Abstract: Over the last two decades, multiple studies have explored the mechanisms
governing mRNA export out of the nucleus, a crucial step in eukaryotic gene expression.
During transcription and processing, mRNAs are assembled into messenger
ribonucleoparticles (mRNPs). mRNPs are then exported through nuclear pore complexes
(NPCs), which are large multiprotein assemblies made of several copies of a limited
number of nucleoporins. A considerable effort has been put into the dissection of mRNA
export through NPCs at both cellular and molecular levels, revealing the conserved
contributions of a subset of nucleoporins in this process, from yeast to vertebrates. Several
reports have also demonstrated the ability of NPCs to sort out properly-processed mRNPs
for entry into the nuclear export pathway. Importantly, changes in mRNA export have been
associated with post-translational modifications of nucleoporins or changes in NPC
composition, depending on cell cycle progression, development or exposure to stress. How
NPC modifications also impact on cellular mRNA export in disease situations, notably
upon viral infection, is discussed.

Keywords: mRNA export; mRNA quality control; nuclear pore complexes (NPCs);
nucleoporin; post-translational modifications
1. Introduction

One of the defining hallmarks of eukaryotic cells is the compartmentalization of their genome, which enables the fine-tuning of gene expression processes, from mRNA synthesis and processing in the nucleus to translation in the cytoplasm. Exchanges of molecules between the two compartments exclusively rely on nuclear pore complexes (NPCs), which are multiprotein assemblies composed of multiple copies of ~30 different nucleoporins (Nups; Figure 1) and whose estimated mass is 60 MDa in yeast and 125 MDa in vertebrates. The overall NPC structure is conserved from yeast to human and is organized according to an eight-fold symmetry, encompassing a stable membrane-embedded scaffold, which delineates a ~40-nm central channel and anchors peripheral structures, namely the nuclear basket and the cytoplasmic filaments [1,2]. A selective barrier to the diffusion through the NPC channel is established by the interaction of several unstructured and hydrophobic FG-domains, composed of multiple clusters of the phenylalanine-glycine (FG) dipeptide separated by hydrophilic linkers [3]. The meshwork thus formed enables either the passive diffusion of small molecules or the selective transport of larger molecules (proteins and ribonucleoparticles) harboring nuclear localization or export signals (NLS/NES). These sequences are recognized by transport receptors (importins/exportins), which can dynamically interact with FG repeats [3]. The directionality and the irreversibility of the diverse protein and RNA transport pathways are provided by the regulated formation and dissociation of transport complexes on both sides of the NPCs [1,2].

In the case of mRNAs, a pre-requisite for nuclear export is the formation of messenger ribonucleoparticles (mRNPs), which encompass multiple proteins transferred to the transcripts during the course of transcription, splicing and 3'-end processing. Acquisition of export competence is associated with the completion of pre-mRNA processing reactions, the release of packaged mRNPs from the transcription site and the recruitment of mRNA export receptors that will ultimately interact with FG-nucleoporins at NPCs. In yeast, the unique mRNA export receptor is the Mex67-Mtr2 heterodimer, whose association with mRNAs requires dedicated RNA-binding adaptors, such as the Yra1 subunit of the TREX (transcription and export) complex, Nab2 or Npl3 [4–6]. The situation appears somehow more complex in metazoans, with the coexistence of two mRNA export pathways. The majority of mRNAs are exported by virtue of their interaction with the orthologue of the Mex67-Mtr2 heterodimer (called Tap-p15 or NXF1-NXT1 in vertebrates), whose association to mRNAs is facilitated by the conserved TREX complex. In contrast, the export of a subset of mRNPs depends on the exportin Crm1, which recognizes distinct NES-containing adaptors, such as NXF3 or LRPPRC, bound to specific cis-acting mRNA elements [7,8].

Recent reviews have paid attention to the molecular mechanisms underlying mRNP assembly and export and to their tight connections with mRNA transcription, processing and nuclear organization, in yeast and/or in metazoans [4–9]. The present review will be focused on the role of NPCs in mRNA export from yeast to human. We will first briefly review the known function of FG-domains, scaffold nucleoporins and NPC-associated proteins in constitutive mRNA export. We will then summarize our current knowledge on the role of NPC-associated proteins in mRNA quality control prior to export, an expanding field of research. Finally, we will show how regulatory mechanisms targeting NPCs have been proposed to interfere with mRNA export during cell cycle and development or in stress and disease situations.
Figure 1. Nucleoporins and nuclear pore complex (NPC)-associated proteins involved in mRNA export. The approximate relative positioning of nucleoporins or NPC subcomplexes within the NPC framework is represented in budding yeast (left) and vertebrates (right) (according to [10]). Phenylalanine-glycine (FG)-nucleoporins appear in red. Nucleoporins (Nups) or NPC-associated proteins with a reported contribution to mRNA export are indicated in bold (see Table 1). The names of proteins involved in mRNA quality control are underlined (see Table 2). Factors targeted by regulatory events occurring in normal or pathological situations and mentioned in the text (Sections 4 and 5) are indicated by a black dot. Proteins carrying an enzymatic activity are boxed in yellow. Alternative names for vertebrate nucleoporins are the following: Nup358 = RanBP2; Gle2 = Rae1; Nup35 = Nup53; Nup58 = Nup45; Elys = MEL28; hCG1 = NPL1. The Y-complex is boxed by a thick black line. Note that the inactivation of each Y-complex subunit has not systematically been proven to trigger mRNA export defects: in yeast, seh1 and sec13 mutants do not affect mRNA export [11]; in mammals, mRNA export inhibition has solely been reported upon Nup133 or Nup107 siRNA-mediated depletion [12,13] or upon expression of dominant negative fragments of Nup133 or Nup160 [14]. ONM, outer nuclear membrane; INM, inner nuclear membrane.
2. Role of NPC Components in Constitutive mRNA Export

Multiple approaches have been used to characterize the main steps of mRNA export through NPCs and the nucleoporins involved in this process. Genetic screens performed in yeast, followed by microscopy detection of poly(A) RNAs by fluorescence in situ hybridization (FISH) in mutants, have been instrumental in identifying most of the nucleoporins contributing to mRNA export [15,16] (Table 1). Imaging in large metazoan cells has further made it possible to gain access to the choreography of mRNP transport through NPCs [5,17]. Early electron microscopy studies had visualized the interactions between the NPC and a large mRNP in the dipteran Chironomus [18,19]. More recently, live tracking of single mRNPs, individually labeled with fluorophores, revealed that nuclear export of mRNAs through NPCs can be divided into three sequential steps: docking of the mRNP at the nucleoplasmic face, transport through the pore channel and release from the cytoplasmic face [20–22].

2.1. FG-Nucleoporins Are Critical for mRNP Transport

The low-affinity interactions between transport receptors and distinct classes of FG-domains found in central and peripheral nucleoporins are the basis for all of the proposed models of translocation [2,3]. Consistently, FG-nucleoporins play a pivotal role in mRNA export through their conserved interaction with mRNA export receptors (Figure 1). The export receptors, Mex67-Mtr2 and Tap-p15, respectively interact with most yeast and vertebrate FG-nucleoporins in vitro, and this interaction is critical for their recruitment at NPCs and, subsequently, for mRNA export in vivo [23–28].

### Table 1. Nucleoporins involved in mRNA export in yeast.

| Symmetric Nups | FG Repeats | Phenotypes Observed upon Inactivation | References |
|----------------|------------|-------------------------------------|------------|
| Nup53          | FG         | V                                  | n.d.       |
| Nup59          | FG         | V                                  | n.d.       |
| Nup133         | ts         | –                                  | [32,33]    |
| Nup133         | ts         | –                                  | [11]       |
| Nup145-C       | ts         | –                                  | [34–36]    |
| Nup84          | ts         | –                                  | [37]       |
| Nup120         | ts         | –                                  | [38,39]    |
| Sec13          | L a        | +                                  |            |
| Seh1           | cs         | +                                  |            |
| Nic96          | L          | +                                  |            |
| Nup188         | V          | +                                  |            |
| Nup192         | L          | +                                  |            |
| Nsp1           | FG, FxFG   | L                                  | +          |
| Nup57          | GLFG       | L                                  | – b        |
| Nup49          | GLFG       | L                                  | –          |
| Nup145-N       | GLFG       | V                                  | +          |
### Table 1. Cont.

| Symmetric Nups | FG Repeats | Viability | mRNA Export | References |
|----------------|------------|-----------|--------------|------------|
| Nup116         | FG, GLFG   | L/ts       | − c          | [31]       |
| Gle2           | ts         | −          |              | [40]       |
| Nup100         | GLFG       | V          | +            |            |
| Ndc1           | L          | n.d.       |              |            |
| Pom34          | V          | n.d.       |              |            |
| Pom152         | V          | +          |              |            |
| Pom33          | V          | +          |              |            |

| Asymmetric Nups | FG Repeats | Viability | mRNA Export | References |
|-----------------|------------|-----------|--------------|------------|
| Nup82           | L          | −         |              | [41,42]    |
| Nup159          | FG         | L         | −            | [43]       |
| Nup42           | FG         | V         | − d          | [44–46]    |
| Gle1            | L          | −         |              | [47]       |
| Dpb5            | L          | −         |              | [48,49]    |
| Nup60           | FxF        | V         | −            | [50]       |
| Nup1            | FxFG       | L/ts       | −            | [28,51,52] |
| Nup2            | FxFG       | V          | − b          | [28]       |
| Mlp1            | V          | +         |              |            |
| Mlp2            | V          | +         |              |            |

The types of FG-repeats [29], as well as the growth phenotypes observed upon inactivation of each yeast nucleoporin [16,30] are indicated: V, viable; L, lethal; ts, thermosensitive; cs, cold-sensitive. mRNA export phenotypes have been assayed using deletion mutants (for non-essential nucleoporins) or truncation or conditional alleles (for essential nucleoporins): (+), normal mRNA export in the corresponding mutant; (−), mRNA export defects reported in the mutant; n.d., not determined. a Sec13 essentiality may be related to its function in the essential process of secretion. b In this case, the effect on mRNA export has only been reported in the context of combined FG deletions [28]. c While the *nup116* deletion mutant exhibits mRNA export defects, most likely caused by nuclear envelope abnormalities, deletion of Nup116 glycine-leucine-phenylalanine-glycine (GLFG) repeats does not trigger mRNA retention. d Nup42 is required for mRNA export under heat shock conditions, but is dispensable for mRNA export under normal growth conditions. e Nup116 and Nup1 essentiality depends on the genetic background [16,30,31].

The detailed analysis of the contribution of each FG-nucleoporin to mRNA export was further genetically dissected through combined deletion of FG-domains in yeast [28]. Central FG-repeats, which typically encompass GLFG motifs, were found to be essential for viability, while peripheral FG-repeats are dispensable for growth [28,29]. From these studies, four FG-nucleoporins have emerged as key players for efficient Mex67 recruitment at NPCs and mRNA export: Nup49, Nup57, Nup1 and Nup2 [28]. The corresponding FG-domains appear to be redundant, since none of them is individually required for mRNA export, and are somehow pathway-specific, since distinct FG-domains are required for protein import [28,29]. In view of their localization at the nuclear basket (Nup1, Nup2) and within the central channel (Nup49, Nup57), these FG-nucleoporins are likely to be the main players in mRNP docking and translocation, respectively. Orthologue components within the vertebrate NPC were also shown to contribute to mRNA export: Nup153, an FG-nucleoporin of the nuclear basket that shares certain features with yeast Nup1 [53,54], and the Nup62 complex [27,55],
which is the orthologue of the yeast Nup57-Nup49-Nsp1 complex (Figure 1), participate in mRNP docking and translocation, respectively. In addition, other vertebrate FG-nucleoporins, such as Nup98 (complexed with Gle2/Rae1), also contribute to mRNA export [56,57].

At the cytoplasmic face of the NPC, the FG-domains of Nup159 and Nup42, albeit not essential for mRNA export, contribute to this process by positioning mRNPs for remodeling steps in yeast (see below, Section 2.3) [58]. Strikingly, FG “swap” experiments, replacing these cytoplasmic FG repeats with repeats of other FG-nucleoporins, demonstrated that all FG motifs are not functionally equivalent [58]. In metazoans, mRNA export defects have also been observed in the absence of two FG-nucleoporins of the cytoplasmic face of NPCs, namely Nup214 [59] and Nup358/RanBP2 [60].

2.2. Non-FG-Nucleoporins May Provide Additional mRNP Binding Sites

In addition to FG-nucleoporins, genetic approaches also identified other nucleoporins as required for mRNA export in yeast, most of them being components of the Nup84 complex (also referred to as Y-complex; Figure 1) [16,61]. Indeed, inactivation of Nup84, Nup85, Nup120, Nup133 or Nup145-C similarly leads to mRNA export defects, without any detectable consequences on protein transport [11,32–35,37–39]. These mutations were also found to trigger NPC clustering, a phenotype that can however be uncoupled from mRNA export defects in some specific nup133 and nup85 mutant alleles [32,62]. Importantly, the function of the Y-complex in mRNA export is conserved in vertebrates and plants [61]. In particular, expression of dominant negative fragments of Nup133 or Nup160 [14], or knockdown of Nup107 or Nup133, which impairs NPC assembly [12,13], inhibits mRNA export in HeLa cells. While the Y-complex could contribute to mRNA export through its function as an essential building block of the NPC scaffold, it could also provide additional binding sites for mRNPs at NPCs. Indeed, the Y-complex was shown to directly interact with Mex67-Mtr2 through its Nup85 subunit in yeast [62,63].

Interestingly, structural studies or fold assignment have identified RNA binding motifs within non-FG domains in mammalian Nup153 [64], Nup35 [65] and RanBP2 [66] and in yeast Nup53 and Nup59 [67]. Since these motifs could also serve protein-protein interaction purposes, their involvement in mRNA export in vivo awaits further validation. An RNA binding surface has also been characterized in the human Nup98-Gle2 complex [68]. The function of this region in mRNA export is further supported by the reported interaction between Gle2 and poly(A) RNAs in cross-linking experiments in HeLa cells [69] and by the mRNA retention phenotypes caused by Gle2 inactivation, both in yeast and vertebrate cells [40,70,71].

2.3. NPC-Associated Factors Control mRNP Docking and Release

At the nucleoplasmic face of NPCs, multiple non-FG factors contribute to mRNP docking prior to export, including the nuclear basket proteins, Mlp1 and Mlp2 (myosin-like proteins), in yeast (see Section 3 and Figure 1). In addition, the conserved TREX2 (transcription and export) complex couples transcription with mRNA export at NPCs [50,72–74]. In yeast, the Sac3 subunit of TREX2 interacts with Nup1 at NPCs via its C-terminal domain and with Mex67-Mtr2 via its N-terminal domain, which contains degenerate FG repeats [50], therefore providing an additional mRNP binding site at the nuclear basket.
mRNP release, a critical step in mRNA export, occurs at the cytoplasmic side of NPCs. Studies from several groups have highlighted an essential function in this process performed by Dbp5 (also called DDX19 in mammals), a conserved DEAD-box ATP-dependent RNA helicase associated with NPC cytoplasmic filaments and required for mRNA export [48,49,75]. Nucleotide-dependent conformational changes of Dbp5 were shown to promote mRNP remodeling events, leading to the displacement of Mex67 and Nab2 from mRNPs in yeast [76,77], thus ensuring the irreversibility of the mRNA transport process. Directionality is further provided by the local activation of Dbp5 at the cytoplasmic side of NPCs. Indeed, the ATP-ADP nucleotide cycle and the remodeling activity of Dbp5 are controlled by two components of the cytoplasmic filaments, Gle1, bound to its cofactor, inositol hexakisphosphate (IP6) [78,79], and the N-terminal non-FG domain of Nup159 (Nup214 in mammals) [80–82]. Besides these two factors, this process requires in yeast: (i) Nup82, a non-FG-Nup anchoring Nup159 to the NPC scaffold; (ii) Nup42, which tethers Gle1 to the cytoplasmic filaments; and (iii) the Nup159 and Nup42 FG-domains that position Mex67-bound mRNPs in close vicinity of Dbp5 [58]. Multiple factors therefore contribute to the termination of mRNP export at the cytoplasmic face of NPCs (Figure 1), and this system is remarkably conserved from yeast to metazoans [75,80,83].

3. mRNA Quality Control at the Nuclear Basket of NPCs

mRNA quality control (QC) designates the mechanisms by which cells discard incompletely processed or improperly assembled mRNPs, avoiding their accumulation, which would be detrimental for protein homeostasis [84]. Although QC is mainly ensured by nuclear and cytoplasmic RNA degradation activities, several reports have indicated that proteins anchored at the nucleoplasmic side of NPCs contribute to a QC step prior to mRNA export. This function of the nuclear basket was initially inferred from studies of its constituents, Mlp1-2, in yeast or its orthologue, Tpr (translocated promoter region), in mammals. While inactivation of these proteins does not affect bulk mRNA export ([85,86] and the references therein), their overexpression results in nuclear accumulation of poly(A) RNAs, both in yeast and mammalian cells [85,87]. At that time, this observation was interpreted as a possible consequence of the titration of factors necessary for efficient mRNA export. This relationship with mRNA export was further confirmed, initially in yeast and, more recently, in mammals.

3.1. Mlp1-2, Central Players in mRNA QC in Yeast

Multiple physical interactions have been identified between Mlp1-2 and mRNPs: beside a direct, well-characterized interaction between Mlp1 and the RNA-binding adaptor, Nab2 [88], recent proteomic analyses have revealed that Mlp1 and Mlp2 interactomes encompass multiple mRNP components [89,90]. These data imply that nuclear basket proteins could be primarily involved in the docking of mRNPs at the nuclear side of NPCs prior to their translocation. Consistent with these findings, specific abolition of the Mlp1-Nab2 interaction diminishes mRNA export efficiency [91]. While this last result suggests that Mlp1 would select Nab2-bound mRNPs and commit them for translocation, there is also evidence that Mlps can specifically anchor and retain improperly assembled mRNPs. Indeed, a persistent association was observed between Mlp2 and a mutant version of the Yra1 adaptor that appears unable to load the Mex67 export receptor onto mRNPs (GFP-yra1-8) [92]. The rescue of the growth defects of yeast yra1 or nab2 mRNP assembly mutants upon loss of Mlp1/2 [92]
further supports the idea that misassembled mRNPs would detrimentally get trapped onto the Mlp1/2 platform and released for export in their absence.

Docking mRNPs to the nuclear basket would not only monitor mRNP composition, but could also check the full completion of mRNA processing reactions. Since Nab2 is a poly(A)-binding protein required for proper poly(A) tail length [93], Mlp1-Nab2 interaction could specifically select the mRNA molecules that have undergone 3' processing. Mlp1 was also proposed to play a role in mRNA QC following splicing. A synthetic lethal screen using *MLP1* inactivation as a bait identified a mutant of the splicing factor Prp18, suggesting that Mlp1 function is essential when splicing is sub-optimal [94]. Using a dedicated *LacZ* reporter gene, it was further shown that *MLP1* deletion triggers the cytoplasmic leakage of intron-containing pre-mRNAs with no detectable effect on their splicing efficiency. Conversely, *MLP1* overexpression specifically traps mRNPs issued from an intron-containing reporter in the nucleus [94]. Similarly, overexpression of Nup211, the *S. pombe* homolog of Mlp1, decreases cytoplasmic leakage of pre-mRNAs accumulating upon pharmacological inhibition of splicing [95]. The QC function of Mlps, therefore, extends to the detection of splicing completion, although the mechanism of recognition of spliced mRNAs remains to be deciphered.

3.2. Multiple NPC-Associated Factors Contribute to mRNA QC in Yeast

Following these first reports, a number of nuclear pore-associated proteins were shown to contribute to NPC-associated QC in yeast (Table 2). Their contribution to QC was mainly scored using the aforementioned leakage reporter system; however, nuclear mRNP retention upon overexpression and genetic interactions with mutants of mRNP components have also been reported in some cases (Table 2). Remarkably, some of these factors (namely Mlp1-2, Pml39, Ulp1) are excluded from the NPCs present in the nucleolus-proximal region of the nuclear envelope, possibly reflecting their intimate connection with mRNP export [94,96,97].

mRNAs targeted by QC mechanisms are ultimately discarded by degradation activities. In this respect, NPC-associated QC has been reported to involve the Swt1 endonuclease, a fraction of which could transiently associate with NPCs, where it has been detected in specific mutant contexts [98]. Other degradation activities, such as the nuclear exosome, might also participate in this process.

NPC-associated QC has also been proposed to require specific post-translational modification events. Remodeling of mRNPs prior to export has been shown to involve ubiquitination-induced dissociation of Yra1 [99]. Since the growth defects of non-ubiquitinable mutants of Yra1 are suppressed upon *MLP1-2* deletion, this post-translational modification could contribute to the release of mRNPs from their docking sites at the nuclear basket. The SUMO-protease Ulp1 was also reported to prevent apparent pre-mRNA leakage, although QC-specific SUMOylated targets await identification [100].

Finally, it is important to point out that a number of non-NPC proteins were proposed to contribute to NPC-associated QC [101,102]. In particular, the SR-like proteins Hrb1 and Gbp2 have been proposed to mark properly spliced mRNPs and to commit them for export, possibly in relation to Mlp1 [102].
Table 2. NPC-associated proteins involved in mRNA QC prior to export in yeast. The proteins identified as contributing to mRNA QC in yeast are presented. QC phenotypes arising upon inactivation or overexpression of the protein are listed. The detection of leakage phenotypes with the LacZ-based reporter system (“pre-mRNA leakage”, (+)), as well as the names of the mRNP mutants that are rescued upon inactivation of the protein, are shown.

| Localization | Molecular function | Inactivation | Overexpression | References |
|--------------|-------------------|--------------|----------------|------------|
|              |                   | Pre-mRNA Leakage | mRNP Mutants rescued | Nuclear mRNP Accumulation |
| Mlp1         | Nuclear basket a | mRNP docking | + | ΔN-nab2
|              |                   |              | yra1-8          | + d,e [85,92,94,99] |
|              |                   |              | yra1-KR        |              |
|              |                   |              | ΔN-nab2        |              |
| Mlp2         | Nuclear basket a | mRNP docking | - | yra1-8 |
|              |                   |              | yra1-KR        | - d [85,92,94,99] |
|              |                   |              | tom1Δ          |              |
| Pml39        | Nuclear basket a | mRNP docking | ? | yra1-8 |
|              |                   |              | ΔN-nab2        | + e,f [96] |
| Nup60        | NPC               | Nuclear basket assembly | ? | n.d. |
|              |                   |              |               | n.d. [94]  |
| Esc1         | Inner nuclear membrane-associated | Nuclear basket assembly | ? | n.d. |
|              |                   |              |               | n.d. [100] |
| Ulp1         | NPC ab            | SUMO deconjugation | + | n.d. |
|              |                   |              |               | n.d. [100] |
| Swt1         | NPC c            | RNA degradation | + | n.d. |
|              |                   |              |               | + d [98]   |

Accumulation of mRNPs in the nucleus upon overexpression of the protein is indicated by a (+). n.d., not determined. a For these proteins, an asymmetrical localization at the nuclear periphery, excluded from the NPCs adjacent to the nucleolus, has been reported. b NPC localization of Ulp1 depends on several molecular determinants, including Nup60/Mlp1-2, the Y-complex and karyopherins [80]. c NPC localization of Swt1 has only been observed in specific mutant contexts [98]. d In this case, nuclear mRNA accumulation has been scored by FISH-based detection of poly(A) RNAs. e In this case, nuclear mRNA accumulation has been scored by FISH-based detection of LacZ mRNAs. f In this case, nuclear mRNP accumulation has been scored by Nab2 localization. Note that Tpr, the Mlp1-2 mammalian orthologue, is the only protein reported to function in a similar pathway in mammals. “?” putative molecular function.

3.3. mRNA QC at Nuclear Pores: A Conserved Pathway in Mammalian Cells?

While NPC-associated QC has been essentially characterized using the budding yeast model, its conservation has been recently highlighted in mammalian cells, in particular through the study of viral mRNA export. Some retroviruses, for instance the MPMV (Mason-Pfizer monkey virus), are known to export RNAs with retained introns through a dedicated cis-acting RNA element referred to as CTE (constitutive transport element), which has the ability to directly recruit the Tap mRNA export receptor (the human orthologue of yeast Mex67). Other retroviruses, such as HIV (human immunodeficiency virus), export their unspliced RNAs using the RRE (Rev-responsive element), a RNA structure that
recruits multiple copies of the NES-containing viral protein Rev, allowing mRNA export through the Crm1 pathway (reviewed in [103]). In recent studies, inactivation of Tpr, the Mlp1-2 human orthologue, was shown to increase the cytoplasmic localization and the translation of the intron-retaining form of a retrovirus-derived reporter RNA in a CTE-dependent manner [86,104]. Similar results were obtained with a non-viral CTE-containing reporter, but not with an RRE-containing construct, highlighting the specificity of this Tpr-dependent pathway for mRNA trafficking through Tap. Importantly, inactivation of Nup153, a nucleoporin previously shown to tether Tpr at the NPC [105], or expression of a Tpr mutant unable to interact with Nup153, similarly triggered the leakage of intron-retaining RNAs into the cytoplasm. Localization of Tpr at NPCs is therefore critical for its function in intron-containing mRNA retention [86].

It is noteworthy that the detection of mRNA QC phenotypes upon inactivation of nuclear pore components has mainly relied on the utilization of dedicated reporter systems, both in yeast and mammalian models. This raises the question of whether NPC-associated QC is biologically significant, eventually under specific physiological situations, and targets endogenous mRNAs. A recent report elegantly addressed this question, pointing to the potential importance of Tpr for the developmentally-programmed nuclear retention of a subset of mRNAs [106]. During neuron formation, a defined set of neuron-specific mRNAs, such as STX1b, undergoes regulated splicing, export and translation, while in non-neuronal cells expressing the splicing regulator, Ptbp1, these same mRNAs are improperly spliced, retained in the nucleus and degraded in a Tpr-dependent manner [106]. This example shows how NPC-associated QC could contribute to the control of gene expression programs in specific situations; whether additional examples of regulation via similar mechanisms exist deserves future investigations.

4. Role of NPCs in the Control of mRNA Export during Cell Cycle, Development and Stress

Transcriptional and post-transcriptional mechanisms are known to modulate the expression of cell cycle- and lineage-specific genes, thereby playing a key role in cell cycle progression, development and differentiation. During response to stress, the activation of specific signaling pathways also leads to changes in protein production, including the induction of molecular chaperones, which are essential for adaptation. Increasing evidence suggests that nucleoporins could contribute to these diverse regulatory events by controlling mRNA trafficking.

4.1. Modifications of NPCs and Cell Cycle-Dependent Changes in mRNA Export

In mammals, cell cycle-driven changes in mRNA export have been associated with oscillations of the levels of the nucleoporin Nup96, a subunit of the Y-complex. During mitosis (M), Nup96 is modified by ubiquitination and subsequently degraded by the proteasome. Interestingly, decreased levels of Nup96, as observed in M and G1, are associated with specific changes in the nuclear export of a subset of mRNAs, some of them encoding cell cycle regulators involved in the G1/S transition [107]. A post-translational modification targeting a unique nucleoporin can therefore regulate the nuclear export of a limited number of target mRNAs, thereby coordinating cell cycle progression. This generic NPC subunit could control mRNA export through direct interactions with specific mRNA-associated factors, either at the NPC or in the nucleoplasm, as proposed in [108]. Furthermore, this function of
Nup96, and possibly additional regulatory mechanisms, could account for the global changes in bulk mRNA export observed during the cell cycle, in view of the decreased mRNA export detected in G1 as compared to G2 human cultured cells [107].

Nucleoporins, including Y-complex subunits, are modified by other post-translational modifications, in particular cell cycle-dependent phosphorylation [109]. While nucleoporin phosphorylation has been demonstrated to contribute to NPC disassembly or to modulate protein transport (see, for instance, [110,111]), it has not been shown to influence mRNA trafficking. However, Cdk1-dependent phosphorylation of Nup1 is required in budding yeast for the localization of some active genes at the nuclear periphery, a process known as gene gating [112]. Dephosphorylation of Nup1 has been proposed to account for the loss of peripheral localization observed for these genes during the S-phase. This regulatory mechanism could drive cell cycle-dependent changes in mRNA trafficking, since gene gating has been proposed to couple transcription with mRNA export at NPCs [112]. The multiple connections previously identified between NPCs and gene expression [2,113] could represent a target for similar regulations.

4.2. NPCs and Cell Cycle-Dependent Cytoplasmic Targeting of mRNAs

NPCs are not only important for the nuclear export of mRNAs, but have also important roles in their cytoplasmic localization following export. Such connections were observed early during flagellation in the green algae, Chlamydomonas reinhardtii, when NPC polarization to the posterior side of the nucleus is associated with the asymmetrical localization of the β2-tubulin transcript in the cytoplasm [114]. Asymmetrical mRNA localization has also been studied in budding yeast. The best characterized example is the mating-type switching regulator Ash1, whose mRNA is specifically localized to the daughter cell prior to cytokinesis. Strikingly, a subset of mRNAs that, similar to ASH1, are regulated during the cell cycle and exhibit asymmetrical localization in the cytoplasm, specifically require the nucleoporin Nup60 for their export out of the nucleus and their cytoplasmic targeting [115]. While this function of Nup60 in the fate of the mRNA remains to be understood, it provides an additional example of a crosstalk between nuclear basket proteins and mRNA metabolism.

4.3. NPC-Associated Proteins and mRNA Export during Development

Several analyses have revealed that NPC-associated proteins contributing to mRNA export are important for developmental processes. In plants, a number of mutants affecting nucleoporins or NPC-associated factors (including Y-complex, Mlps/Tpr and Ulp1 orthologues) exhibit poly(A) RNA export defects in association with multiple physiological or developmental abnormalities (reviewed in [116]). Plant mutants of the Y-complex also display altered levels for mRNAs encoding core circadian clock components, further supporting the notion that NPCs could contribute to the regulation of mRNA export and stability for a defined subset of mRNAs [117]. Of note, Y-complex mutations also lead to mRNA export defects in association with developmental deficiencies in metazoans. Nup96+/− heterozygous mice display alterations of the immune system and increased susceptibility to viral infections in association with defined mRNA export defects in immune cells [118]. In these different situations, it remains to be demonstrated whether abnormal export of specific mRNAs would be the unique cause of the developmental defects.
4.4. NPCs and Regulation of mRNA Export upon Stress

It is known that upon heat shock (HS), the export of heat shock protein (HSP)-encoding mRNAs occurs efficiently, favoring chaperone production, while poly(A) non-HSP mRNAs are specifically retained within the nucleus, both in yeast and mammalian cells [119,120]. Although in yeast, the HSP mRNA export process involves the core mRNA export machinery, including Mex67 and NPC components [46,119], it depends on fewer factors than bulk mRNA export [121], suggesting that it could be more resistant to stress-induced alterations of export activities.

Recently, the MAP kinase Slt2 was found to be critical for HS-induced retention of non-HSP mRNAs in yeast [122], suggesting the existence of phosphorylation events, either within mRNPs or at NPCs, that could trigger export inhibition. In addition, during HS, Mlp1 leaves the NPCs and forms intranuclear foci that sequester some mRNA-binding proteins, possibly affecting their recruitment onto mRNAs [122]. Identifying which signaling events ultimately lead to Mlp1 dissociation from NPCs will be required to refine our understanding of these processes. Notably, its mammalian orthologue, Tpr, is phosphorylated by several kinases, including MAP kinases [123], although the functional impact of these modifications on mRNA export remains to be determined. Tpr is also functionally important for HSP mRNA export through its interaction with the HS-induced transcriptional activator HSF1 [124]. The mechanisms used to favor HSP mRNA export at NPCs, hence, differ between species: in yeast, dissociation of the nuclear basket component Mlp1 may possibly inhibit non-HSP mRNA export, while docking of HSF1-bound HSP genes at the Tpr/nuclear basket would favor HSP mRNA export in mammals.

Other stress situations have been shown to target mRNA export at NPCs in yeast, either by triggering nucleoporin phosphorylation or by altering NPC composition. Phosphorylation of Nup1, Nup2 and Nup60 by the stress-activated kinase, Hog1, occurs upon osmotic stress, and these modifications have been proposed to contribute to optimal expression and export of stress-inducible mRNAs [125]. Other studies report that Gle2 and Dbp5 dissociate from NPCs in different stress conditions leading to inhibition of mRNA export [126,127]. In this last case, however, it remains to be determined how exposure to stress ultimately influences NPC composition.

5. NPCs and Dysregulation of mRNA Export in Disease Situations

In agreement with their key role at the interface between the nucleus and the cytoplasm, several NPC components have been identified as modified in different pathological situations, including genetic diseases, cancers and viral infections [103,128–130]. Since the integrity of the mRNA export process has not been investigated systematically in all of these situations, we will focus here on the cases for which mRNA export defects have been reported.

5.1. Alteration of the NPC Scaffold and Dysregulation of mRNA Export

Only a few non-FG-nucleoporins have been associated with diseases. Mutation of a central scaffold nucleoporin, Nup155, is responsible for a cardiac disorder referred to as atrial fibrillation (AF) [131]. Strikingly, both the missense Nup155 mutation found in AF, that affects Nup155 targeting to NPCs, and a reduction of Nup155 levels trigger a specific inhibition of HSP70 mRNA export [131]. AF-associated
mRNA export defects might be actually caused by improper localization of Gle1. Indeed, nuclear retention of HSP70 mRNAs occurs in association with Gle1 delocalization upon knockdown of hCG1, which interacts with Nup155 and Gle1 [132]. However, to what extent these molecular events underlie the etiology of AF remains to be determined.

5.2. Alteration of the Cytoplasmic Filaments and Dysregulation of mRNA Export

Mutations in Gle1 have been described in LCCS-1 (lethal congenital contracture syndrome 1), a genetic disease characterized by a complete fetal immobility in association with neuronal and muscular defects [133]. Further analyses of a zebrafish model of Gle1 depletion revealed neurogenic and non-neurogenic developmental defects that cause LCCS-1-like phenotypes [134]. The molecular alterations caused by the Gle1 mutations linked to LCCS-1 were investigated in yeast and HeLa cells. The main homozygous mutation found in LCCS-1 cases results in the insertion of a proline-phenylalanine-glutamine (PFQ) tripeptide within the essential N-terminal coiled-coil domain of Gle1, disturbing Gle1 oligomerization at NPCs and subsequently triggering mRNA export defects [135]. Interestingly, other Gle1 mutations found in LCCS-1 or LAAHD (lethal arthrogryposis with anterior horn cell disease), a related disease, lead to delocalization of Gle1 from NPCs [136]. Defects in Gle1-dependent mRNP release at the cytoplasmic face of NPCs are therefore likely to contribute to both LCCS-1 and LAAHD diseases.

Remodeling of the cytoplasmic filaments has also been observed in another disease-related situation. The translation initiation factor eIF4E, an oncogenic protein that is upregulated in about 30% of cancers [137], is known to function as a specific mRNA export adaptor for a subset of mRNAs [7,8]. Overexpression of eIF4E alters the cytoplasmic face of the NPC by increasing Gle1 and Dbp5 levels, while reducing Nup358/RanBP2 stability and relocalizing Nup214 in the nucleoplasm [138]. This remodeling of the cytoplasmic filaments appears to somehow favor the export of eIF4E target mRNAs, although the underlying molecular mechanisms remain to be determined. Such oncogene-mediated reprogramming of the NPC and its impact on mRNA export and gene expression are expected to contribute to cellular transformation [138].

5.3. FG-Nucleoporins Targeted by Viruses and Inhibition of Cellular mRNA Export

DNA viruses, whose genome is transcribed in the host nucleus, and RNA viruses, which primarily replicate in the cytoplasm, have evolved multiple strategies to inhibit the export of cellular mRNAs. These mechanisms could prevent the expression of factors of innate immunity, favor the translation of viral RNAs and, in certain situations, their nuclear export [103,129]. In some cases, viruses inhibit cellular mRNA export by triggering changes in the NPC.

Notably, RNA viruses from both Enterovirus and Cardiovirus genera can block cellular mRNA export in association with the alteration of the NPC structure [139–142]. On the one hand, the protease 2A (2Apro) of Enteroviruses triggers the cleavage of Nup153, Nup98 and Nup62, precisely removing the FG-domains in the latter case ([143] and the references therein). Expression of 2Apro, but not of an inactive version of the protease, leads to a block of cellular mRNA export in HeLa cells [139]. On the other hand, the Leader protein (L) of Cardioviruses triggers hyperphosphorylation of Nup62, Nup153, Nup214 and Nup98, most likely by hijacking cellular kinases [144–146]. Concomitantly, expression of the L protein causes mRNA export inhibition [146]. Viruses thus impair cellular mRNA export by
Genes 2014, 5 targeting the same subset of FG-nucleoporins, albeit with different molecular strategies. Of note, protein import is also altered in infected cells, raising the possibility that mRNA export inhibition could partially result from defective recycling of mRNP export factors [144,145,147].

At least two other RNA viruses specifically target Nup98. The M protein of members of the Vesiculovirus genus can inhibit bulk mRNA export [148,149]. Remarkably, the M protein can form a tripartite complex with Nup98 and Gle2 in which it occupies the RNA binding motif of Gle2 [150–153]. As the M protein is at least partially localized at the nuclear rim, formation of this complex at NPCs may compete with mRNP binding [150]. Likewise, the NS1 protein of influenza A virus can inhibit cellular mRNA export by binding to Tap-p15 and Gle2 and by altering Nup98 protein levels [71,154].

Remarkably, treatment with interferon-gamma (IFNγ), which is known to establish an anti-viral state in the cells, induces the expression of both Nup98 and Gle2 and fully reverts the mRNA export inhibition induced by Vesiculovirus infection or Enterovirus 2Apro expression [139,155,156]. On the contrary, Nup98+/- or Gle2+/- mouse cells display defects in the export of mRNAs encoding immune factors and, consistently, are highly susceptible to influenza virus-mediated cell death [71]. Nup98/Gle2-dependent mRNA export is therefore critical for resistance to viral infections and appears to be a preferred target of viruses.

6. Conclusions

Increasing evidence suggests that mRNA export can be modulated by regulatory events targeting key players in this process at the NPC (Figure 1). As detailed above (Sections 4 and 5), three non-exclusive types of nucleoporin modifications have been reported, or proposed, to affect mRNA export: (i) a change in protein levels (caused by variations in stability or expression); (ii) delocalization from NPCs; and (iii) modification at NPCs, including phosphorylation, cleavage or altered oligomerization. These modifications can occur in normal or pathological situations and suggest that NPCs could integrate the information arising from multiple signaling pathways. In this respect, FG-nucleoporins and the Y-complex appear as preferred targets for a number of regulatory events. In the future, it will be important not only to identify novel modifications targeting these proteins, but also to characterize the consequences on mRNA export of previously described modifications, such as Y-complex phosphorylation [109] or ubiquitination [157]. Additional studies will be required to determine the molecular consequences of such modifications on mRNP binding and translocation.

Remarkably, only a few enzymatic activities are associated with NPCs (Figure 1); yet, they all target mRNAs and/or mRNA-associated proteins. While the helicase activity of Dbp5 is crucial for mRNP remodeling and release upon export, the endonuclease activity of Swt1 appears important for mRNA QC prior to export in yeast. Of note, the SUMO-protease activity of yeast Ulp1 and the SUMO-ligase activity of mammalian Nup358/RanBP2 have both been shown to target mRNA-associated proteins [90,158]. Whether these modifications could also contribute to the regulation of mRNA export remains an open question.

Acknowledgments

We are very grateful to Valérie Doye for support, to Domenico Libri and members of our lab for critical reading of the manuscript and to Anne-Lise Haenni for style supervision. This work was
supported by the Centre National de la Recherche Scientifique, the Fondation ARC pour la Recherche sur le Cancer (“Projet ARC”, to Benoit Palancade) and Ligue Nationale contre le Cancer (Comité d’Ile de France, to Benoit Palancade). Amandine Bonnet was the recipient of a post-doctoral fellowship from the Ligue Nationale contre le Cancer.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Wente, S.R.; Rout, M.P. The nuclear pore complex and nuclear transport. Cold Spring Harb. Perspect. Biol. 2010, 2, a000562.
2. Floch, A.G.; Palancade, B.; Doye, V. Fifty years of nuclear pores and nucleocytoplasmic transport studies: Multiple tools revealing complex rules. Methods Cell Biol. 2014, 122, 1–40.
3. Terry, L.J.; Wente, S.R. Flexible gates: Dynamic topologies and functions for FG nucleoporins in nucleocytoplasmic transport. Eukaryot. Cell 2009, 8, 1814–1827.
4. Nino, C.A.; Herissant, L.; Babour, A.; Dargemont, C. mRNA nuclear export in yeast. Chem. Rev. 2013, 113, 8523–8545.
5. Oeffinger, M.; Zenklusen, D. To the pore and through the pore: A story of mRNA export kinetics. Biochim. Biophys. Acta 2012, 1819, 494–506.
6. Tutucci, E.; Stutz, F. Keeping mRNPs in check during assembly and nuclear export. Nat. Rev. Mol. Cell Biol. 2011, 12, 377–384.
7. Culjkovic-Kraljacic, B.; Borden, K.L. Aiding and abetting cancer: mRNA export and the nuclear pore. Trends Cell Biol. 2013, 23, 328–335.
8. Natalizio, B.J.; Wente, S.R. Postage for the messenger: Designating routes for nuclear mRNA export. Trends Cell Biol. 2013, 23, 365–373.
9. Bjork, P.; Wieslander, L. Mechanisms of mRNA export. Semin. Cell Dev. Biol. 2014, 32, 47–54.
10. Wozniak, R.; Burke, B.; Doye, V. Nuclear transport and the mitotic apparatus: An evolving relationship. Cell Mol. Life Sci. 2010, 67, 2215–2230.
11. Siniossoglou, S.; Wimmer, C.; Rieger, M.; Doye, V.; Tekotte, H.; Weise, C.; Emig, S.; Segref, A.; Hurt, E.C. A novel complex of nucleoporins, wich includes Sec13p and a Sec13p homolog, is essential for normal nuclear pores. Cell 1996, 84, 265–275.
12. Boehmer, T.; Enninga, J.; Dales, S.; Blobel, G.; Zhong, H. Depletion of a single nucleoporin, Nup107, prevents the assembly of a subset of nucleoporins into the nuclear pore complex. Proc. Natl. Acad. Sci. USA 2003, 100, 981–985.
13. Walther, T.C.; Alves, A.; Pickersgill, H.; Loidice, I.; Hetzer, M.; Galy, V.; Hulsmann, B.B.; Kocher, T.; Wilm, M.; Allen, T.; et al. The conserved Nup107-160 complex is critical for nuclear pore complex assembly. Cell 2003, 113, 195–206.
14. Vasu, S.; Shah, S.; Orjalo, A.; Park, M.; Fischer, W.H.; Forbes, D.J. Novel vertebrate nucleoporins Nup133 and Nup160 play a role in mRNA export. J. Cell Biol. 2001, 155, 339–354.
15. Amberg, D.C.; Goldstein, A.L.; Cole, C.N. Isolation and characterization of RAT1: An essential gene of Saccharomyces cerevisiae required for the efficient nucleocytoplasmic trafficking of mRNA. *Genes Dev.* **1992**, *6*, 1173–1189.

16. Doye, V.; Hurt, E. From nucleoporins to nuclear pore complexes. *Curr. Opin. Cell Biol.* **1997**, *9*, 401–411.

17. Sheinberger, J.; Shav-Tal, Y. The dynamic pathway of nuclear RNA in eukaryotes. *Nucleus* **2013**, *4*, 195–205.

18. Kiseleva, E.; Goldberg, M.W.; Allen, T.D.; Akey, C.W. Active nuclear pore complexes in Chironomus: Visualization of transporter configurations related to mRNP export. *J. Cell Sci.* **1998**, *111*, 223–236.

19. Mehlin, H.; Daneholt, B.; Skoglund, U. Structural interaction between the nuclear pore complex and a specific translocating RNP particle. *J. Cell Biol.* **1995**, *129*, 1205–1216.

20. Grunwald, D.; Singer, R.H. In vivo imaging of labelled endogenous beta-actin mRNA during nucleocytoplasmic transport. *Nature* **2010**, *467*, 604–607.

21. Mor, A.; Suliman, S.; Ben-Yishay, R.; Yunger, S.; Brody, Y.; Shav-Tal, Y. Dynamics of single mRNP nucleocytoplasmic transport and export through the nuclear pore in living cells. *Nat. Cell Biol.* **2010**, *12*, 543–552.

22. Siebrasse, J.P.; Kaminski, T.; Kubitscheck, U. Nuclear export of single native mRNA molecules observed by light sheet fluorescence microscopy. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 9426–9431.

23. Katahira, J.; Strasser, K.; Podtelejnikov, A.; Mann, M.; Jung, J.U.; Hurt, E. The Mex67p-mediated nuclear mRNA export pathway is conserved from yeast to human. *EMBO J.* **1999**, *18*, 2593–2609.

24. Strasser, K.; Bassler, J.; Hurt, E. Binding of the Mex67p/Mtr2p heterodimer to FXFG, GLFG, and FG repeat nucleoporins is essential for nuclear mRNA export. *J. Cell Biol.* **2000**, *150*, 695–706.

25. Bachi, A.; Braun, I.C.; Rodrigues, J.P.; Pante, N.; Ribbeck, K.; von Kobbe, C.; Kutay, U.; Wilm, M.; Gorlich, D.; Carmo-Fonseca, M.; *et al.* The C-terminal domain of TAP interacts with the nuclear pore complex and promotes export of specific CTE-bearing RNA substrates. *RNA* **2000**, *6*, 136–158.

26. Strawn, L.A.; Shen, T.; Wente, S.R. The GLFG regions of Nup116p and Nup100p serve as binding sites for both Kap95p and Mex67p at the nuclear pore complex. *J. Biol. Chem.* **2001**, *276*, 6445–6452.

27. Levesque, L.; Guzik, B.; Guan, T.; Coyle, J.; Black, B.E.; Rekosh, D.; Hammarskjold, M.L.; Paschal, B.M. RNA export mediated by tap involves NXT1-dependent interactions with the nuclear pore complex. *J. Biol. Chem.* **2001**, *276*, 44953–44962.

28. Terry, L.J.; Wente, S.R. Nuclear mRNA export requires specific FG nucleoporins for translocation through the nuclear pore complex. *J. Cell Biol.* **2007**, *178*, 1121–1132.

29. Strawn, L.A.; Shen, T.; Shulga, N.; Goldfarb, D.S.; Wente, S.R. Minimal nuclear pore complexes define FG repeat domains essential for transport. *Nat. Cell Biol.* **2004**, *6*, 197–206.

30. Giaever, G.; Chu, A.M.; Ni, L.; Connelly, C.; Riles, L.; Veronneau, S.; Dow, S.; Lucau-Danila, A.; Anderson, K.; Andre, B.; *et al.* Functional profiling of the Saccharomyces cerevisiae genome. *Nature* **2002**, *418*, 387–391.

31. Wente, S.R.; Blobel, G. A temperature-sensitive NUP116 null mutant forms a nuclear envelope seal over the yeast nuclear pore complex thereby blocking nucleocytoplasmic traffic. *J. Cell Biol.* **1993**, *123*, 275–284.
32. Doye, V.; Wepf, R.; Hurt, E.C. A novel nuclear pore protein Nup133p with distinct roles in poly(A)+ RNA transport and nuclear pore distribution. *EMBO J.* 1994, 13, 6062–6075.

33. Li, O.; Heath, C.V.; Amberg, D.C.; Dockendorff, T.C.; Copeland, C.S.; Snyder, M.; Cole, C.N. Mutation or deletion of the Saccharomyces cerevisiae RAT3/NUP133 gene causes temperature-dependent nuclear accumulation of poly(A)+ RNA and constitutive clustering of nuclear pore complexes. *Mol. Biol. Cell* 1995, 6, 401–417.

34. Fabre, E.; Boelens, W.C.; Wimmer, C.; Mattaj, I.W.; Hurt, E.C. Nup145p is required for nuclear export of mRNA and binds homopolymeric RNA in vitro via a novel conserved motif. *Cell* 1994, 78, 275–289.

35. Dockendorff, T.C.; Heath, C.V.; Goldstein, A.L.; Snay, C.A.; Cole, C.N. C-Terminal truncations of the yeast nucleoporin Nup145p produce a rapid temperature-conditional mRNA export defect and alterations to nuclear structure. *Mol. Cell. Biol.* 1997, 17, 906–920.

36. Teixeira, M.T.; Siniosoglou, S.; Podtelejnikov, S.; Benichou, J.C.; Mann, M.; Dujon, B.; Hurt, E.; Fabre, E. Two functionally distinct domains generated by in vivo cleavage of Nup145p: A novel biogenesis pathway for nucleoporins. *EMBO J.* 1997, 16, 5086–5097.

37. Goldstein, A.L.; Snay, C.A.; Heath, C.V.; Cole, C.N. Pleiotropic nuclear defects associated with a conditional allele of the novel nucleoporin Rat9p/Nup85p. *Mol. Biol. Cell* 1996, 7, 917–934.

38. Aitchison, J.D.; Blobel, G.; Rout, M.P. Nup120p: A yeast nucleoporin required for NPC distribution and mRNA transport. *J. Cell Biol.* 1995, 131, 1659–1675.

39. Heath, C.V.; Copeland, C.S.; Amberg, D.C.; del Priore, V.; Snyder, M.; Cole, C.N. Nuclear pore complex clustering and nuclear accumulation of poly(A)+ RNA associated with mutation of the Saccharomyces cerevisiae RAT2/NUP120 gene. *J. Cell Biol.* 1995, 131, 1677–1697.

40. Murphy, R.; Watkins, J.L.; Wente, S.R. GLE2, a *Saccharomyces cerevisiae* homologue of the *Schizosaccharomyces pombe* export factor RAE1, is required for nuclear pore complex structure and function. *Mol. Biol. Cell* 1996, 7, 1921–1937.

41. Grandi, P.; Emig, S.; Weise, C.; Hucho, F.; Pohl, T.; Hurt, E.C. A novel nuclear pore protein Nup82p which specifically binds to a fraction of Nsp1p. *J. Cell Biol.* 1995, 130, 1263–1273.

42. Hurwitz, M.E.; Blobel, G. NUP82 is an essential yeast nucleoporin required for poly(A)+ RNA export. *J. Cell Biol.* 1995, 130, 1275–1281.

43. Saavedra, C.A.; Hammell, C.M.; Heath, C.V.; Cole, C.N. Yeast heat shock mRNAs are exported through a distinct pathway defined by Rip1p. *Genes Dev.* 1997, 11, 2845–2856.

44. Stutz, F.; Kantor, J.; Zhang, D.; McCarthy, T.; Neville, M.; Rosbash, M. The yeast nucleoporin rip1p contributes to multiple export pathways with no essential role for its FG-repeat region. *Genes Dev.* 1997, 11, 2857–2868.

45. Vainberg, I.E.; Dower, K.; Rosbash, M. Nuclear export of heat shock and non-heat-shock mRNA occurs via similar pathways. *Mol. Cell. Biol.* 2000, 20, 3996–4005.

46. Murphy, R.; Wente, S.R. An RNA-export mediator with an essential nuclear export signal. *Nature* 1996, 383, 357–360.
48. Snay-Hodge, C.A.; Colot, H.V.; Goldstein, A.L.; Cole, C.N. Dbp5p/Rat8p is a yeast nuclear pore-associated DEAD-box protein essential for RNA export. *EMBO J.* **1998**, *17*, 2663–2676.
49. Tseng, S.S.; Weaver, P.L.; Liu, Y.; Hitomi, M.; Tartakoff, A.M.; Chang, T.H. Dbp5p, a cytosolic RNA helicase, is required for poly(A)+ RNA export. *EMBO J.* **1998**, *17*, 2651–2662.
50. Fischer, T.; Strasser, K.; Racz, A.; Rodriguez-Navarro, S.; Oppizzi, M.; Ihrig, P.; Lechner, J.; Hurt, E. The mRNA export machinery requires the novel Sac3p-Thp1p complex to dock at the nucleoplasmic entrance of the nuclear pores. *EMBO J.* **2002**, *21*, 5843–5852.
51. Bogerd, A.M.; Hoffman, J.A.; Amberg, D.C.; Fink, G.R.; Davis, L.I. Nup1 mutants exhibit pleiotropic defects in nuclear pore complex function. *J. Cell Biol.* **1994**, *127*, 319–332.
52. Schlaich, N.L.; Hurt, E.C. Analysis of nucleocytoplasmic transport and nuclear envelope structure in yeast disrupted for the gene encoding the nuclear pore protein Nup1p. *Eur. J. Cell Biol.* **1995**, *67*, 8–14.
53. Bastos, R.; Lin, A.; Enarson, M.; Burke, B. Targeting and function in mRNA export of nuclear pore complex protein Nup153. *J. Cell Biol.* **1996**, *134*, 1141–1156.
54. Ullman, K.S.; Shah, S.; Powers, M.A.; Forbes, D.J. The nucleoporin nup153 plays a critical role in multiple types of nuclear export. *Mol. Biol. Cell* **1999**, *10*, 649–664.
55. Dargemont, C.; Schmidt-Zachmann, M.S.; Kuhn, L.C. Direct interaction of nucleoporin p62 with mRNA during its export from the nucleus. *J. Cell Sci.* **1995**, *108*, 257–263.
56. Powers, M.A.; Forbes, D.J.; Dahlberg, J.E.; Lund, E. The vertebrate GLFG nucleoporin, Nup98, is an essential component of multiple RNA export pathways. *J. Cell Biol.* **1997**, *136*, 241–250.
57. Pritchard, C.E.; Fornerod, M.; Kasper, L.H.; van Deursen, J.M. RAE1 is a shuttling mRNA export factor that binds to a GLEBS-like NUP98 motif at the nuclear pore complex through multiple domains. *J. Cell Biol.* **1999**, *145*, 237–254.
58. Adams, R.L.; Terry, L.J.; Wente, S.R. Nucleoporin FG domains facilitate mRNP remodeling at the cytoplasmic face of the nuclear pore complex. *Genetics* **2014**, *197*, 1213–1224.
59. Van Deursen, J.; Boer, J.; Kasper, L.; Grosveld, G. G2 arrest and impaired nucleocytoplasmic transport in mouse embryos lacking the proto-oncogene CAN/Nup214. *EMBO J.* **1996**, *15*, 5574–5583.
60. Forler, D.; Rabut, G.; Ciccarelli, F.D.; Herold, A.; Kocher, T.; Niggeweg, R.; Bork, P.; Ellenberg, J.; Izaurrealde, E. RanBP2/Nup358 provides a major binding site for NXF1-p15 dimers at the nuclear pore complex and functions in nuclear mRNA export. *Mol. Cell. Biol.* **2004**, *24*, 1155–1167.
61. Gonzalez-Aguilera, C.; Askjaer, P. Dissecting the NUP107 complex: Multiple components and even more functions. *Nucleus* **2012**, *3*, 340–348.
62. Yao, W.; Lutzmann, M.; Hurt, E. A versatile interaction platform on the Mex67-Mtr2 receptor creates an overlap between mRNA and ribosome export. *EMBO J.* **2008**, *27*, 6–16.
63. Santos-Rosa, H.; Moreno, H.; Simos, G.; Segref, A.; Fahrenkrog, B.; Pante, N.; Hurt, E. Nuclear mRNA export requires complex formation between Mex67p and Mtr2p at the nuclear pores. *Mol. Cell. Biol.* **1998**, *18*, 6826–6838.
64. Ball, J.R.; Dimaano, C.; Bilak, A.; Kurchan, E.; Zundel, M.T.; Ullman, K.S. Sequence preference in RNA recognition by the nucleoporin Nup153. *J. Biol. Chem.* **2007**, *282*, 8734–8740.
65. Handa, N.; Kukimoto-Niino, M.; Akasaka, R.; Kishishita, S.; Murayama, K.; Terada, T.; Inoue, M.; Kigawa, T.; Kose, S.; Imamoto, N.; et al. The crystal structure of mouse Nup35 reveals atypical RNP motifs and novel homodimerization of the RRM domain. J. Mol. Biol. 2006, 363, 114–124.

66. Kassube, S.A.; Stuwe, T.; Lin, D.H.; Antonuk, C.D.; Napetschnig, J.; Blobel, G.; Hoelz, A. Crystal structure of the N-terminal domain of Nup358/RanBP2. J. Mol. Biol. 2012, 423, 752–765.

67. Devos, D.; Dokudovskaya, S.; Williams, R.; Alber, F.; Eswar, N.; Chait, B.T.; Rout, M.P.; Sali, A. Simple fold composition and modular architecture of the nuclear pore complex. Proc. Natl. Acad. Sci. USA 2006, 103, 2172–2177.

68. Ren, Y.; Seo, H.S.; Blobel, G.; Hoelz, A. Structural and functional analysis of the interaction between the nucleoporin Nup98 and the mRNA export factor Rae1. Proc. Natl. Acad. Sci. USA 2010, 107, 10406–10411.

69. Kraemer, D.; Blobel, G. mRNA binding protein mRNP 41 localizes to both nucleus and cytoplasm. Proc. Natl Acad. Sci. USA 1997, 94, 9119–9124.

70. Bharathi, A.; Ghosh, A.; Whalen, W.A.; Yoon, J.H.; Pu, R.; Dasso, M.; Dhar, R. The human RAEl gene is a functional homologue of Schizosaccharomyces pombe rae1 gene involved in nuclear export of Poly(A)+ RNA. Gene 1997, 198, 251–258.

71. Satterly, N.; Tsai, P.L.; van Deursen, J.; Nussenzveig, D.R.; Wang, Y.; Faria, P.A.; Levay, A.; Levy, D.E.; Fontoura, B.M. Influenza virus targets the mRNA export machinery and the nuclear pore complex. Proc. Natl. Acad. Sci. USA 2007, 104, 1853–1858.

72. Jani, D.; Lutz, S.; Marshall, N.J.; Fischer, T.; Kohler, A.; Ellisdon, A.M.; Hurt, E.; Stewart, M.; Sus1, Cdc31, and the Sac3 CID region form a conserved interaction platform that promotes nuclear pore association and mRNA export. Mol. Cell 2009, 33, 727–737.

73. Jani, D.; Lutz, S.; Hurt, E.; Laskey, R.A.; Stewart, M.; Wickramasinghe, V.O. Functional and structural characterization of the mammalian TREX-2 complex that links transcription with nuclear messenger RNA export. Nucleic Acids Res. 2012, 40, 4562–4573.

74. Umlauf, D.; Bonnet, J.; Waharte, F.; Fournier, M.; Stierle, M.; Fischer, B.; Brino, L.; Devys, D.; Tora, L. The human TREX-2 complex is stably associated with the nuclear pore basket. J. Cell Sci. 2013, 126, 2656–2667.

75. Schmitt, C.; von Kobbe, C.; Bachi, A.; Pante, N.; Rodrigues, J.P.; Boscheron, C.; Rigaut, G.; Wilm, M.; Seraphin, B.; Carmo-Fonseca, M.; et al. Dbp5, a DEAD-box protein required for mRNA export, is recruited to the cytoplasmic fibrils of nuclear pore complex via a conserved interaction with CAN/Nup159p. EMBO J. 1999, 18, 4332–4347.

76. Lund, M.K.; Guthrie, C. The DEAD-box protein Dpb3p is required to dissociate Mex67p from exported mRNPs at the nuclear rim. Mol. Cell 2005, 20, 645–651.

77. Tran, E.J.; Zhou, Y.; Corbett, A.H.; Wente, S.R. The DEAD-box protein Dpb5 controls mRNA export by triggering specific RNA: Protein remodeling events. Mol. Cell 2007, 28, 850–859.

78. Alcazar-Roman, A.R.; Tran, E.J.; Guo, S.; Wente, S.R. Inositol hexakisphosphate and Gle1 activate the DEAD-box protein Dpb5 for nuclear mRNA export. Nat. Cell Biol. 2006, 8, 711–716.

79. Weirich, C.S.; Erzberger, J.P.; Flick, J.S.; Berger, J.M.; Thorner, J.; Weis, K. Activation of the DExD/H-box protein Dpb5 by the nuclear-pore protein Gle1 and its coactivator InsP6 is required for mRNA export. Nat. Cell Biol. 2006, 8, 668–676.
80. Von Moeller, H.; Basquin, C.; Conti, E. The mRNA export protein DBP5 binds RNA and the cytoplasmic nucleoporin NUP214 in a mutually exclusive manner. *Nat. Struct. Mol. Biol.* 2009, 16, 247–254.

81. Noble, K.N.; Tran, E.J.; Alcazar-Roman, A.R.; Hodge, C.A.; Cole, C.N.; Wente, S.R. The Dbp5 cycle at the nuclear pore complex during mRNA export II: Nucleotide cycling and mRNP remodeling by Dbp5 are controlled by Nup159 and Gle1. *Genes Dev.* 2011, 25, 1065–1077.

82. Montpetit, B.; Thomsen, N.D.; Helmke, K.J.; Seeliger, M.A.; Berger, J.M.; Weis, K. A conserved mechanism of DEAD-box ATPase activation by nucleoporins and InsP6 in mRNA export. *Nature* 2011, 472, 238–242.

83. Hodge, C.A.; Tran, E.J.; Noble, K.N.; Alcazar-Roman, A.R.; Ben-Yishay, R.; Scarcelli, J.J.; Folkmann, A.W.; Shav-Tal, Y.; Wente, S.R.; Cole, C.N. The Dbp5 cycle at the nuclear pore complex during mRNA export I: Dbp5 mutants with defects in RNA binding and ATP hydrolysis define key steps for Nup159 and Gle1. *Genes Dev.* 2011, 25, 1052–1064.

84. Schmid, M.; Jensen, T.H. Transcription-associated quality control of mRNP. *Biochim. Biophys. Acta* 2013, 1829, 158–168.

85. Kosova, B.; Pante, N.; Rollenhagen, C.; Podtelejnikov, A.; Mann, M.; Aebi, U.; Hurt, E. Mlp2p, a component of nuclear pore attached intranuclear filaments, associates with nic96p. *J. Biol. Chem.* 2000, 275, 343–350.

86. Rajanala, K.; Nandicoori, V.K. Localization of nucleoporin Tpr to the nuclear pore complex is essential for Tpr mediated regulation of the export of unspliced RNA. *PLoS One* 2012, 7, e29921.

87. Bangs, P.; Burke, B.; Powers, C.; Craig, R.; Purohit, A.; Doxsey, S. Functional analysis of Tpr: Identification of nuclear pore complex association and nuclear localization domains and a role in mRNA export. *J. Cell Biol.* 1998, 143, 1801–1812.

88. Green, D.M.; Johnson, C.P.; Hagan, H.; Corbett, A.H. The C-terminal domain of myosin-like protein 1 (Mlp1p) is a docking site for heterogeneous nuclear ribonucleoproteins that are required for mRNA export. *Proc. Natl. Acad. Sci. USA* 2003, 100, 1010–1015.

89. Niepel, M.; Molloy, K.R.; Williams, R.; Farr, J.C.; Meinema, A.C.; Vecchietti, N.; Cristea, I.M.; Chait, B.T.; Rout, M.P.; Strambio-De-Castilla, C. The nuclear basket proteins Mlp1p and Mlp2p are part of a dynamic interactome including Esc1p and the proteasome. *Mol. Biol. Cell* 2013, 24, 3920–3938.

90. Bretes, H.; Rouviere, J.O.; Leger, T.; Oeffinger, M.; Devaux, F.; Doye, V.; Palancade, B. Sumoylation of the THO complex regulates the biogenesis of a subset of mRNPs. *Nucleic Acids Res.* 2014, 42, 5043–5058.

91. Fasken, M.B.; Stewart, M.; Corbett, A.H. Functional significance of the interaction between the mRNA-binding protein, Nab2, and the nuclear pore-associated protein, Mlp1, in mRNA export. *J. Biol. Chem.* 2008, 283, 27130–27143.

92. Vinciguerra, P.; Iglesias, N.; Camblong, J.; Zenklusen, D.; Stutz, F. Perinuclear Mlp proteins downregulate gene expression in response to a defect in mRNA export. *EMBO J.* 2005, 24, 813–823.

93. Hector, R.E.; Nykamp, K.R.; Dheur, S.; Anderson, J.T.; Non, P.J.; Urbinati, C.R.; Wilson, S.M.; Minvielle-Sebastia, L.; Swanson, M.S. Dual requirement for yeast hnRNP Nab2p in mRNA poly(A) tail length control and nuclear export. *EMBO J.* 2002, 21, 1800–1810.
94. Galy, V.; Gadal, O.; Fromont-Racine, M.; Romano, A.; Jacquier, A.; Nehrbass, U. Nuclear retention of unspliced mRNAs in yeast is mediated by perinuclear Mlp1. Cell 2004, 116, 63–73.

95. Lo, C.W.; Kaida, D.; Nishimura, S.; Matsuyama, A.; Yashiroda, Y.; Taoka, H.; Ishigami, K.; Watanabe, H.; Nakajima, H.; Tani, T.; et al. Inhibition of splicing and nuclear retention of pre-mRNA by spliceostatin A in fission yeast. Biochem. Biophys. Res. Commun. 2007, 364, 573–577.

96. Palancade, B.; Zuccolo, M.; Loeillet, S.; Nicolas, A.; Doye, V. Pml39, a novel protein of the nuclear periphery required for nuclear retention of improper messenger ribonucleoparticles. Mol. Biol. Cell 2005, 16, 5258–5268.

97. Zhao, X.; Wu, C.Y.; Blobel, G. Mlp-dependent anchorage and stabilization of a desumoylating enzyme is required to prevent clonal lethality. J. Cell Biol. 2004, 167, 605–611.

98. Skruzny, M.; Schneider, C.; Racz, A.; Weng, J.; Tollervey, D.; Hurt, E. An endoribonuclease functionally linked to perinuclear mRNP quality control associates with the nuclear pore complexes. PLoS Biol. 2009, 7, e8.

99. Iglesias, N.; Tutucci, E.; Gwizdek, C.; Vinciguerra, P.; von Dach, E.; Corbett, A.H.; Dargemont, C.; Stutz, F. Ubiquitin-mediated mRNP dynamics and surveillance prior to budding yeast mRNA export. Genes Dev. 2010, 24, 1927–1938.

100. Lewis, A.; Felberbaum, R.; Hochstrasser, M. A nuclear envelope protein linking nuclear pore basket assembly, SUMO protease regulation, and mRNA surveillance. J. Cell Biol. 2007, 178, 813–827.

101. Dziembowski, A.; Ventura, A.P.; Rutz, B.; Caspary, F.; Faux, C.; Halgand, F.; Laprevote, O.; Seraphin, B. Proteomic analysis identifies a new complex required for nuclear pre-mRNA retention and splicing. EMBO J. 2004, 23, 4847–4856.

102. Hackmann, A.; Wu, H.; Schneider, U.M.; Meyer, K.; Jung, K.; Krebber, H. Quality control of spliced mRNAs requires the shuttling SR proteins Gbp2 and Hrb1. Nat. Commun. 2014, 5, 3123.

103. Kuss, S.K.; Mata, M.A.; Zhang, L.; Fontoura, B.M. Nuclear imprisonment: Viral strategies to arrest host mRNA nuclear export. Viruses 2013, 5, 1824–1849.

104. Coyle, J.H.; Bor, Y.C.; Rekosh, D.; Hammarskjold, M.L. The Tpr protein regulates export of mRNAs with retained introns that traffic through the Nxf1 pathway. RNA 2011, 17, 1344–1356.

105. Hase, M.E.; Cordes, V.C. Direct interaction with nup153 mediates binding of Tpr to the periphery of the nuclear pore complex. Mol. Biol. Cell 2003, 14, 1923–1940.

106. Yap, K.; Lim, Z.Q.; Khandelia, P.; Friedman, B.; Makeyev, E.V. Coordinated regulation of neuronal mRNA steady-state levels through developmentally controlled intron retention. Genes Dev. 2012, 26, 1209–1223.

107. Chakraborty, P.; Wang, Y.; Wei, J.H.; van Deursen, J.; Yu, H.; Malureanu, L.; Dasso, M.; Forbes, D.J.; Levy, D.E.; Seemann, J.; et al. Nucleoporin levels regulate cell cycle progression and phase-specific gene expression. Dev. Cell 2008, 15, 657–667.

108. Wozniak, R.W.; Goldfarb, D.S. Cyclin-like oscillations in levels of the nucleoporin Nup96 control G1/S progression. Dev. Cell 2008, 15, 643–644.

109. Glavy, J.S.; Krutchinsky, A.N.; Cristea, I.M.; Berke, I.C.; Boehmer, T.; Blobel, G.; Chait, B.T. Cell-cycle-dependent phosphorylation of the nuclear pore Nup107-160 subcomplex. Proc. Natl. Acad. Sci. USA 2007, 104, 3811–3816.
110. Laurell, E.; Beck, K.; Krupina, K.; Theerthagiri, G.; Bodenmiller, B.; Horvath, P.; Aebersold, R.; Antonin, W.; Kutay, U. Phosphorylation of Nup98 by multiple kinases is crucial for NPC disassembly during mitotic entry. *Cell* **2011**, *144*, 539–550.

111. Makhnevych, T.; Lusk, C.P.; Anderson, A.M.; Aitchison, J.D.; Wozniak, R.W. Cell cycle regulated transport controlled by alterations in the nuclear pore complex. *Cell* **2003**, *115*, 813–823.

112. Brickner, D.G.; Brickner, J.H. Cdk phosphorylation of a nucleoporin controls localization of active genes through the cell cycle. *Mol. Biol. Cell* **2010**, *21*, 3421–3432.

113. Capelson, M.; Doucet, C.; Hetzer, M.W. Nuclear pore complexes: Guardians of the nuclear genome. *Cold Spring Harb. Symp. Quant. Biol.* **2010**, *75*, 585–597.

114. Colon-Ramos, D.A.; Salisbury, J.L.; Sanders, M.A.; Shenoy, S.M.; Singer, R.H.; Garcia-Blanco, M.A. Asymmetric distribution of nuclear pore complexes and the cytoplasmic localization of beta2-tubulin mRNA in *Chlamydomonas reinhardtii*. *Dev. Cell* **2003**, *4*, 941–952.

115. Powrie, E.A.; Zenklusen, D.; Singer, R.H. A nucleoporin, Nup60p, affects the nuclear and cytoplasmic localization of ASH1 mRNA in *S. cerevisiae*. *RNA* **2011**, *17*, 134–144.

116. Meier, I. mRNA export and sumoylation-Lessons from plants. *Biochim. Biophys. Acta* **2012**, *1819*, 531–537.

117. MacGregor, D.R.; Gould, P.; Foreman, J.; Griffiths, J.; Bird, S.; Page, R.; Stewart, K.; Steel, G.; Young, J.; Paszkiewicz, K.; et al. High expression of osmotically responsive genes1 is required for circadian periodicity through the promotion of nucleo-cytoplasmic mRNA export in *Arabidopsis*. *Plant Cell* **2013**, *25*, 4391–4404.

118. Faria, A.M.; Levay, A.; Wang, Y.; Kamphorst, A.O.; Rosa, M.L.; Nussenzveig, D.R.; Balkan, W.; Chook, Y.M.; Levy, D.E.; Fontoura, B.M. The nucleoporin Nup96 is required for proper expression of interferon-regulated proteins and functions. *Immunity* **2006**, *24*, 295–304.

119. Saavedra, C.; Tung, K.S.; Amberg, D.C.; Hopper, A.K.; Cole, C.N. Regulation of mRNA export in response to stress in *Saccharomyces cerevisiae*. *Genes Dev.* **1996**, *10*, 1608–1620.

120. Gallouzi, I.E.; Brennan, C.M.; Stenberg, M.G.; Swanson, M.S.; Eversole, A.; Maizels, N.; Steitz, J.A. HuR binding to cytoplasmic mRNA is perturbed by heat shock. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 3073–3078.

121. Rollenhagen, C.; Hodge, C.A.; Cole, C.N. Following temperature stress, export of heat shock mRNA occurs efficiently in cells with mutations in genes normally important for mRNA export. *Eukaryot. Cell* **2007**, *6*, 505–513.

122. Carmody, S.R.; Tran, E.J.; Apponi, L.H.; Corbett, A.H.; Wente, S.R. The mitogen-activated protein kinase Slt2 regulates nuclear retention of non-heat shock mRNAs during heat shock-induced stress. *Mol. Cell. Biol.* **2010**, *30*, 5168–5179.

123. Rajanala, K.; Sarkar, A.; Jhingan, G.D.; Priyadarshini, R.; Jalan, M.; Sengupta, S.; Nandicoori, V.K. Phosphorylation of nucleoporin Tpr governs its differential localization and is required for its mitotic function. *J. Cell Sci.* **2014**, *127*, 3505–3520.

124. Skaggs, H.S.; Xing, H.; Wilkerson, D.C.; Murphy, L.A.; Hong, Y.; Mayhew, C.N.; Sarge, K.D. HSF1-TPR interaction facilitates export of stress-induced HSP70 mRNA. *J. Biol. Chem.* **2007**, *282*, 33902–33907.
125. Regot, S.; de Nadal, E.; Rodriguez-Navarro, S.; Gonzalez-Novo, A.; Perez-Fernandez, J.; Gadal, O.; Seisenbacher, G.; Ammerer, G.; Posas, F. The Hog1 stress-activated protein kinase targets nucleoporins to control mRNA export upon stress. *J. Biol. Chem.* 2013, 288, 17384–17398.

126. Izawa, S.; Takemura, R.; Inoue, Y. Gle2p is essential to induce adaptation of the export of bulk poly(A)+ mRNA to heat shock in *Saccharomyces cerevisiae*. *J. Biol. Chem.* 2004, 279, 35469–35478.

127. Takemura, R.; Inoue, Y.; Izawa, S. Stress response in yeast mRNA export factor: Reversible changes in Rat8p localization are caused by ethanol stress but not heat shock. *J. Cell Sci.* 2004, 117, 4189–4197.

128. Basel-Vanagaite, L.; Muncher, L.; Straussberg, R.; Pasmanik-Chor, M.; Yahav, M.; Rainshtein, L.; Walsh, C.A.; Magal, N.; Taub, E.; Drasinover, V.; et al. Mutated nup62 causes autosomal recessive infantile bilateral striatal necrosis. *Ann. Neurol.* 2006, 60, 214–222.

129. Le Sage, V.; Mouland, A.J. Viral subversion of the nuclear pore complex. *Viruses* 2013, 5, 2019–2042.

130. Simon, D.N.; Rout, M.P. Cancer and the nuclear pore complex. *Adv. Exp. Med. Biol.* 2014, 773, 285–307.

131. Zhang, X.; Chen, S.; Yoo, S.; Chakrabarti, S.; Zhang, T.; Ke, T.; Oberti, C.; Yong, S.L.; Fang, F.; Li, L.; et al. Mutation in nuclear pore component NUP155 leads to atrial fibrillation and early sudden cardiac death. *Cell* 2008, 135, 1017–1027.

132. Kendirgi, F.; Rexer, D.J.; Alcazar-Roman, A.R.; Onishko, H.M.; Wente, S.R. Interaction between the shuttling mRNA export factor Gle1 and the nucleoporin hCG1: A conserved mechanism in the export of Hsp70 mRNA. *Mol. Biol. Cell* 2005, 16, 4304–4315.

133. Nousiainen, H.O.; Kestila, M.; Pakkasjarvi, N.; Honkala, H.; Kuure, S.; Tallila, J.; Vuopala, K.; Ignatius, J.; Herva, R.; Peltonen, L. Mutations in mRNA export mediator GLE1 result in a fetal motoneuron disease. *Nat. Genet.* 2008, 40, 155–157.

134. Jao, L.E.; Appel, B.; Wente, S.R. A zebrafish model of lethal congenital contracture syndrome 1 reveals Gle1 function in spinal neural precursor survival and motor axon arborization. *Development* 2012, 139, 1316–1326.

135. Folkmann, A.W.; Collier, S.E.; Zhan, X.; Aditi; Ohn, M.D.; Wente, S.R. Gle1 functions during mRNA export in an oligomeric complex that is altered in human disease. *Cell* 2013, 155, 582–593.

136. Folkmann, A.W.; Dawson, T.R.; Wente, S.R. Insights into mRNA export-linked molecular mechanisms of human disease through a Gle1 structure-function analysis. *Adv. Biol. Regul.* 2014, 54, 74–91.

137. Borden, K.L.; Culjkovic-Kraljacic, B. Ribavirin as an anti-cancer therapy: Acute myeloid leukemia and beyond? *Leuk. Lymphoma* 2010, 51, 1805–1815.

138. Culjkovic-Kraljacic, B.; Baguet, A.; Volpon, L.; Amri, A.; Borden, K.L. The oncogene eIF4E reprograms the nuclear pore complex to promote mRNA export and oncogenic transformation. *Cell Rep.* 2012, 2, 207–215.

139. Castello, A.; Izquierdo, J.M.; Welnowska, E.; Carrasco, L. RNA nuclear export is blocked by poliovirus 2A protease and is concomitant with nucleoporin cleavage. *J. Cell Sci.* 2009, 122, 3799–3809.
140. Gustin, K.E.; Sarnow, P. Inhibition of nuclear import and alteration of nuclear pore complex composition by rhinovirus. *J. Virol.* 2002, 76, 8787–8796.

141. Lidsky, P.V.; Hato, S.; Bardina, M.V.; Aminev, A.G.; Palmenberg, A.C.; Sheval, E.V.; Polyakov, V.Y.; van Kuppeveld, F.J.; Agol, V.I. Nucleocytoplasmic traffic disorder induced by cardioviruses. *J. Virol.* 2006, 80, 2705–2717.

142. Porter, F.W.; Bochkov, Y.A.; Albue, A.J.; Wiese, C.; Palmenberg, A.C. A picornavirus protein interacts with Ran-GTPase and disrupts nucleocytoplasmic transport. *Proc. Natl. Acad. Sci. USA* 2006, 103, 12417–12422.

143. Park, N.; Skern, T.; Gustin, K.E. Specific cleavage of the nuclear pore complex protein Nup62 by a viral protease. *J. Biol. Chem.* 2010, 285, 28796–28805.

144. Bardina, M.V.; Lidsky, P.V.; Sheval, E.V.; Fominykh, K.V.; van Kuppeveld, F.J.; Polyakov, V.Y.; Agol, V.I. Mengovirus-induced rearrangement of the nuclear pore complex: Hijacking cellular phosphorylation machinery. *J. Virol.* 2009, 83, 3150–3161.

145. Porter, F.W.; Palmenberg, A.C. Leader-induced phosphorylation of nucleoporins correlates with nuclear trafficking inhibition by cardioviruses. *J. Virol.* 2009, 83, 1941–1951.

146. Ricour, C.; Delhaye, S.; Hato, S.V.; Olenyik, T.D.; Michel, B.; van Kuppeveld, F.J.; Gustin, K.E.; Michiels, T. Inhibition of mRNA export and dimerization of interferon regulatory factor 3 by Theiler’s virus leader protein. *J. Gen. Virol.* 2009, 90, 177–186.

147. Gustin, K.E.; Sarnow, P. Effects of poliovirus infection on nucleo-cytoplasmic trafficking and nuclear pore complex composition. *EMBO J.* 2001, 20, 240–249.

148. Her, L.S.; Lund, E.; Dahlberg, J.E. Inhibition of Ran guanosine triphosphatase-dependent nuclear transport by the matrix protein of vesicular stomatitis virus. *Science* 1997, 276, 1845–1848.

149. Petersen, J.M.; Her, L.S.; Dahlberg, J.E. Multiple vesiculoviral matrix proteins inhibit both nuclear export and import. *Proc. Natl. Acad. Sci. USA* 2001, 98, 8590–8595.

150. Von Kobbe, C.; van Deursen, J.M.; Rodrigues, J.P.; Sitterlin, D.; Bachi, A.; Wu, X.; Wilm, M.; Carmo-Fonseca, M.; Izaurrealde, E. Vesicular stomatitis virus matrix protein inhibits host cell gene expression by targeting the nucleoporin Nup98. *Mol. Cell* 2000, 6, 1243–1252.

151. Chakraborty, P.; Seemann, J.; Mishra, R.K.; Wei, J.H.; Weil, L.; Nussenzveig, D.R.; Heiber, J.; Barber, G.N.; Dasso, M.; Fontoura, B.M. Vesicular stomatitis virus inhibits mitotic progression and triggers cell death. *EMBO Rep.* 2009, 10, 1154–1160.

152. Rajani, K.R.; Pettit Kneller, E.L.; McKenzie, M.O.; Horita, D.A.; Chou, J.W.; Lyles, D.S. Complexes of vesicular stomatitis virus matrix protein with host Rae1 and Nup98 involved in inhibition of host transcription. *PLoS Pathog.* 2012, 8, e1002929.

153. Quan, B.; Seo, H.S.; Blobel, G.; Ren, Y. Vesiculoviral matrix (M) protein occupies nucleic acid binding site at nucleoporin pair (Rae1*Nup98). *Proc. Natl Acad. Sci. USA* 2014, 111, 9127–9132.

154. Chen, J.; Huang, S.; Chen, Z. Human cellular protein nucleoporin hNup98 interacts with influenza A virus NS2/nuclear export protein and overexpression of its GLFG repeat domain can inhibit virus propagation. *J. Gen. Virol.* 2010, 91, 2474–2484.

155. Enninga, J.; Levy, D.E.; Blobel, G.; Fontoura, B.M. Role of nucleoporin induction in releasing an mRNA nuclear export block. *Science* 2002, 295, 1523–1525.
156. Faria, P.A.; Chakraborty, P.; Levay, A.; Barber, G.N.; Ezelle, H.J.; Enninga, J.; Arana, C.; van Deursen, J.; Fontoura, B.M. VSV disrupts the Rae1/mrnp41 mRNA nuclear export pathway. *Mol. Cell* **2005**, *17*, 93–102.

157. Hayakawa, A.; Babour, A.; Sengmanivong, L.; Dargemont, C. Ubiquitylation of the nuclear pore complex controls nuclear migration during mitosis in *S. cerevisiae*. *J. Cell Biol.* **2012**, *196*, 19–27.

158. Vassileva, M.T.; Matunis, M.J. SUMO modification of heterogeneous nuclear ribonucleoproteins. *Mol. Cell. Biol.* **2004**, *24*, 3623–3632.

© 2014 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).