of RBPs from cargo mRNA. One of these models proposes that GLE1–$InsP_6$ is involved in binding of ATP to DBP5 and stimulation of its ATPase activity[69], whereas the other suggests that GLE1–$InsP_6$ instead facilitates

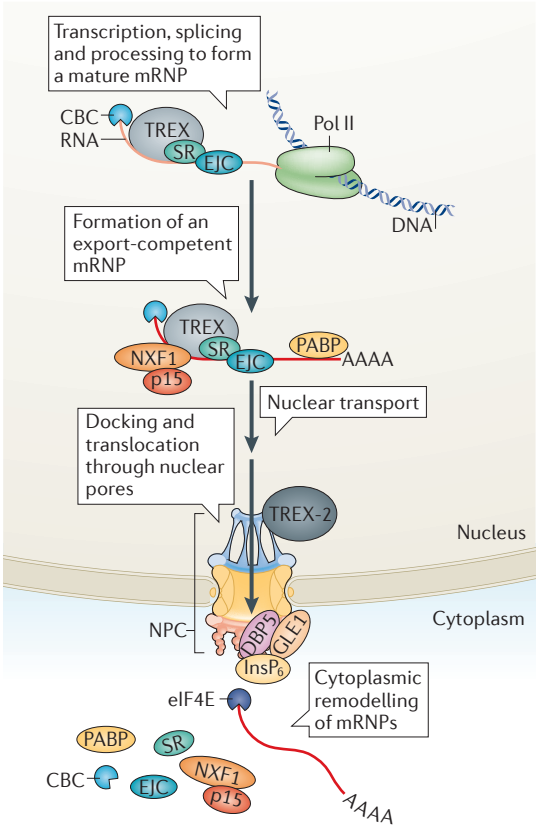

Figure 1 | **Steps of mRNA export from nuclear transcription to the cytoplasm.** The life cycle of a messenger ribonucleoprotein particle (mRNP) is shown, from its biogenesis and maturation into an export-competent form to its subsequent transport from sites of transcription and processing in the nucleus to the cytoplasm, where it is extensively remodelled. These steps are all coupled; for example, transcription-export complex TREX is recruited to the nascent mRNP by the splicing machinery. After a mature mRNP has been generated, the conserved nuclear RNA export factor 1 (NXF1) is recruited to the mRNP through direct interactions with several TREX components and SR splicing factors. Cargo mRNAs from both TREX and TREX-2 are transferred to NXF1 and its cofactor p15 for transit through the nuclear pore by interacting directly with the nucleoporins that line the pore. The kinetics of translocation of mRNAs from sites of transcription through nuclear pore complexes (NPCs) in mammalian cells suggest that transport to NPCs can take several minutes, whereas translocation through NPCs takes milliseconds. It is unknown whether TREX and TREX-2 cooperate to export the same transcripts or mediate alternative export routes and whether TREX-2 is recruited to transcripts in the nuclear interior as in the case of TREX. CBC, cap-binding complex; eIF4E, eukaryotic translation initiation factor 4E; EJC, exon–junction complex; $InsP_6$, inositol hexakisphosphate; PABP, poly(A)-binding protein; Pol II, RNA polymerase II.

Box 2 | **Role of inositol phosphates and phosphoinositides in regulating mRNA export**

Soluble inositol phosphates such as inositol hexakisphosphate ($InsP_6$) and phosphoinositides such as phosphatidylinositol-3,4,5-trisphosphate ($PtdIns(3,4,5)P_3$) have important signalling roles throughout the cell and can regulate mRNA export in yeast and mammals. For example, $InsP_6$ regulates the activity of ATP-dependent RNA helicase Dbp5 in a nucleoporin Gle1-dependent manner at the cytoplasmic face of the nuclear pore complex during mRNA export[66,70]. Indeed, inactivation of yeast $InsP_5$ 2-kinase, which phosphorylates $InsP_5$ to generate $InsP_6$, results in mRNA export defects[149]. Nuclear phosphoinositides also have been shown to regulate mRNA export. The mRNA export activity of transcription-export complex (TREX) component ALY, as well as its residence in nuclear speckle domains, can be regulated through binding to $PtdIns(4,5)P_2$ and $PtdIns(3,4,5)P_3$ (REF. 43). ALY is required for the sequence-based selection of transcripts that maintain genome integrity for nuclear export[15]. This recognition is regulated by the PI3-kinase activity of inositol polyphosphate multikinase, which is a nuclear kinase that generates inositol phosphates $Ins(1,3,4,5)P_4$ and $InsP_5$, as well as $PtdIns(3,4,5)P_3$ (REFS 117–119), and the depletion of which also inhibits the nuclear export of mRNAs encoding essential factors that maintain genome integrity[15].

removal of the remodelled mRNP from DBP5 (REF. 65). Although the precise molecular mechanisms are still being determined, these studies reinforce the idea that local remodelling of mRNPs by an RNA helicase that is activated at the cytoplasmic face of the NPCs is of crucial importance in imposing mRNA export directionality and preparing mRNA for translation by the ribosome.

Examples of selectivity of mRNA export

Evidence is accumulating that mRNA export in mammals can be selective, although it remains possible that a large proportion of mRNAs are exported by bulk export pathways. Diverse biological processes, including DNA repair, maintenance of pluripotency, gene expression, stress responses, cell proliferation, cell survival and haematopoiesis[14–22] can be regulated by selective mRNA export and, in most of these cases, although not all, selectivity is mediated by components of the TREX and TREX-2 complexes.

TREX complex composition and interactions. TREX has an integrating role in the gene expression pathway, in that it links multiple mRNA processing steps with mRNA export[26]. The mRNA export pathway was initially characterized in yeast; however, there are differences between yeast and metazoan cells in the coupling of mRNA export to upstream processes, probably owing to the much greater incidence of introns in metazoan genes. Whereas the TREX complex is recruited co-transcriptionally in yeast[3], it is recruited predominantly by the splicing machinery in metazoa[2]. The assembly of the TREX complex is ATP-dependent[71]; it binds to the 5′ end of mRNA during splicing in humans[1] and consists of conserved core subunits[2–4,18,21,71–84] including ALY, RNA helicase UAP56 (also known as DDX39B) and a subcomplex called THO, which consists of at least six subunits[3,73] (FIG. 2; TABLE 1).

TREX subunits interact with multiple components of the transcription and splicing machineries. In mammalian cells, several TREX subunits are found in purified spliceosomes[85], probably because they interact with the core of the exon–junction complex (EJC), which is deposited upstream of exon–exon junctions that are generated by splicing[86]. SR splicing factors, which promote recruitment of the spliceosome to 5′ and 3′ splice sites through binding to exonic and intronic sequences in pre-mRNA, can also couple splicing to export through their interactions with NXF1 (REFS 87–90). Following splicing, these nuclear–cytoplasmic shuttling proteins remain bound to mature mRNA as it transits through nuclear pores[87–90].

TREX complexes also participate in the export of transcripts that are encoded by intron-less genes, independent of splicing. These transcripts contain cytoplasmic accumulation regions, which promote export of intron-less mRNA by sequence-dependent recruitment of TREX components[91]. Export of intron-less histone mRNAs is also promoted by the stem–loop-binding protein SLBP through recruitment to the 3′ end of the transcripts and through interactions with the cap-binding complex and negative elongation factors[92,93].

Contribution of TREX to mRNA export selectivity. Several TREX components have recently been shown to contribute to selective export of mRNA and thus to regulation of specific biological processes (FIG. 3; TABLE 2). Selectivity of the mRNAs exported by transport factors was first demonstrated in yeast for RNA annealing protein Yra1 (the yeast orthologue of ALY in mammals) and mRNA export factor Mex67 (REF. 94) (the yeast orthologue of NXF1). Selectivity was subsequently shown in *D. melanogaster* for the THO subcomplex[76] and other factors[77], although there is conflicting evidence as to whether NXF1 exports a small subset of or almost all mRNAs[94–96].

In yeast, selectivity of mRNA recognition by transport factors has recently been illustrated by genome-wide studies[97,98]. Although all yeast TREX components are recruited to all active yeast genes during transcript elongation[99,100], a recent study in humans showed that TREX component ALY is not absolutely required for global transcription[101], suggesting that specificity of TREX for different kinds of transcript at early stages of gene expression may differ between yeast and humans. In mammalian cells, several TREX components export distinct subsets of mRNA (TABLE 2).THO complex subunit 5 homologue (THOC5) has a key role in the maintenance of haematopoiesis, as THOC5 conditional knockout mice display severe anaemia and leucocytopenia[19]. This is probably due to its function in preferentially regulating the nuclear export of mRNAs encoding factors that are crucial for haematopoietic development[18]. Furthermore, THOC2 and THOC5 can regulate the balance between stem cell specification and differentiation by regulating

Pluripotency
The potential ability of a cell to differentiate into any cell type of the three germ layers.

Spliceosomes
Large ribonucleoprotein complexes that catalyse the removal of intronic sequences from nuclear pre-mRNA. A spliceosome consists of five small nuclear ribonucleoproteins (snRNPs) and non-snRNP proteins, and it is remodelled extensively during its assembly and activation.

Exon–junction complex
(EJC). A multi-protein complex that is deposited onto newly synthesized and spliced mRNA ~24 nt upstream of exon–exon junctions.

SR splicing factors
A family of RNA-binding splicing initiators that contain a domain rich in consecutive repeats of serine–arginine residues.

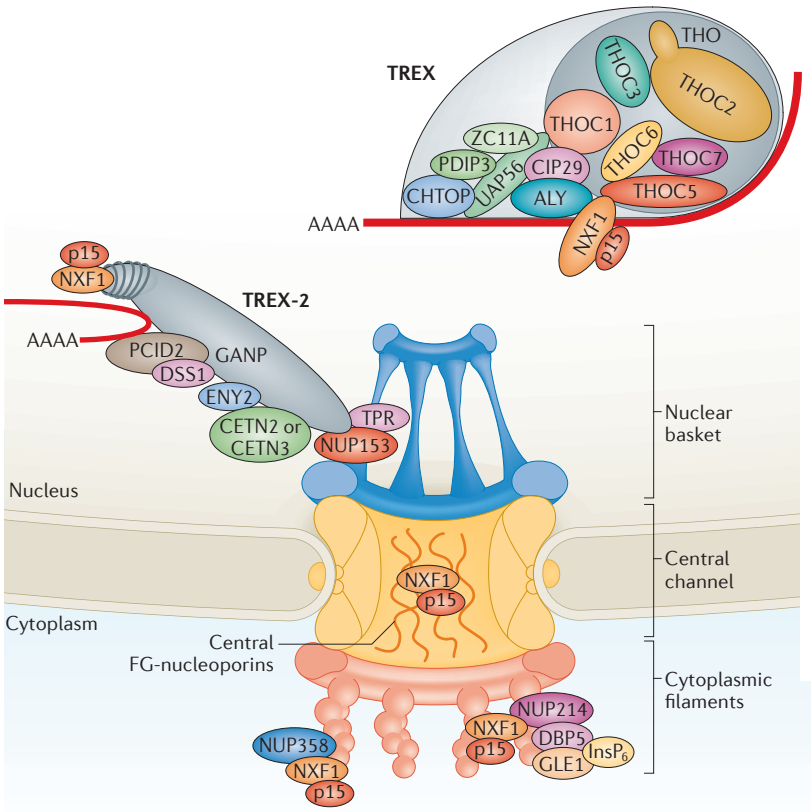

Figure 2 | **Interactions between nuclear pore complex components and mRNA export complexes.** One of the final steps in the mRNA export pathway involves docking and translocation of messenger ribonucleoprotein particles through nuclear pore complexes (NPCs). A schematic of an NPC is shown, with its central structure, cytoplasmic pore filaments and nuclear basket. Interactions between mRNA export factors and specific NPC components during the export process are indicated. For example, nuclear RNA export factor 1 (NXF1) interacts directly with repeats of phenylalanine–glycine (FG) residues, which are present in a subset of the nucleoporins that line the central NPC transport channel. These include nuclear pore complex protein NUP153, which is associated with the nuclear basket, and cytoplasmic filament-associated NUP214 and NUP358. Simplified cartoon representations of transcription-export complexes TREX and TREX-2 are also shown, with their molecular composition based on available structural data. TREX is composed of the THO subcomplex (darker grey area), together with RNA-binding component ALY, DEAD-box type RNA helicase UAP56 and additional factors that have ATP-dependent interactions with UAP56. Several components of TREX interact directly with NXF1 and can shuttle between the nucleus and the cytoplasm. Mammalian TREX-2 interacts with the nuclear basket through NUP153 and nucleoprotein TPR, with all TREX-2 subunits binding to the scaffold of germinal centre-associated nuclear protein (GANP). In yeast Sac3 and in human GANP, α-helical and winged-helix domains bind to other components of TREX-2. TREX-2 also interacts directly with NXF1 through the amino-terminal domain of GANP, which contains regions of homology to nucleoporins, including a cluster of six FG repeats (indicated by dark grey lines). CETN, centrin; CHTOP, chromatin target of PRMT1 protein; ENY2, enhancer of yellow 2 transcription factor homologue; $InsP_6$, inositol hexakisphosphate; PCID2, PCI domain-containing protein 2; PDIP3, polymerase δ-interacting protein 3; THOC, THO complex subunit; ZC11A, zinc finger CCCH domain-containing protein 11A.

the nuclear export of mRNAs and thus expression of proteins that are required for establishment of pluripotency, such as homeobox protein NANOG and transcription factor SOX2 (REF. 16). Indeed, expression of THOC2 and THOC5 correlates with the pluripotent state of embryonic stem (ES) cells, and their depletion results in the loss of ES cell self-renewal and inhibits reprogramming and blastocyst development[16]. THOC5 and ALY also promote the export of mRNA that encodes heat shock 70 kDa proteins (HSP70s), which are crucial factors in the response to heat stress[21].

Repair of DNA double-strand breaks can also be controlled by selective mRNA export, which involves a mechanism that is regulated by the TREX component ALY and by IPMK and its catalytic product PtdIns(3,4,5)P_3. IPMK and ALY preserve genome integrity by controlling the nuclear export of transcripts encoding proteins that are essential for accurate genome duplication and repair[15] (BOX 1; TABLE 2). This includes several transcripts that are involved in DNA repair by homologous recombination, such as RAD51 recombinase (*RAD51*), checkpoint kinase 1 (*CHEK1*) and Fanconi anaemia, complementation group D2 (*FANCD2*). By contrast, transcripts from several genes that are involved in DNA repair by non-homologous end joining (NHEJ) are unaffected. Importantly, selective transport is observed both before and after exposure to DNA-damaging agents, suggesting that IPMK functions constitutively in the nuclear export of transcripts encoding proteins that are involved in homologous recombination. Remarkably, binding of ALY to *RAD51* is regulated by the PI3K activity of IPMK, and indeed PtdIns(3,4,5)P_3 can partially restore ALY recognition of homologous recombination factor transcripts in IPMK-depleted cells. Importantly, IPMK-depleted cells are sensitive to various genotoxic lesions and accumulate structural chromosomal aberrations such as chromatid breaks and radial structures, which are typical of defective DNA repair by homologous recombination[15]. Although this example provides evidence that DNA repair can be regulated by selective mRNA export, it is known that RNA metabolism itself is altered during the DNA damage response, suggesting a more complex mode of regulation that deserves analysis in future studies.

Collectively, these recent findings indicate that specific mRNA export factors can modulate diverse processes such as DNA repair, haematopoiesis and maintenance of pluripotency, thus demonstrating the potential impact that selective mRNA export can have on biological function. The finding that TREX components ALY and THOC5 selectively export transcripts encoding proteins that mediate such essential emergency responses as DNA repair by homologous recombination and the heat shock response emphasizes the importance of selective mRNA export for cell survival. Whereas THOC2 and THOC5 expression in ES cells are important for the maintenance of pluripotency[16], ALY and UAP56 are not required. This raises the possibility that cell type-specific TREX complexes may exist and regulate selectivity, although these studies have not tested whether the complete TREX complexes contribute to selectivity.

The TREX-2 complex. A second complex that links transcription to export is TREX-2 (FIG. 2; TABLE 1). A crucial unresolved question is whether TREX and TREX-2 act on the same set of transcripts or are alternative adaptors acting on different transcript subsets. TREX-2 was initially identified in yeast as having a role in the export and localization of transcripts such as Gal genes

Table 1 | **Components of transcription-export complexes TREX and TREX-2**

Metazoan protein	Yeast orthologue	Role	Refs
TREX			
THOC1	Hpr1	Core subunit of THO subcomplex	3,72,73
THOC2	Tho2	Core subunit of THO subcomplex	3,72,73
THOC3	Tex1	Core subunit of THO subcomplex	3,72,73
ALY	Yra1	mRNA-binding adaptor	4,74,75
THOC5	Not known	RNA-binding metazoa-specific subunit	18,21,76
THOC6	Not known	Metazoa-specific subunit	2,76
THOC7	Not known	Metazoa-specific subunit	21,77
UAP56	Sub2	DEAD-box type helicase	78,79
CIP29	Tho1	ATP-dependent interaction with UAP56	71
CHTOP	Not known	mRNA-binding adaptor	80
PDIP3	Not known	ATP-dependent interaction with UAP56	81
ZC11A	Not known	ATP-dependent interaction with UAP56	81
UIF	Not known	Peripheral component of TREX	82
TREX-2			
GANP	Sac3	Scaffold for TREX-2 complex; has domain with homology to nucleoporins	5,7,9,12,14
ENY2	Sus1	Also subunit of SAGA transcription activation complex	5,7,102
PCID2	Thp1	Forms part of winged-helix domain that binds to nucleic acids	5,6,9
Centrin 2 and centrin 3	Cdc31	Also part of centrosome	5,8,150
DSS1	Sem1	Also part of proteasome and interacts with breast cancer susceptibility protein 2	6,151–153

CHTOP, chromatin target of PRMT1 protein; GANP, germinal centre-associated nuclear protein; PCID2, PCI domain-containing protein 2; PDIP3, polymerase δ-interacting protein 3; SAGA, SPT–ADA–GCN5–acetyltransferase; THOC, THO complex subunit; UIF, UAP56-interacting factor; ZC11A, zinc finger CCCH domain-containing protein 11A.

to NPCs[8,9,28,102,103]. It is partly conserved in humans, with GANP functioning as a scaffold to which all the other subunits of TREX-2 bind[5,12]. Some domains of GANP are orthologues of yeast Sac3. In Sac3 and in human GANP, α-helical and winged-helix domains bind other components of TREX-2, namely transcription and mRNA export factor ENY2, PCI domain-containing protein 2 (PCID2), centrins and 26S proteasome complex subunit DSS1 (REFS 5–7). ENY2 is also a component of the SAGA (SPT–ADA–GCN5–acetyltransferase) transcription activation complex, although the localization of TREX-2 to the nuclear periphery is independent of SAGA[56]. TREX-2 is also associated with transcription, as both ENY2 and GANP interact with RNA polymerase II[5].

The role of TREX-2 in mammalian mRNA export is much less well characterized than that of TREX; however, recent crystal structures of TREX-2 components have provided important insights into its mechanism. The long scaffold domain of GANP integrates several other components. Thus, the centrin-interaction domain of GANP forms a gently undulating α-helix, to which two chains of ENY2 and centrins bind[5,7]. Furthermore, the Sac3-homology domain of GANP (or its equivalent in Sac3) forms a winged-helix domain that juxtaposes with the corresponding winged-helix domain in PCID2 (Thp1 in yeast), stabilized by DSS1 (Sem1 in yeast), to form a platform that binds to nucleic acids[6]. GANP contains three other important domains: a putative RNA-binding domain, an amino-terminal region with striking similarity to nucleoporins and a large carboxy-terminal region of complete identity to another protein, MCM3AP. Strangely, MCM3AP is transcribed from a promoter within an intron of GANP and has an unrelated function within the nucleus[104]. These features are consistent with the spatial distribution of GANP, which is concentrated at the nuclear envelope but is also present throughout the nucleus[12,56,105]. Interestingly, the N-terminal domain of GANP contains a cluster of 6 nucleoporin-like FG repeats in a region that has 23–32% identity to several nucleoporins[12]. How mRNAs are transferred from TREX-2 to NXF1 is uncertain, but NXF1 interacts directly with the N-terminal domain of GANP. Thus, the higher concentration of FG repeats in FG-nucleoporins at NPCs may displace GANP and TREX-2 from NXF1, releasing it and its associated cargo mRNAs to pass through NPCs for translation in the cytoplasm[12].

Contribution of TREX-2 to mRNA export selectivity. Recent findings have suggested that TREX-2 components also selectively export specific subsets of mRNA (FIG. 3; TABLE 2). Depletion of TREX-2 components, including GANP, results in retention of poly(A)$^+$ RNA in the nucleus and subsequent cell death, but neither the

Homologous recombination
An error-free mechanism for repairing DNA double-strand breaks through DNA strand exchange. It is dependent on the recombinase DNA repair protein RAD51 homologue 1 and the tumour suppressor breast cancer susceptibility protein 2 (BRCA2).

Non-homologous end joining
(NHEJ). An error-prone mechanism for repairing DNA double-strand breaks through re-ligation of the broken ends without the need for a homologous template. It is dependent on the KU70–KU80 and XRCC4–XLF–DNA ligase IV complexes.

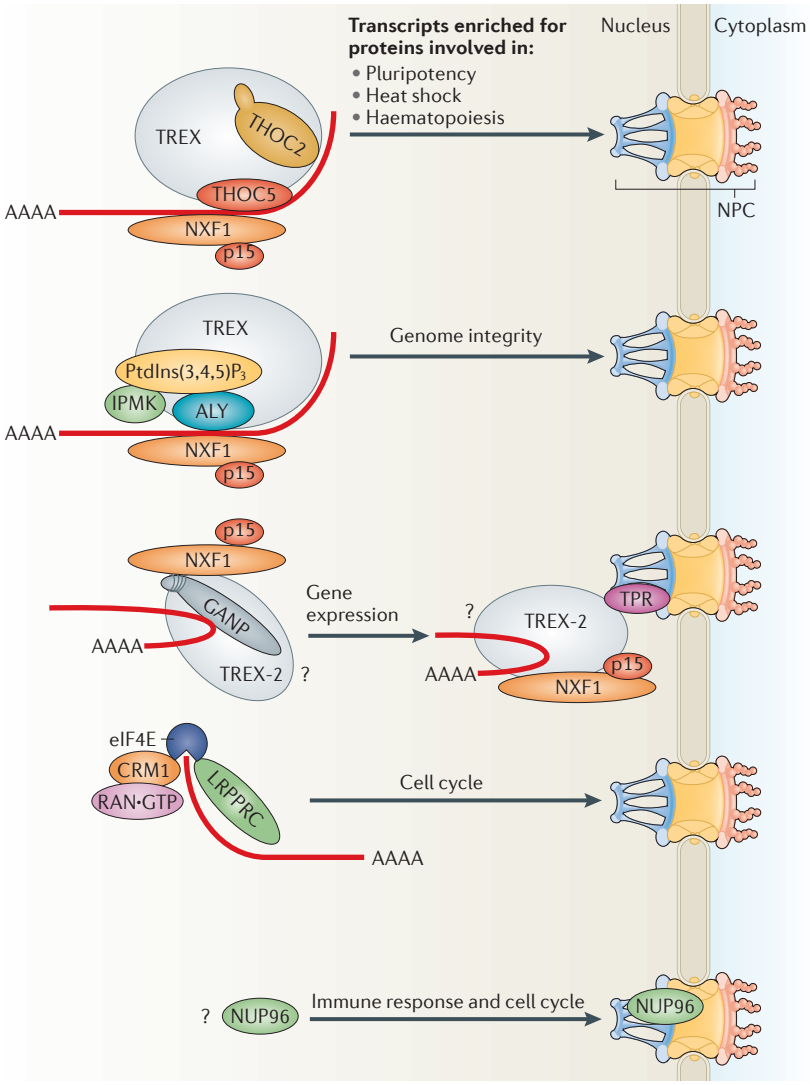

Figure 3 | **Examples of biological pathways that are regulated by selective mRNA export.** Components of transcription-export complex TREX, such as ALY, THO complex subunit 2 (THOC2) and THOC5, contribute to the selective export of a subset of mRNAs and thus to regulation of specific biological processes including maintenance of pluripotency, haematopoiesis, heat shock and safeguarding of genome integrity. TREX-2, through germinal centre-associated nuclear protein (GANP), also functions in the export of transcripts that are required for gene expression. Only the components of TREX and TREX-2 complexes that have been shown to contribute to selectivity are indicated. It is unknown whether the complete TREX and TREX-2 complexes contribute to selectivity, and thus they are represented as transparent in the figure. Although most mRNAs use TREX, TREX-2 and nuclear RNA export factor 1 (NXF1) receptors to transit through nuclear pore complexes (NPCs), a subset of mRNAs use chromosome region maintenance 1 protein homologue (CRM1), which is the main protein export receptor. Eukaryotic translation initiation factor 4E (eIF4E) and CRM1 preferentially export a subset of mRNAs that encode proteins involved in proliferation, survival, metastasis and invasion. Nucleoporins such as nuclear pore complex protein NUP96, which is a constituent of the NUP107–NUP160 complex, may contribute to the export of specific subsets of transcripts, such as those encoding cell cycle regulators and immune response factors. Whether NUP96 achieves this by modulating interactions of mRNA export factors at the NPC or in the nuclear interior, where a proportion of NUP96 is thought to localize, is unknown. Each of these potential pathways, together with the functional subset of transcripts that they export, is shown schematically. One important unresolved question is whether TREX and TREX-2 mediate alternative export routes, or whether they cooperate to export the same transcripts. IPMK, inositol polyphosphate multikinase; LRPPRC, leucine-rich PPR motif-containing protein; PtdIns(3,4,5)P_3, phosphatidylinositol-3,4,5-trisphosphate.

export block nor the rate of death is as severe as those that are caused by depletion of the general export factor NXF1 (REF. 14). A possible explanation is that GANP transports only a subset of the transcripts that are transported by NXF1, which has been confirmed by comparing the transcripts that are lost from the cytoplasm in response to depletion of either GANP or NXF1. Surprisingly, GANP promotes the nuclear export of classes of mRNA that are involved in gene expression, such as those involved in mRNA processing and splicing, and mRNP and ribosome biogenesis[14]. GANP-specific transcripts are highly expressed and have shorter half-lives than GANP-independent transcripts. Comparing the export rates of two transcripts that require GANP with those of two that require NXF1 but not GANP showed that GANP-dependent export was faster. This raises the possibility that GANP (and hence TREX-2) mediates a priority fast-track export route for transcripts that control cell behaviour, presumably facilitating rapid adaptation to changing cellular environments.

How could TREX-2 create a fast-track export route for mRNAs? Several components of TREX-2 accumulate at NPCs[5,12,56], although there are differences between the localization of GANP and that of ENY2 and PCID2. A proportion of GANP is also seen within the nuclear interior, and inhibition of transcription by 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) reduces the amount of GANP at NPCs. By contrast, substantial proportions of ENY2 and PCID2 associate very stably with the nuclear envelope and are not displaced by inhibition of transcription by α-amanitin or actinomycin D. One way to reconcile these observations is the possibility that GANP shuttles between sites of transcription and the nuclear envelope, binding to ENY2 and PCID2 only at the NPC and dissociating from them to re-enter the nuclear interior. This possibility remains to be tested.

The function of GANP in accelerating export of transcripts from the nucleus may depend on its N-terminus, which binds to the general export factor NXF1 that in turn binds to FG repeats of pore proteins, raising the possibility that the N-terminus of GANP sequesters NXF1 within the nuclear interior and prioritizes export of transcripts that are bound to TREX-2. Further investigation will be required to determine whether TREX and TREX-2 mediate alternative export routes or whether they cooperate to export the same transcripts.

Eukaryotic translation initiation factor 4E- and CRM1-dependent selective mRNA export. Although most mRNAs use TREX, TREX-2 and NXF1 receptors to transit through NPCs, a subset of mRNAs use CRM1, the major protein-export receptor (reviewed in REFS 106,107). Proteins are actively transported out of the nucleus by a family of conserved nuclear transport receptors that recognize leucine-rich nuclear export signals (NESs), which bind directly to nucleoporins that line the central channel. Ribosomal RNA (rRNA), small nuclear RNAs (snRNAs), microRNAs and tRNAs are also exported using a CRM1-dependent pathway that is broadly similar to that used by proteins[108]. Whereas short transcripts such as snRNAs are exported by CRM1 and

Table 2 | **Biological pathways regulated by selective mRNA export and factors required for export**

Selective mRNA export factor	Component of TREX or TREX-2	Function	Biological pathway (transcript examples)	Refs
IPMK	Neither	Kinase involved in synthesis of inositol phosphates and PtdIns(3,4,5)P_3	Genome duplication and repair; cell cycle (*RAD51*, *CHEK1* and *FANCD2*)	15
ALY	TREX	RNA-binding adaptor of TREX	Genome duplication and repair; cell cycle; heat shock (*RAD51*, *CHEK1*, *FANCD2* and HSP70)	15,21,94
THOC2	TREX	Core subunit of THO and TREX	Maintenance of pluripotency (*NANOG*, *SOX2* and *KLF4*)	16
THOC5	TREX	RNA-binding metazoa-specific subunit of TREX	Maintenance of pluripotency; haematopoiesis; heat shock (*NANOG*, *SOX2*, *KLF4* and HSP70)	16,18, 19,21
GANP	TREX-2	Scaffold protein for TREX-2; exports a subset of mRNA, the transport of which depends on NXF1	Gene expression; RNA processing (*SP1*, *RPS23* and *ARPP19*)	14
eIF4E	Neither	Binds to m^7G cap of mRNA; export is CRM1-dependent and NXF1-independent	Cell proliferation and cell survival (cyclin D1 and *MYC*)	17,20, 22,113
NUP96	Neither	Component of nuclear pore complex	Immune response; cell cycle (MHC I, MHC II, β2 microglobulin and *CDK6*)	122

ARPP19, cAMP-regulated phosphoprotein, 19kDa; CDK6, cyclin-dependent kinase 6; *CHEK1*, checkpoint kinase 1; CRM1, chromosome region maintenance 1 protein homologue; eIF4E, eukaryotic translation initiation factor 4E; *FANCD2*, Fanconi anaemia, complementation group D2; GANP, germinal centre-associated nuclear protein; HSP70, heat shock 70 kDa protein; IPMK, inositol polyphosphate multikinase; *KLF4*, Kruppel-like factor 4; m^7G, 7-methylguanosine; MHC, major histocompatibility complex; NUP96, nuclear pore complex protein 96; NXF1, nuclear RNA export factor 1; PtdIns(3,4,5)P_3, phosphatidylinositol-3,4,5-trisphosphate; *RAD51*, RAD51 recombinase; *RPS23*, ribosomal protein S23; *SOX2*, SRY-box 2; THOC, THO complex subunit; TREX, transcription-export complex.

phosphorylated adaptor RNA export protein (PHAX), transcripts that are longer than 200–300 nt selectively bind to heterogeneous nuclear ribonucleoprotein C, which inhibits binding of PHAX and recruitment of CRM1 to RNA, thus committing the transcript to the mRNA export pathway[109]. CRM1 itself does not bind to RNA, instead recruiting NES-containing adaptor proteins that bind directly to RNA or to other RBPs. For example, AU-rich elements are recognized by RBP Hu-antigen R (HuR; also known as ELAVL1) and its protein ligands, which interact with CRM1 (REF. 110). NXF3, which is an RBP related to NXF1, also functions in CRM1-dependent RNA export, although the transcripts that it exports are unknown[111]. Interestingly, eIF4E and CRM1 preferentially export a subset of mRNAs that encode proteins involved in proliferation, survival, metastasis and invasion[20,22,112,113] (FIG. 3). Importantly, export of these transcripts does not require NXF1, suggesting that competition with the bulk mRNA export pathway for specific classes of mRNA may be one mechanism by which cells can respond efficiently to extracellular stimuli.

Potential mechanisms of selectivity

Selectivity may be linked to the coordinate regulation of the production of functionally related proteins by mRNP complexes in post-transcriptional RNA regulons[114–116]. Functionally related genes that are preferentially transcribed during cell growth, development or cancer, for example, may be regulated post-transcriptionally by specific mRNA-binding proteins that recognize sequence elements that are conserved among the mRNAs[107,114,115]. Many recent findings support this view. For example, RNAs that are exported by eukaryotic translation initiation factor 4E (eIF4E) and CRM1 contain an element of ~50 nt in their 3′ UTRs that has a common secondary structure[22]. These mRNPs also contain some factors that are used by the canonical mRNA export machinery but, importantly, do not contain either NXF1 or ALY[20]. Both THOC5 and THOC2 interact with mRNAs that encode NANOG and SOX2 in RNA immunoprecipitation assays[16], and indeed THOC5 shows RNA-binding activity *in vitro*[21]. However, the specific sequence elements of these pluripotency-promoting mRNAs that are recognized by the THO subcomplex remain to be determined.

Further insights into the mechanism that regulates transcript-selective mRNA export have been obtained by determining how ALY-dependent recognition of sequence motifs is mediated by IPMK, which is implicated in the synthesis of inositol phosphates (Ins(1,3,4,5)P_4, InsP_5 and InsP_6) and PtdIns(3,4,5)P_3 (REFS 117–119). ALY can bind to PtdIns(3,4,5)P_3 but not to inositol phosphates[15,43], suggesting that IPMK-catalysed synthesis of PtdIns(3,4,5)P_3 in the nucleus regulates transcript selection for export by ALY through the recognition of sequence motifs that are present in the 3′ UTRs of target transcripts[15]. Despite these advances, the mechanisms of selectivity remain poorly understood. For example, how many proteins bind to each individual mRNA during export, and how is binding selectivity achieved? RBPs

tend to bind to RNA with relatively low affinity, and it is difficult to formulate a general code for RNA recognition. Although each mRNA will have many potential binding sites that show both redundancy and diversity, RNA secondary structure is likely to have a large effect on sequence accessibility and recognition. Thus, binding selectivity might be achieved by combinatorial modularity, in which several RBPs with distinct but relatively degenerate specificities will bind to multiple recognition sequences that are present in each specific transcript.

Another potential mechanism for selectivity may involve nuclear pores themselves. Both actively transcribed and repressed genes interact with NPCs, which could affect export of the resulting transcripts. Indeed, nucleoporins may contribute to the export of specific subsets of transcripts[120–122]. For example, NUP96 levels have been shown to regulate export of transcripts that encode cell cycle regulators in a cell cycle phase-specific manner[121]. NUP96 is degraded during mitosis, providing a potential link between cell cycle signalling and mRNA export selectivity. Furthermore, macrophages from *Nup96*$^{+/-}$ mice show reduced nuclear export of transcripts that encode immune-response factors[122]. Reduction of NUP155 levels, which is associated with cardiac atrial fibrillation, can also result in inhibition of HSP70 mRNA export[120]. These findings raise the intriguing possibility that NPC rearrangements could provide a mechanism for mRNA export selectivity.

Selective mRNA export and human disease

Defects in RNA production are important causative factors in various diseases, including cancer[123]. Sustained proliferative signalling is one of the hallmarks of cancer and is underpinned by selective changes in gene expression[124]. As RNA processing is an obligate step in the gene expression pathway, it was initially surprising that mutations in genes that are involved in RNA processing pathways could lead to disease progression: such mutations would be very likely to cause widespread stress, resulting in cell death and thereby preventing sustainable disease. However, the proteins that are implicated in disease function in various RNA biogenesis and maturation steps, including transcription, splicing, processing, export and ribosome biogenesis, thus illustrating the regulated and selective nature of mRNA processing. Indeed, driver mutations in cancers such as myelodysplasia and leukaemia have been identified in the genes encoding splicing factor 3B subunit 1, which anchors the U2 snRNP to pre-mRNA, and splicing factor U2AF 65 kDa subunit, a factor that binds to the polypyrimidine tract of introns and promotes recruitment of the U2 snRNP[125–127]. Notably, there is accumulating evidence that dysregulation of mRNA export may contribute to the development of cancer[107]. For example, TREX-2 component GANP is upregulated in lymphomas[128], and expression of TREX components ALY, CIP29 protein and THOC1 is altered in various cancers, including oral, liver, pancreatic, lung, ovarian and colon[129–132].

Interestingly, eIF4E, which uses CRM1 to export transcripts encoding proteins that are required for cell proliferation and survival, is upregulated in many cancers and promotes tumorigenesis[133,134]. Although eIF4E has a well-established role in translation, its selective mRNA export function also contributes to its oncogenic potential, at least in part by functioning with cytoplasmic nucleoporin NUP358 (also known as RANBP2)[17]. These studies suggest that cancer cells may sustain chronic proliferation by altering pathways that regulate transcript-selective nuclear export of mRNA.

Mutations in another mRNA export factor have also been implicated in autosomal recessive motor neuron disease[135] and in amyotrophic lateral sclerosis (ALS)[136]. Mutations in *GLE1* are responsible for lethal congenital contracture syndrome 1 (LCCS1)[135]. LCCS1 is characterized by immobility of the fetus, accompanied by lack of anterior horn motor neurons and severe atrophy of skeletal muscles and of the ventral spinal cord[137,138]. The mutation results in a three amino acid insertion in the N-terminal coiled-coil domain of GLE1 that affects its oligomerization[135,139]. Recent work has suggested that LCCS1 pathology is due to perturbations of GLE1 oligomerization and shuttling that disrupt efficient nuclear export of mRNA at NPCs[139]. It is surprising that pathologies resulting from this mutation do not manifest during early embryonic development. However, if this mutation does not completely abolish mRNA export, but rather reduces its efficiency, then the cumulative effect of subtle changes in gene expression may not be apparent until late in the fetal development process.

Concluding remarks

During the past five years, studies have described the complexity of the mRNA export pathway in metazoa in remarkable detail. A combination of approaches in various developmental contexts has demonstrated that specific mRNA export factors can modulate the efficiency of DNA repair, gene expression, stress responses and proliferation, as well as developmental processes such as pluripotency maintenance and haematopoiesis. This body of work demonstrates the potential impact that selective mRNA export can have on biological function in different tissues and may provide an explanation as to why the mRNA export machinery is dysregulated in several human cancers.

Several important unresolved questions remain in the field. Why is mRNA export selective and how widespread is its selectivity? How are selective mRNA export pathways regulated and what signalling pathways activate them? Do TREX and TREX-2 perform parallel or sequential functions, or do they define two alternative pathways? There is increasing evidence that post-translational modifications are likely to have key roles in the regulation of the mRNA export machinery and its coupling to upstream and downstream steps[27]. These signalling pathways may also be dysregulated in disease, raising the possibility that factors involved in selective mRNA export might be attractive future therapeutic targets. Another emerging question is the potential contribution of mRNA export complexes to preventing genomic instability in humans. RNA–DNA hybrid structures, known as R-loops, form during transcription and are linked to chromosome rearrangements

or loss, recombination and mutation[140]. RNA metabolic processes have a role in preventing formation of R-loops. Thus, mutants of the TREX and TREX-2 complexes in yeast accumulate co-transcriptional R-loops[141,142]. Recent evidence suggests that TREX also prevents formation of R-loops in humans[143] and that TREX-2 and breast cancer type 2 susceptibility protein (BRCA2) may cooperate to prevent R-loop formation[144] through mechanisms that remain to be characterized.

Selective mRNA export is a newly identified and potentially important mechanism to regulate the human transcriptome. Therefore, the study of mRNA export deserves the same attention as studies of transcription, splicing and translation for the understanding of gene expression control. Altering mRNA export may be important not only in disease progression, but also in preventing genomic instability that may facilitate acquisition of hallmarks that are crucial for tumorigenesis.

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Competing interests statement
The authors declare no competing interests.