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## RANBP2 EVOLUTION AND HUMAN DISEASE

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### Abstract

RANBP2/Nup358 (Ran Binding Protein 2) is a nucleoporin and a key component of the nuclear pore complex. Through its multiple functions (e.g. SUMOylation, regulation of nucleocytoplasmic transport) and subcellular localizations (e.g. at the nuclear envelope, kinetochores, annulate lamellae), it is involved in many cellular processes. RANBP2 dysregulation or mutation leads to the development of human pathologies, such as Acute Necrotizing Encephalopathy 1 (ANE1), cancer, neurodegenerative diseases and it is also involved in viral infections. The chromosomal region containing the *RANBP2* gene is highly dynamic, with high structural variation and recombination events that led to the appearance of a gene family called *RGPD* (RANBP2 and GCC2 Protein Domains), with multiple gene loss/duplication events during ape evolution. Although *RGPD* homoplasmy and maintenance during evolution suggest they might confer an advantage to their hosts, their functions are still unknown and understudied. In this review, we discuss the appearance and importance of RANBP2 in metazoans and its function-related pathologies, caused by an alteration of its expression levels (through promoter activity, post-transcriptional or post-translational modifications), its localization or genetic mutations.

Keywords: NPC, nucleocytoplasmic transport, RANBP2, RGPD, evolution, disease, ANE1

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## Abbreviations

AGO: Argonaute  
AI: Artificial intelligence  
AL : annulate lamellae  
ANE1/ANE: Acute Necrotizing Encephalopathy  
BBB: Blood-brain barrier  
CCDC138: Coiled-Coil Domain Containing 138  
CNS: central nervous system  
COX11: Cytochrome C oxydase  
CRM1: Chromosomal Maintenance 1  
CSF: Cerebro-spinal fluid  
EM: electron microscopy  
FG-repeats: Phenylalanine-Glycine repeats  
GCC2: GRIP and coiled-coil domain containing 2  
HIV-1: Human Immunodeficiency virus type 1  
HK1: Hexokinase 1  
HP1: Heterochromatin protein 1  
HSV-1: Herpes-simplex virus 1  
IAV: Influenza virus type A  
INCENP: Inner centromere protein  
KBD: Kinesin-binding domain  
LIMS1: LIM zinc finger domain containing 1  
mRNA: messenger RNA  
miRNA: micro-RNA  
mRNP: messenger ribonucleoprotein  
NPHP1: Nephronophthisis 1  
NES: Nuclear export signal  
NLS: Nuclear localization signal  
NPC: Nuclear pore complex  
NTD: N-terminal domain  
NTR: nuclear transport receptor  
Nup: Nucleoporin  
NXF1: Nuclear RNA export factor 1  
OE: Oligomerization element  
P-bodies: Processing-bodies  
RANBP2: Ran Binding protein 2  
RANBP2<sup>NTD</sup>: RANBP2 N-terminal domain  
RanGEF: Ran guanine nucleotide exchange factor  
RanGAP: RanGTPase activating protein  
RanGTP: Guanosine triphosphate Ran  
RBD: Ran binding domain  
RGPD: RANBP2 and GCC2 Protein Domains  
RNP: Ribonucleoprotein  
SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus 2  
SSCR: Signal sequence coding region  
TPR: Tetratricopeptide  
TREX: Transcription-export complex  
UsnRNA: U small nuclear RNA  
ZF: Zinc-finger

In eukaryotic cells, nuclear pore complexes (NPCs) are transport channels embedded in the nuclear envelope that regulate the selective transport of molecules between the nucleus and the cytoplasm. These giant macromolecular structures – ranging from ~60 MDa in yeast and ~110 MDa in humans – are composed of approximately 30 different proteins called nucleoporins (Nups) present in multiple copies and arranged in an eight-fold symmetrical structure [1,2]. Nups serve as building blocks for NPCs and regulate nucleo-cytoplasmic trafficking of macromolecules. In particular, Nups containing unstructured phenylalanine-glycine (FG) repeats interact with nuclear transport receptors (NTRs; [3]) and form a barrier to passive diffusion of macromolecules [1,4,5].

Nup358, also called RANBP2 (Ran Binding Protein 2), is an FG-containing Nup that is localized on the cytoplasmic face of NPCs. It is the largest Nup (358 kDa), the main constituent of NPC cytoplasmic fibrils and appears to have multiple functions, some of which are still debated. While the majority of Nups and the central structures of NPCs are highly conserved across eukaryotes [6,7], some have evolved specifically in metazoans or even vertebrates. RANBP2 is one such example since it is only found in metazoans.

In this review, we examine the structure and reported functions of mammalian RANBP2 both as a component of NPCs and away from the nuclear envelope. We then discuss the evolution of RANBP2 in vertebrates and structural variations of primate RANBP2 that gave rise to RGD (RANBP2 and GCC2 Protein Domains). Lastly, we consider how alterations in the functions or expression levels of RANBP2, or mutations in the gene *RANBP2* can lead to human disease. Given the many cellular functions of RANBP2, including many that are unrelated to the regulation of nucleo-cytoplasmic transport, RANBP2 has been linked to a range of pathologies, such as Acute Necrotizing Encephalopathy 1 (ANE1), cancer, neurodegenerative diseases and viral infection.

## **1. RANBP2, A KEY COMPONENT OF THE NUCLEAR PORE COMPLEX**

### **1.1. The nuclear pore complex structure, composition and localization**

The first observations of NPCs were performed by electron microscopy (EM) in the 1950s on nuclear membranes isolated from amphibian oocytes [8]. Further observations revealed that pore complexes are cylindrical assemblies presenting with different architectures on the nuclear and cytoplasmic sides [9] and appear as octagonal structures in surface views [10]. Pores from different species appeared to have the same shape and approximately the same size, pointing to an evolutionary conserved structural organization. However, recent works revealed key structural differences between species [1] and considerable structural plasticity in the inner ring of the pore complexes, resulting in a range of transport channel diameters between constricted and dilated [11–13].

In humans, the NPC has an outer diameter of ~120 nm and an inner transport channel of ~40-60 nm. Its overall architecture is divided into three main components: a symmetric core, cytoplasmic filaments and a nuclear basket. The symmetric core, or central ring, surrounds the central transport channel and serves as a scaffold for the filaments and the basket, on the cytoplasmic and nuclear faces of the pore, respectively (please refer to [1] for an in-depth review). The spokes that radiate out of the symmetric core into the cytoplasm were first observed by transmission and scanning EM [14,15]. Each pore contains eight cytoplasmic fibrils of 35-50 nm in length and is composed of cytoplasmic Nups, the main component being RANBP2 [16–18]. In recent years, the structure of human NPCs has been extensively characterized and the crystal and cryogenic-EM structures of NPC domains and components have been resolved (reviewed in: [4,19–21]).

The overall structure of the NPC is dynamic, particularly in proliferating cells, where NPCs undergo mitotic disassembly, post-mitotic reassembly and interphase assembly [22,23]. Moreover, the structure of NPCs varies between cell types and tissues and their composition and localization can change in response to different cellular signals [24]. Nups may also be found at other subcellular

locations other than the nuclear envelope, for instance in annulate lamellae, at stress granules and processing bodies (P-bodies) [25,26] (**Figure 1**).

Annulate lamellae (AL) are a membrane-bound subcompartment of the endoplasmic reticulum (ER) that were first identified in 1955 [27]. They appear as stacks of ER-derived membranes that contain Nups, or even fragments of NPCs, and are present in a variety of cell types. Since they are most abundant in rapidly dividing cells, AL are thought to play a role as storage units for NPC building blocks during post-mitotic assembly [25]. Additionally, AL are induced by viral infection and may be usurped by viruses for their replication or serve as viral factories [25,28,29]. Stress granules and P-bodies are RNA-containing biomolecular condensates that share some similarities in terms of structure and composition and are both induced by cellular stress.

## 1.2. RANBP2 structure and protein domains

The human RANBP2 protein was identified for the first time in 1995 by two independent groups [16,17]. It is an unusually large protein, the largest Nup, composed of 3,224 amino acid residues with a predicted molecular weight of 358 kDa. It contains multiple domains, including an N-terminal domain (RANBP2<sup>NTD</sup>), four Ran binding domains (RBD), eight zinc finger (ZF) domains of the Cys2-Cys2 type, numerous FG and XFXFG repeats (9 and 13 respectively), a cyclophilin A homologous domain, and a recently identified E3 SUMO1-ligase domain [30] (**Figure 2**).

The RANBP2<sup>NTD</sup> is a ~900 residue  $\alpha$ -helical region that has been biochemically and structurally characterized [18,31]. It contains a leucine-rich region of 700 amino acids necessary for nuclear envelope recruitment [32], and tetratricopeptide repeats (TPRs) and an oligomerization element (OE) (residues 802-832) that mediate oligomerization [18,31,33]. The four RBDs mediate binding to the small GTPase Ran, while the E3 domain allows RanGAP binding and SUMOylation [34]. The C-terminal domain of RANBP2 adopts a cyclophilin-like fold and has a weak prolyl-isomerase activity [35] (**Figure 2**).

Advanced structure determination and artificial intelligence (AI) modeling revealed that RANBP2 proteins assemble as pentamers on each cytoplasmic filament, anchored in the Y complexes of the cytoplasmic ring [12,18,33,36,37]. Time lapse microscopy further revealed that while core NPC components assemble within one minute post-mitosis, the addition of the large RANBP2 proteins constitutes the last step of assembly after 1 hour or longer [23].

## 2. RANBP2 FUNCTIONS

RANBP2 has multiple and diverse functions, notably resulting from the combination of the intrinsic properties of the individual protein domains (e.g. SUMO modification) and of the various subcellular localizations of RANBP2 (e.g. NPCs, AL, kinetochores etc) (**Figure 3**).

### 2.1. RANBP2 and protein import

While metabolites and small molecules (< 40kDa) diffuse freely through the NPC, larger molecules need an active transport to enter the nucleus [38]. Their Nuclear Localization Signal (NLS) sequences or folded domains are recognized by NTRs called karyopherins, and the cargo-NTR complex is then translocated across the NPC through sequential interactions with FG-repeats of different Nups and released in the nucleus [39]. Interactions between cargoes and NTRs are orchestrated by the nucleotide state of Ran, which is regulated by the nuclear-localized Ran guanine nucleotide exchange factor (RanGEF) and the cytoplasmic-localized RanGTPase activating protein (RanGAP) [38].

Although RANBP2 contains FG repeats, it has been suggested that it is not strictly necessary for nuclear import since occlusion or depletion of RANBP2 does not impede the import of small cargoes [40,41], and yeast cells do not encode RANBP2 homologs. However, its knockdown in human cells reduces the efficient transport of proteins by both the importin  $\alpha/\beta$  and the transportin pathways [42–44]. Additionally, RANBP2 serves as a docking site for SUMOylated RanGAP, contains four binding sites for

the guanosine triphosphate Ran (RanGTP) and SUMOylates the GTPase Ran [16,34,45–47], suggesting that RANBP2 may facilitate nuclear import by increasing the recycling rate of import receptors and stimulating the hydrolysis of RanGTP by Ran.

## 2.2. RANBP2 and mRNA export

Messenger RNA (mRNA) molecules exit the nucleus in complex with multiple RNA-binding proteins and associated proteins. These mRNA protein complexes (mRNPs) dock at the nuclear basket, are exported through NPCs and released in the cytoplasm. The principal mRNP export factor is NXF1-NXT1, which, like karyopherins, interacts with FG-containing Nups but transports mRNPs in a RanGTP-independent manner [48,49]. The NXF1-NXT1 heterodimer operates with adaptor RNA binding proteins such as the transcription-export complex (TREX) or SR proteins [49]. The protein export receptor CRM1 does not have a major role in mRNA export.

RANBP2 may impact mRNA export in a number of ways. One study reported that knockdown of RANBP2 in HeLa cells causes the cytoplasmic accumulation of phosphorylated SR proteins, which deregulated the alternative splicing of pre-mRNAs [50]. This may be an indirect effect since knockdown of RANBP2 also caused the cytoplasmic accumulation of the karyopherin TNPO3, which is required for the nuclear import of SR proteins [50]. Another study showed that RANBP2 provides a major binding site for NXF1-NXT1, preventing its dispersion in the cytoplasm after mRNP export, which presumably would optimize its recycling back to the nucleus [51]. In *Drosophila* and mouse models, RANBP2 depletion results in an altered mRNA export from the nucleus [44,51]. However, in human cell lines (HeLa and U2OS), little or no impact of RANBP2 depletion was observed on mRNA export [18,42,52]. These differences could be due to species-specific differences in the NPC machinery between the different cell models used in each study. Alternatively, RANBP2 might play a regulatory role for some specific transcripts, for example by regulating the export of mRNAs by the eukaryotic translation initiation factor eIF4E [53].

## 2.3. RANBP2 and SUMOylation

SUMO-1 is a small ubiquitin-like protein that is covalently linked to lysine residues of target proteins through isopeptide bonds. SUMOylation of target proteins involves an enzymatic cascade mediated by an E1 activating enzyme, an E2 conjugating enzyme (Ubc9) and an E3 protein ligase [54]. RANBP2 contains a small E3 SUMO ligase domain that enables it to attach SUMO-1 peptides on target proteins [30].

RANBP2 is able to SUMOylate a variety of substrates *in vitro*, such as Sp100 or Mdm2 [30,55]. In mammalian cells, RANBP2 was also shown to SUMOylate the GTPase Ran [34], the mitosis-specific SUMO substrates Topoisomerase II $\alpha$  and Borealin [56,57], Argonaute proteins [58], and the restriction factor TRIM5 $\alpha$  [59].

The main effect of SUMOylation by RANBP2 is to impact the localization of their target proteins. The localization of RANBP2 or its SUMOylation substrates to microtubules or kinetochores is especially compelling [32,60]. RANBP2 also binds to microtubule motors and adaptors such as kinesin-1 or Bicaudal D2, suggesting it may participate in the anterograde transport of cargoes or in the positioning of organelles such as mitochondria or the nucleus [61–65].

The variety of substrates targeted by RANBP2 likely accounts for the many cellular processes RANBP2 has been linked with, such as nuclear transport, gene expression, chromosome segregation during mitosis, chromatin regulation or even antiviral activity. The effect of RANBP2 on translational repression is particularly intriguing. RANBP2 binds to [66,67] and SUMOylates AGO [58], enhancing miRNA-mediated silencing. RANBP2 also binds to another miRISC complex component, GW182 [67,68]. While the SUMOylation of mRNP-associated AGO proteins increases their stability, RANBP2 may also be involved in connecting the target mRNA with miRISC [67]. It is interesting to speculate that these events can occur in AL, since AL were seen to dynamically associate with mRNP granules, P-bodies or stress granules [67], where mRNA silencing by miRNAs is believed to occur [69,70].

### 3. EVOLUTION OF RANBP2

#### 3.1. *RANBP2* homologs in metazoan and evolution in vertebrates

The human *RANBP2* is encoded in the chromosome 2, by a long gene of more than 66,000 base pairs containing 29 exons (**Figure 2**). Although a total of 20 transcript variants are predicted, only four are confirmed and encode for protein isoforms of 3,224 to 3,251 aa – the predicted ones ranging from 875-3,259 aa total. At present, very little is known about these isoforms and whether they may account for the different subcellular localizations and functions reported for *RANBP2*.

In vertebrates, *RANBP2* is conserved in a genomic locus flanked by *GCC2* (GRIP and coiled-coil domain containing 2) and *LIMS1* (LIM zinc finger domain containing 1) on one side, and *CCDC138* (Coiled-Coil Domain Containing 138) on the other (Ensembl and NCBI). Orthologs of *RANBP2* are found in most vertebrate species genome currently available. The encoded proteins have similar architecture, with highly conserved domains and residues through vertebrate evolution. Zebrafish and human *RANBP2* share 48% amino acid identity. Outside of vertebrates, a very distant *RANBP2*/*Nup358* homolog has been described in *Drosophila* [71] and it plays key functional roles in the nuclear pore complex. However, although there are some functional domains in common, the overall architecture is different, and human and *Drosophila* *RANBP2* only share 27% amino acid identity. The presence and the evolution of *RANBP2* homologs in other non-vertebrate species remain largely to be characterized. Very diverse species, including plants, zebrafish and nematodes, encode for proteins with *RanBP2*-type ZFs that bind RNAs, but these proteins have distinct functions and evolutionary history, and only have these ZF domains in common with human *RANBP2* [72,73]. Determining the evolutionary origin of *RANBP2* is therefore an important objective of future research to understand its ancient evolutionary history and the acquisition of such fundamental cellular protein.

#### 3.2. Extreme structural variations of primate *RANBP2* during ape divergence, leading to the birth of *RGPDs*

The region containing the *RANBP2* gene on human chromosome 2 is extremely dynamic and a hotspot for recombination [74,75]. Evidence suggests that *RANBP2* underwent recent duplication, in the last several million years of ape evolution, giving rise to a gene family called *RGPD* (*RANBP2* and *GCC2* Protein Domains) [75,76].

*RGPD* genes arose from partial duplication, fusion and genomic rearrangement of sequences derived from *RANBP2* and *GCC2*. It is thought that the fusion of *RANBP2* and *GCC2*, which involved the deletions of some *RANBP2* exons (part of exons 20 and 21, and all of exons 22-29), generated a progenitor locus that then underwent further duplication and gene conversion events during ape divergence [76,77].

Although gene duplications occur at high frequency in eukaryotes [78], the duplication of *RANBP2* is rather striking in that it is an ape-specific intrachromosomal duplication of a gene that presently appears as a single copy in other sequenced metazoan genomes.

Besides humans, only gibbons, orangutans, gorillas, bonobos and chimpanzees encode for *RGPDs*. There is no evidence of *RGPD*-like genes in any other primate or mammal [77]. Each ape species encodes for a different set of *RGPD* genes: one copy in gibbons, three in orangutans, four in gorillas, six in chimpanzees and seven in humans (i.e. *RGPD1-8* without any *RGPD7*). Strikingly, a recent study revealed that the multiple copies of *RGPD* arose mostly independently in the five different ape lineages, which constitutes an extreme example of homoplasia [77]. Only *RGPD2* in African great apes (gorillas, chimpanzees and humans) appears syntenic and orthologous. Human *RGPD5*, *RGPD6* and *RGPD8* are closely related and *RGPD6* is a human-specific gene copy that has arisen from *RGPD5* as the most recent duplication event (~5.2kya [77]). Remarkably, the high nucleotide identity between *RGPD5* and *RGPD6* has led to predisposition of inversion and microdeletion between these two genes. Because the interval between these *RGPDs* encodes for the *nephronophthisis* (*NPHP1*) gene, these deletion events are dramatically associated with Joubert syndrome [77,79].

### 3.3. Possible functions of RGPD

Gene duplications may be maintained during evolution if they are advantageous, for instance by bringing more favorable gene dosage, or an entirely new gene function (i.e. neofunctionalization), or subfunctionalization of the copies. In the case of *RGPDs*, there is experimental evidence that all seven RGPDs are expressed in human cells [76]. However, we still do not know their function and how they compare to RANBP2. RGPD proteins lack many RANBP2 domains, such as the whole ZF region, two RBDs, the E3 SUMO ligase and cyclophilin-homology domains. Moreover, since RGPD is a fusion of RANBP2 to the trans-Golgi component GCC2 [76], one might expect RGPD proteins to localize to the trans-Golgi and that this localization might confer new gene functions to *RGPDs* compared with *RANBP2*.

Other possible functions of RGPDs have been proposed. First, it was originally identified as a testes-specific Nup, named BS-63 and localizing to the cytoplasmic side of NPC, and as a binding partner for both Ran and Transportin-1 (karyopherin beta 2) [80], which might suggest that it plays a role in nucleocytoplasmic transport, or could point to the cross-reacting detection of RANBP2 in these experiments because of high homology between antigens. In subsequent protein interaction landscape studies, RGPD proteins were identified as part of a mitotic complex including RANBP2 and RanGAP1 among others [81], suggesting it might be involved in chromatin segregation. Additionally, RGPDs may play an important role in the post-translational modification of proteins since it was identified in an interaction screen in association with cytoplasmic deubiquitinating enzymes USP14 and USP20 [82].

The genomic and genetic diversification of the *RGPD* gene family could also result from genetic conflicts with pathogens resulting from past epidemics during ape evolution. Testing the ape RGPDs against a wide range of viruses would be an exciting next step to determine if they have antiviral functions.

## 4. HUMAN DISEASES LINKED TO RANBP2

As RANBP2 plays a major role in many cell functions, its mutation or dysregulation is associated with the development of diseases. Molecular causes for disease development can either involve its expression levels (through promoter activity, post-transcriptional or post-translational modifications), its localization or genetic mutations.

### 4.1. Acute Necrotizing Encephalopathy (ANE)

Mutations in RANBP2<sup>NTD</sup> are associated with a high susceptibility to Acute Necrotizing Encephalopathy 1 (ANE1, also known as ADANE and IIAE3) [83–85]. Episodes are frequently triggered by a febrile infection, typically by Influenza A Virus (IAV) and more recently Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) [86,87]. In ANE1 patients, high fever can lead to seizures and loss of consciousness, rapidly progressing into encephalopathy and coma. Brain imaging is characterized by multiple and symmetrical hemorrhagic lesions of the deep grey matter of the brain. While non-RANBP2 ANE cases are predominant, these tend to be sporadic, non-recurrent, and occur at all ages. In contrast, patients with autosomal dominant missense mutations in RANBP2<sup>NTD</sup> develop recurrent rapid-onset episodes with poorer prognosis almost exclusively in children, leading to severe cognitive impairment or death [83,88,89].

Most ANE1 affected family members are obligate carriers of a c.1880C/T; pThr585Met mutation in RANBP2. The T585 residue is highly conserved in all mammalian RANBP2 proteins and the T585M mutation was never observed in control individuals [83]. Interestingly, however, although the T585M mutation is not present in RANBP2 of healthy individuals, four of the seven human RGPDs carry the mutation. Other *de novo* missense mutations have also been reported in ANE1 individuals, T653I, I656V, W681C [83,90]. Compellingly, all the reported ANE1-associated mutations are located in the same domain, the RANBP2<sup>NTD</sup>, highlighting a potentially critical role of this region of RANBP2 in the pathology. While none of these mutations have been shown to affect the structure of the NTD, a



reduced thermosolubility of RANBP2 mutants was observed, pointing to a possible mechanistic link to the fever-induced nature of the pathology [18].

Unlike encephalitis, ANE1 is not associated with the infiltration of peripheral immune cells, antibodies or pathogens in the brain or cerebrospinal fluid (CSF) [83,91]. Therefore, central nervous system (CNS) injury is thought to be the result of an indirect activation of cells resident in the brain that perform key immunity, metabolic, or neuroprotective tasks (e.g. microglia and astrocytes) [92]. Moreover, the incomplete penetrance of RANBP2 mutations suggests that they induce encephalopathy only in certain circumstances. Although the mechanisms responsible for this activation are still unknown, several hypotheses, related to the RANBP2 functions, have been suggested [93].

#### 4.1.1 Metabolic dysfunction

It has been proposed that the CNS lesions observed in ANE1 are reminiscent of neuropathologic findings in mitochondrial disorders such as Leigh syndrome and Wernicke encephalopathy, suggesting the involvement of energy metabolism in the pathology [83,94]. Although no functional deficiencies could be detected in isolated mitochondria, it was noted that oxygen consumption remained high in the absence of ADP, suggesting a loose coupling of oxidative phosphorylation that may favor severe uncoupling during fever [94]. Additionally, muscle biopsies from some patients, but not others, showed evidence of mitochondrial stress [94,95].

These clinical observations are supported by mechanistic studies linking RANBP2 to mitochondrial transport and function. First, RANBP2 determines mitochondrial positioning through its interaction with KIF5B/C, and ectopic expression of the kinesin-binding domain of RANBP2 leads to the perinuclear clustering of mitochondria and a deficit in mitochondrial membrane potential in rodent cells [62]. Second, the RANBP2<sup>NTD</sup> associates with cytochrome C oxidase COX11 and hexokinase 1, thus indirectly regulating hexokinase 1 levels in brain [96]. Concordantly, mice haploinsufficient for *RANBP2* present metabolic deficiencies such as hexokinase 1 insufficiency in the brain [96], and it is interesting to note that the predominant mutated version of RANBP2 (T585M) presents a reduced interaction with COX11 [97]. These observations suggest that RANBP2 mutations could predispose to energy failure in the brain during fever or an inflammatory state, thereby causing ANE [97].

A recent study reported elevated levels in the neuroinflammatory metabolites neopterin and quinolinic acid in several infection-triggered encephalopathy syndromes [92]. These findings are important because they are the first description of potential biomarkers for ANE1 and other encephalopathies. Moreover, since quinolinic acid is a neurotoxin, they illustrate how metabolites could cause CNS damage in ANE1.

#### 4.1.2 Excessive inflammatory response

Clinically, hospitalized ANE1 patients do not have obvious signs of massive and uncontrolled systemic release of interferon and pro-inflammatory cytokines that might be indicative of a cytokine storm [98]. However, some abnormal biomarkers have been reported, such as elevated inflammatory cytokines and pleocytosis of inflammatory cells in the CSF of ANE1 patients, as well as elevated IL1- $\beta$  and IL-6 serum levels [91,99]. This suggests that the inflammatory response to infection might be responsible for the brain lesions. In accordance with this, several pro-inflammatory cytokines have been shown to destabilize the blood-brain barrier (BBB) permeability [85], as has been reported for instance following IL-6 overexpression in mice [100].

Several molecular mechanisms have been investigated to explain how mutated RANBP2 might exacerbate the inflammatory response. As RANBP2 is involved in mRNA export and translation, these functions could be impacted by ANE1 mutations and could explain the increase of pro-inflammatory cytokines in patients. First, RANBP2 was shown to be necessary for the translation of mRNAs encoding secretory proteins using shRNA-based knockdown [52], although subsequent work using rapid auxin-targeted degradation indicated this translational defect is not limited to secretory proteins [18], suggesting a more general role for RANBP2 in the remodeling of mRNPs as they emerge from the

nuclear pore. Second, evidence suggests that RANBP2 contributes to the miRNA silencing of IL6 mRNA through interaction with miRISC complex components and SUMOylation of AGO during mRNA export, leading to its stabilization on the target mRNA [58]. Additionally, RANBP2 directly interacts with another miRISC complex component, GW182, and evidence suggests that the mutated form of RANBP2 (T585M) shows a reduced interaction with GW182 [68]. Further work will be necessary to determine whether the effect of RANBP2 on mRNA stability is specific to some cytokines or has a more general effect.

#### 4.2. Cancer

Through its E3 SUMO ligase function, RANBP2 is involved in controlling gene expression [101], chromosome decatenation [56], cell cycle and cell proliferation [102]. Contradicting roles have been reported for RANBP2 in cancer, as both a tumor suppressor and an oncogenic role have been described. RANBP2 has been reported to be up-regulated in cervical cancer cells [103], and to promote cancer progression by regulating gene expression [104,105] and nucleo-cytoplasmic translocation [102]. Additionally, RANBP2 has a tumor-suppressor role by SUMOylating proteins such as Topoisomerase II $\alpha$  [56], PML-IV [106] and the transcriptional repressor Small Heterodimer Partner [101]. Improper SUMOylation can thus lead to oncogenesis, as it has been observed by Satow et al. who showed that  $\beta$ -catenin sequesters PML-IV in cancer cells and inhibits its SUMOylation by RANBP2. This prevents the proper PML body assembly and results in oncogenesis [106].

Overall, RANBP2 plays a critical role in various cellular processes and its dysfunction has been linked to oncogenesis, although the mechanistic details seem to be complex.

#### 4.3. Neurodegenerative diseases

Parkinson's disease is a neurodegenerative disorder that affects neurons in the substantia nigra area of the brain. Some familial cases of Parkinson's disease present mutations in the *parkin* gene, which encodes an E3 ubiquitin-ligase [107]. Parkin was reported to selectively bind to RANBP2 and ubiquitinate it, leading to its degradation by the proteasome [108]. It has been suggested that RANBP2 and parkin could share some mechanistic similarities that are critical to the survival or function of dopaminergic neurons [109]. Among other locations in the cell, RANBP2 and parkin can both localize at the mitochondria, where parkin has a neuroprotective effect that has been linked to the regulation of mitophagy [62,97,110].

Alzheimer's disease is a progressive neurodegenerative disease impairing cognitive abilities. Several studies have suggested that the nucleo-cytoplasmic transport pathway may be altered [111,112] and nuclear irregularities were observed in the neurons of Alzheimer's patients [113]. Nucleo-cytoplasmic transport impairment in Alzheimer's patients is putatively associated with the interaction of the Tau protein with Nup98 and consequent mislocalization of Nup98 [111,112,114,115]. In fact, dysfunctional nucleocytoplasmic trafficking appears to be a common feature of tauopathies [116]. Although RANBP2 has not been directly linked to Alzheimer's disease, one study reported a reduced expression of RAN in the brain of Alzheimer's disease patients, which could indirectly impact RANBP2 [116].

#### 4.4. Viral infections

Multiple studies have highlighted prominent roles for RANBP2 in virus infection [84]. First, viruses can differentially regulate the expression of RANBP2 or change its compartmentalization to establish a favorable environment for their replication. For instance, RANBP2 is upregulated during Hepatitis C virus infection, both at the mRNA and protein levels [117]. Moreover, RANBP2 is targeted by Vaccinia virus to the viral factories, where it is thought to impact translation by recruiting Nup62 and the translation initiation factor eIF4E [118]. RANBP2 is also involved in the biogenesis of AL in the cytoplasm [119], and these are thought to be beneficial to viral replication [25]. A re-localization of RANBP2 to the cytoplasm has also been described for Human Immunodeficiency virus type 1 (HIV-1) [64]. Interestingly, the re-localization of nuclear components to the cytoplasm can be a strategy employed by cytoplasmic viruses such as human rhinovirus, to exploit nuclear functions [120].

Second, RANBP2 can directly assist nuclear viruses to either enter or exit the nucleus, as reported for Adenovirus, Herpes Simplex Virus type 1 (HSV-1), and HIV-1. For Adenovirus, RANBP2 participates in nuclear import of viral genomes in concert with transportin 1 [121]. For HSV-1, changes in the structure of the nuclear envelope and in post-translational modifications on RANBP2 have been observed [122–125], which may favor viral exit. Additionally, the viral tegument protein VP1/2 interacts with RANBP2, thus favoring capsid attachment to the nuclear envelope [126]. For HIV-1, capsid docking at the NPC is also dependent on RANBP2 [127,128]. Evidence suggests that HIV-1 infection causes RANBP2 to relocate from the NPC towards cytosolic HIV-1 capsids by the kinesin motor KIF5B, that RANBP2 binds to capsids via its C-terminal domain and facilitates HIV-1 nuclear entry [35,64,127,129,130]. Additionally, RANBP2 has also been shown to facilitate the uncoating of some viruses, which may contribute to improved nuclear targeting. For instance, RANBP2 binds to KIF5C during Adenovirus infection, indirectly linking the viral capsid to the molecular motor and this leads to the disassembly of the viral capsid and disruption of the NPCs [131].

Third, RANBP2 can also participate in cellular counter defense mechanisms to inhibit virus replication. For instance, viruses have been shown to disrupt stress granule assembly to facilitate their replication [132] and for the Cricket paralysis virus, this involves the depletion of RANBP2 [26]. RANBP2 depletion has also been shown to increase infection by Japanese encephalitis virus indicating that it participates in the host response to viral infection [133]. Through its E3 SUMO ligase activity, RANBP2 was also shown to modify the restriction factor TRIM5 $\alpha$ , and thereby modulate the innate immune response to infections by retroviruses [59,134,135].

## Conclusion

Despite almost 30 years since the discovery of RANBP2 and many landmark papers, further work will be required to better understand, for instance, why RANBP2 evolved specifically in metazoans, why its duplication in primates underwent positive selection, what are the functions of non-mammalian RANBP2 proteins, and the precise mechanisms that link RANBP2 to human disease.

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## Figure legends

**Figure 1:** Cellular localization of RANBP2. During the interphase, RANBP2 is located at the nuclear pores in the nuclear pore complex (NPC), in annulate lamellae (AL) at the endoplasmic reticulum (ER) and in RNA-rich condensates such as processing bodies (P-bodies) or stress granules and at ER-mitochondria contact sites. During mitosis, RANBP2 is targeted to chromosome kinetochores. Schematic representation of organelles is not to scale.

**Figure 2:** Gene and protein organization of RANBP2. In the human genome, the RANBP2 gene is located on chromosome 2 at the position q13 (chromosome representation obtained from the UCSC Genome Browser database) and contains 29 exons (green squares, gene representation obtained from NCBI website). The RANBP2 protein is composed of the following domains: an N-terminal domain (NTD) containing tetratricopeptide repeats (TPR), an oligomerization element (OE), four Ran-binding domains (RBD1 to RBD4), eight zinc finger motifs, a kinesin-binding domain (KBD), an E3 SUMO-ligase domain and a C-terminal cyclophilin-like domain.

**Figure 3:** At the nuclear pores, RANBP2 is involved in protein import, RanGTP hydrolysis (yellow circles), protein SUMOylation as well as mRNA export and remodeling (which mostly occurs through mRNA interaction with the NXF1-NXT1 export receptor). In the cytoplasm, RANBP2 is involved in mRNA

silencing in annulate lamellae and/or in P-bodies/stress granules, as well as in cargo transport by the kinesin-1 on microtubules. During mitosis, RANBP2 is targeted to kinetochores where it indirectly allows sister chromatid decatenation.

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## References

- 1 Lin DH & Hoelz A (2019) The Structure of the Nuclear Pore Complex (An Update). *Annu Rev Biochem* **88**, 725–783.
- 2 Beck M & Hurt E (2017) The nuclear pore complex: understanding its function through structural insight. *Nat Rev Mol Cell Biol* **18**, 73–89.
- 3 Allen NPC, Huang L, Burlingame A & Rexach M (2001) Proteomic Analysis of Nucleoporin Interacting Proteins. *Journal of Biological Chemistry* **276**, 29268–29274.
- 4 Hampoelz B, Andres-Pons A, Kastritis P & Beck M (2019) Structure and Assembly of the Nuclear Pore Complex. *Annu Rev Biophys* **48**, 515–536.
- 5 Knockenhauer KE & Schwartz TU (2016) The Nuclear Pore Complex as a Flexible and Dynamic Gate. *Cell* **164**, 1162–1171.
- 6 Makarov AA, Padilla-Mejia NE & Field MC (2021) Evolution and diversification of the nuclear pore complex. *Biochem Soc Trans* **49**, 1601–1619.
- 7 Fernandez-Martinez J & Rout MP (2021) One Ring to Rule them All? Structural and Functional Diversity in the Nuclear Pore Complex. *Trends Biochem Sci* **46**, 595–607.
- 8 Callan HG & Tomlin SG (1950) Experimental studies on amphibian oocyte nuclei I. Investigation of the structure of the nuclear membrane by means of the electron microscope. *Proc R Soc Lond B Biol Sci* **137**, 367–378.
- 9 Watson ML (1959) Further Observations on the Nuclear Envelope of the Animal Cell. *J Biophys Biochem Cytol* **6**, 147–156.
- 10 Gall JG (1967) OCTAGONAL NUCLEAR PORES. *Journal of Cell Biology* **32**, 391–399.
- 11 Akey CW, Singh D, Ouch C, Echeverria I, Nudelman I, Varberg JM, Yu Z, Fang F, Shi Y, Wang J, Salzberg D, Song K, Xu C, Gumbart JC, Suslov S, Unruh J, Jaspersen SL, Chait BT, Sali A, Fernandez-Martinez J, Ludtke SJ, Villa E & Rout MP (2022) Comprehensive structure and functional adaptations of the yeast nuclear pore complex. *Cell* **185**, 361-378.e25.
- 12 Mosalaganti S, Obarska-Kosinska A, Siggel M, Taniguchi R, Turoňová B, Zimmerli CE, Buczak K, Schmidt FH, Margiotta E, Mackmull MT, Hagen WJH, Hummer G, Kosinski J & Beck M (2022) AI-based structure prediction empowers integrative structural analysis of human nuclear pores. *Science (1979)* **376**, eabm9506.
- 13 Zila V, Margiotta E, Turoňová B, Müller TG, Zimmerli CE, Mattei S, Allegretti M, Börner K, Rada J, Müller B, Lusic M, Kräusslich HG & Beck M (2021) Cone-shaped HIV-1 capsids are transported through intact nuclear pores. *Cell* **184**, 1032-1046.e18.
- 14 Jarnik M & Aebi U (1991) Toward a more complete 3-D structure of the nuclear pore complex. *J Struct Biol* **107**, 291–308.
- 15 Goldberg MW & Allen TD (1993) The nuclear pore complex: three-dimensional surface structure revealed by field emission, in-lens scanning electron microscopy, with underlying structure uncovered by proteolysis. *J Cell Sci* **106 ( Pt 1)**, 261–274.
- 16 Wu J, Matunis MJ, Kraemer D, Blobel G & Coutavas E (1995) Nup358, a cytoplasmically exposed nucleoporin with peptide repeats, Ran-GTP binding sites, zinc fingers, a cyclophilin A homologous domain, and a leucine-rich region. *J Biol Chem* **270**, 14209–14213.
- 17 Yokoyama N, Hayashi N, Seki T, Panté N, Ohba T, Nishii K, Kuma K, Hayashida T, Miyata T, Aebi U, Fukui M & Nishimoto T (1995) A giant nucleopore protein that binds Ran/TC4. *Nature 1995 376:6536* **376**, 184–188.
- 18 Bley CJ, Nie S, Mobbs GW, Petrovic S, Gres AT, Liu X, Mukherjee S, Harvey S, Huber FM, Lin DH, Brown B, Tang AW, Rundlet EJ, Correia AR, Chen S, Regmi SG, Stevens TA, Jette CA,

- Dasso M, Patke A, Palazzo AF, Kossiakoff AA & Hoelz A (2022) Architecture of the cytoplasmic face of the nuclear pore. *Science* **376**, eabm9129.
- 19 Huang G, Zeng C & Shi Y (2023) Structure of the nuclear pore complex goes atomic. *Curr Opin Struct Biol* **78**, 102523.
- 20 Petrovic S, Mobbs GW, Bley CJ, Nie S, Patke A & Hoelz A (2022) Structure and Function of the Nuclear Pore Complex. *Cold Spring Harb Perspect Biol* **14**, a041264.
- 21 Tai L, Yin G, Sun F & Zhu Y (2023) Cryo-electron Microscopy Reveals the Structure of the Nuclear Pore Complex. *J Mol Biol* **435**, 168051.
- 22 Kutay U, Jühlen R & Antonin W (2021) Mitotic disassembly and reassembly of nuclear pore complexes. *Trends Cell Biol* **31**, 1019–1033.
- 23 Otsuka S, Tempkin JOB, Zhang W, Politi AZ, Rybina A, Hossain MJ, Kueblbeck M, Callegari A, Koch B, Morero NR, Sali A & Ellenberg J (2023) A quantitative map of nuclear pore assembly reveals two distinct mechanisms. *Nature* **2023 613:7944** **613**, 575–581.
- 24 Raices M & D'Angelo MA (2012) Nuclear pore complex composition: a new regulator of tissue-specific and developmental functions. *Nat Rev Mol Cell Biol* **13**, 687–699.
- 25 Eymieux S, Blanchard E, Uzbekov R, Hourieux C & Roingeard P (2021) Annulate lamellae and intracellular pathogens. *Cell Microbiol* **23**, e13328.
- 26 Sadasivan J, Vlok M, Wang X, Nayak A, Andino R & Jan E (2022) Targeting Nup358/RanBP2 by a viral protein disrupts stress granule formation. *PLoS Pathog* **18**, e1010598.
- 27 Palade GE (1955) Studies on the endoplasmic reticulum. II. Simple dispositions in cells in situ. *J Biophys Biochem Cytol* **1**, 567–582.
- 28 Kim KSW & Boatman ES (1967) Electron microscopy of monkey kidney cell cultures infected with rubella virus. *J Virol* **1**, 205–214.
- 29 Cardinali G, Gentile M, Cirone M, Zompetta C, Frati L, Faggioni A & Torrisi MR (1998) Viral glycoproteins accumulate in newly formed annulate lamellae following infection of lymphoid cells by human herpesvirus 6. *J Virol* **72**, 9738–9746.
- 30 Pichler A, Gast A, Seeler JS, Dejean A & Melchior F (2002) The nucleoporin RanBP2 has SUMO1 E3 ligase activity. *Cell* **108**, 109–120.
- 31 Kassube SA, Stuwe T, Lin DH, Antonuk CD, Napetschnig J, Blobel G & Hoelz A (2012) Crystal structure of the N-terminal domain of Nup358/RanBP2. *J Mol Biol* **423**, 752–765.
- 32 Joseph J & Dasso M (2008) The nucleoporin Nup358 associates with and regulates interphase microtubules. *FEBS Lett* **582**, 190–196.
- 33 Fontana P, Dong Y, Pi X, Tong AB, Hecksel CW, Wang L, Fu TM, Bustamante C & Wu H (2022) Structure of cytoplasmic ring of nuclear pore complex by integrative cryo-EM and AlphaFold. *Science* **376**, eabm9326.
- 34 Sakin V, Richter SM, Hsiao HH, Urlaub H & Melchior F (2015) Sumoylation of the GTPase Ran by the RanBP2 SUMO E3 Ligase Complex. *J Biol Chem* **290**, 23589.
- 35 Lin DH, Zimmermann S, Stuwe T, Stuwe E & Hoelz A (2013) Structural and functional analysis of the C-terminal domain of Nup358/RanBP2. *J Mol Biol* **425**, 1318–1329.
- 36 Tai L, Zhu Y, Ren H, Huang X, Zhang C & Sun F (2022) 8 Å structure of the outer rings of the *Xenopus laevis* nuclear pore complex obtained by cryo-EM and AI. *Protein Cell* **13**, 760–777.
- 37 Zhu X, Huang G, Zeng C, Zhan X, Liang K, Xu Q, Zhao Y, Wang P, Wang Q, Zhou Q, Tao Q, Liu M, Lei J, Yan C & Shi Y (2022) Structure of the cytoplasmic ring of the *Xenopus laevis* nuclear pore complex. *Science (1979)* **376**, eabl8280.
- 38 Stewart M (2007) Molecular mechanism of the nuclear protein import cycle. *Nature Reviews Molecular Cell Biology* **2007 8:3** **8**, 195–208.

- 39 Wing CE, Fung HYJ & Chook YM (2022) Karyopherin-mediated nucleocytoplasmic transport. *Nat Rev Mol Cell Biol* **23**, 307–328.
- 40 Walther TC, Pickersgill HS, Cordes VC, Goldberg MW, Allen TD, Mattaj IW & Fornerod M (2002) The cytoplasmic filaments of the nuclear pore complex are dispensable for selective nuclear protein import. *J Cell Biol* **158**, 63–77.
- 41 Hutten S & Kehlenbach RH (2006) Nup214 is required for CRM1-dependent nuclear protein export in vivo. *Mol Cell Biol* **26**, 6772–6785.
- 42 Hutten S, Flotho A, Melchior F & Kehlenbach RH (2008) The Nup358-RanGAP Complex Is Required for Efficient Importin  $\alpha/\beta$ -dependent Nuclear Import. *Mol Biol Cell* **19**, 2300.
- 43 Hutten S, Wälde S, Spillner C, Hauber J & Kehlenbach RH (2009) The nuclear pore component Nup358 promotes transportin-dependent nuclear import. *J Cell Sci* **122**, 1100–1110.
- 44 Hamada M, Haeger A, Jeganathan KB, van Ree JH, Malureanu L, Wälde S, Joseph J, Kehlenbach RH & van Deursen JM (2011) Ran-dependent docking of importin-beta to RanBP2/Nup358 filaments is essential for protein import and cell viability. *J Cell Biol* **194**, 597–612.
- 45 Matunis MJ, Wu J & Blobel G (1998) SUMO-1 Modification and Its Role in Targeting the Ran GTPase-activating Protein, RanGAP1, to the Nuclear Pore Complex. *J Cell Biol* **140**, 499.
- 46 Melchior F, Guan T, Yokoyama N, Nishimoto T & Gerace L (1995) GTP hydrolysis by Ran occurs at the nuclear pore complex in an early step of protein import. *Journal of Cell Biology* **131**, 571–581.
- 47 Reverter D & Lima CD (2005) Insights into E3 ligase activity revealed by a SUMO-RanGAP1-Ubc9-Nup358 complex. *Nature* **435**, 687–692.
- 48 Köhler A & Hurt E (2007) Exporting RNA from the nucleus to the cytoplasm. *Nat Rev Mol Cell Biol* **8**, 761–773.
- 49 Björk P & Wieslander L (2014) Mechanisms of mRNA export. *Semin Cell Dev Biol* **32**, 47–54.
- 50 Saitoh N, Sakamoto C, Hagiwara M, Agredano-Moreno LT, Jiménez-García LF & Nakao M (2012) The distribution of phosphorylated SR proteins and alternative splicing are regulated by RANBP2. *Mol Biol Cell* **23**, 1115–1128.
- 51 Forler D, Rabut G, Ciccarelli FD, Herold A, Köcher T, Niggeweg R, Bork P, Ellenberg J & Izaurralde E (2004) 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* **24**, 1155–1167.
- 52 Mahadevan K, Zhang H, Akef A, Cui XA, Gueroussov S, Cenik C, Roth FP & Palazzo AF (2013) RanBP2/Nup358 Potentiates the Translation of a Subset of mRNAs Encoding Secretory Proteins. *PLoS Biol* **11**, e1001545.
- 53 Culjkovic-Kraljacic B, Baguet A, Volpon L, Amri A & Borden KLB (2012) The Oncogene eIF4E Reprograms the Nuclear Pore Complex to Promote mRNA Export and Oncogenic Transformation. *Cell Rep* **2**, 207–215.
- 54 Gareau JR & Lima CD (2010) The SUMO pathway: Emerging mechanisms that shape specificity, conjugation and recognition. *Nat Rev Mol Cell Biol* **11**, 861–871.
- 55 Miyauchi Y, Yogosawa S, Honda R, Nishida T & Yasuda H (2002) Sumoylation of Mdm2 by protein inhibitor of activated STAT (PIAS) and RanBP2 enzymes. *J Biol Chem* **277**, 50131–50136.

- 56 Dawlaty MM, Malureanu L, Jeganathan KB, Kao E, Sustmann C, Tahk S, Shuai K, Grosschedl R & van Deursen JM (2008) Resolution of Sister Centromeres Requires RanBP2-Mediated SUMOylation of Topoisomerase II $\alpha$ . *Cell* **133**, 103–115.
- 57 Klein UR, Haindl M, Nigg EA & Muller S (2009) RanBP2 and SENP3 function in a mitotic SUMO2/3 conjugation-deconjugation cycle on Borealin. *Mol Biol Cell* **20**, 410–418.
- 58 Shen Q, Wang YE, Truong M, Mahadevan K, Wu JJ, Zhang H, Li J, Smith HW, Smibert CA & Palazzo AF (2021) RanBP2/Nup358 enhances miRNA activity by sumoylating Argonautes. *PLoS Genet* **17**, e1009378.
- 59 Maarifi G, Fernandez J, Portilho DM, Boulay A, Dutrieux J, Oddos S, Butler-Browne G, Nisole S & Arhel NJ (2018) RanBP2 regulates the anti-retroviral activity of TRIM5 $\alpha$  by SUMOylation at a predicted phosphorylated SUMOylation motif. *Communications Biology* 2018 1:1 **1**, 1–11.
- 60 Joseph J, Liu ST, Jablonski SA, Yen TJ & Dasso M (2004) The RanGAP1-RanBP2 complex is essential for microtubule-kinetochore interactions in vivo. *Current Biology* **14**, 611–617.
- 61 Cai Y, Singh BB, Aslanukov A, Zhao H & Ferreira PA (2001) The Docking of Kinesins, KIF5B and KIF5C, to Ran-binding Protein 2 (RanBP2) Is Mediated via a Novel RanBP2 Domain. *Journal of Biological Chemistry* **276**, 41594–41602.
- 62 Cho KI, Cai Y, Yi H, Yeh A, Aslanukov A & Ferreira PA (2007) Association of the Kinesin-Binding Domain of RanBP2 to KIF5B and KIF5C Determines Mitochondria Localization and Function. *Traffic* **8**, 1722–1735.
- 63 Splinter D, Tanenbaum ME, Lindqvist A, Jaarsma D, Flotho A, Yu K Lou, Grigoriev I, Engelsma D, Haasdijk ED, Keijzer N, Demmers J, Fornerod M, Melchior F, Hoogenraad CC, Medema RH & Akhmanova A (2010) Bicaudal D2, Dynein, and Kinesin-1 Associate with Nuclear Pore Complexes and Regulate Centrosome and Nuclear Positioning during Mitotic Entry. *PLoS Biol* **8**, e1000350.
- 64 Dharan A, Talley S, Tripathi A, Mamede JI, Majetschak M, Hope TJ & Campbell EM (2016) KIF5B and Nup358 Cooperatively Mediate the Nuclear Import of HIV-1 during Infection. *PLoS Pathog* **12**, e1005700.
- 65 Cui H, Noell CR, Behler RP, Zahn JB, Terry LR, Russ BB & Solmaz SR (2019) Adapter Proteins for Opposing Motors Interact Simultaneously with Nuclear Pore Protein Nup358. *Biochemistry* **58**, 5085–5097.
- 66 Deshmukh P, Markande S, Fandade V, Ramtirtha Y, Madhusudhan MS & Joseph J (2021) The miRISC component AGO2 has multiple binding sites for Nup358 SUMO-interacting motif. *Biochem Biophys Res Commun* **556**, 45–52.
- 67 Sahoo MR, Gaikwad S, Khuperkar D, Ashok M, Helen M, Yadav SK, Singh A, Magre I, Deshmukh P, Dhanvijay S, Sahoo PK, Ramtirtha Y, Madhusudhan MS, Gayathri P, Seshadri V & Joseph J (2017) Nup358 binds to AGO proteins through its SUMO-interacting motifs and promotes the association of target mRNA with miRISC. *EMBO Rep* **18**, 241–263.
- 68 Deshmukh P, Singh A, Khuperkar D & Joseph J (2021) Acute necrotizing encephalopathy-linked mutations in Nup358 impair interaction of Nup358 with TNRC6/GW182 and miRNA function. *Biochem Biophys Res Commun* **559**, 230–237.
- 69 Sen GL & Blau HM (2005) Argonaute 2/RISC resides in sites of mammalian mRNA decay known as cytoplasmic bodies. *Nat Cell Biol* **7**, 633–636.
- 70 Liu J, Rivas F V., Wohlschlegel J, Yates JR, Parker R & Hannon GJ (2005) A role for the P-body component GW182 in microRNA function. *Nat Cell Biol* **7**, 1161–1166.



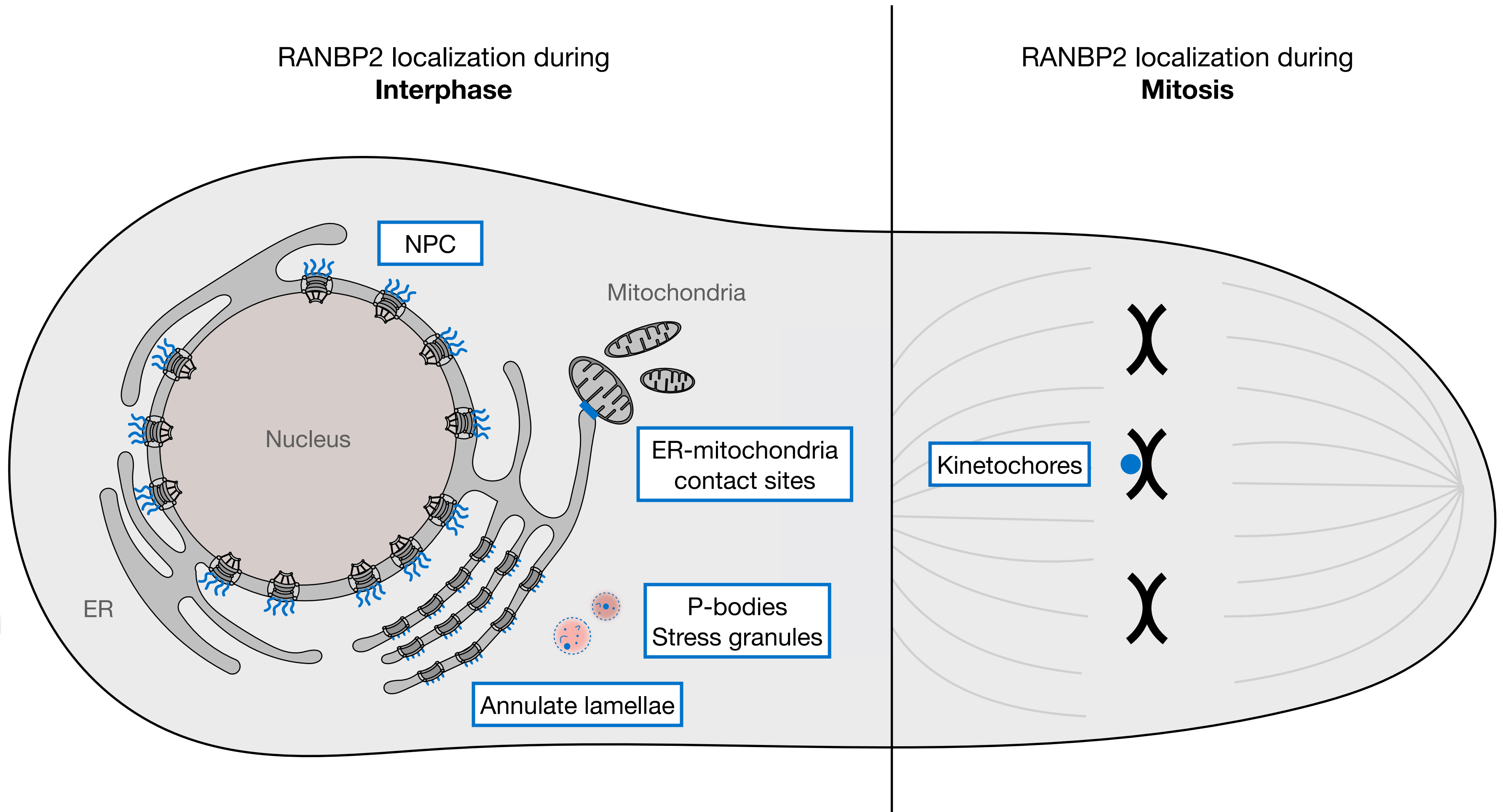
- 71 Chen S, Lyanguzova M, Kaufhold R, Plevock Haase KM, Lee H, Arnautov A & Dasso M (2021) Association of RanGAP to nuclear pore complex component, RanBP2/Nup358, is required for pupal development in *Drosophila*. *Cell Rep* **37**, 110151.
- 72 Gipson AB, Hanson MR & Bentolila S (2022) The RanBP2 zinc finger domains of chloroplast RNA editing factor OZ1 are required for protein–protein interactions and conversion of C to U. *The Plant Journal* **109**, 215–226.
- 73 De Franco S, Vandenameele J, Brans A, Verlaine O, Bendak K, Damblon C, Matagne A, Segal DJ, Galleni M, Mackay JP & Vandevenne M (2019) Exploring the suitability of RanBP2-type Zinc Fingers for RNA-binding protein design. *Scientific Reports 2019 9:1* **9**, 1–13.
- 74 Bailey JA, Gu Z, Clark RA, Reinert K, Samonte R V., Schwartz S, Adams MD, Myers EW, Li PW & Eichler EE (2002) Recent segmental duplications in the human genome. *Science* **297**, 1003–1007.
- 75 Hillier LDW, Graves TA, Fulton RS, Fulton LA, Pepin KH, Minx P, Wagner-McPherson C, Layman D, Wylie K, Sekhon M, Becker MC, Fewell GA, Delehaunty KD, Miner TL, Nash WE, Krenitzki C, Oddy L, Du H, Sun H, Bradshaw-Cordum H, Ali J, Carter J, Cordes M, Harris A, Isak A, Van Brunt A, Nguyen C, Du F, Courtney L, Kalicki J, Ozersky P, Abbott S, Armstrong J, Belter EA, Caruso L, Cedroni M, Cotton M, Davidson T, Desai A, Elliott G, Erb T, Fronick C, Gaige T, Haakenson W, Haglund K, Holmes A, Harkins R, Kim K, Kruchowski SS, Strong CM, Grewal N, Goyea E, Hou S, Levy A, Martinka S, Mead K, McLellan MD, Meyer R, Randall-Maher J, Tomlinson C, Dauphin-Kohlberg S, Kozlowicz-Reilly A, Shah N, Swearingen-Shahid S, Snider J, Strong JT, Thompson J, Yoakum M, Leonard S, Pearman C, Trani L, Radionenko M, Waligorski JE, Wang C, Rock SM, Tin-Wollam AM, Maupin R, Latreille P, Wendl MC, Yang SP, Pohl C, Wallis JW, Spieth J, Bieri TA, Berkowicz N, Nelson JO, Osborne J, Ding L, Meyer R, Sabo A, Shotland Y, Sinha P, Wohldmann PE, Cook LL, Hickenbotham MT, Eldred J, Williams D, Jones TA, She X, Ciccarelli FD, Izaurralde E, Taylor J, Schmutz J, Myers RM, Cox DR, Huang X, McPherson JD, Mardis ER, Clifton SW, Warren WC, Chinwalla AT, Eddy SR, Marra MA, Ovcharenko I, Furey TS, Miller W, Eichler EE, Bork P, Suyama M, Torrents D, Waterston RH & Wilson RK (2005) Generation and annotation of the DNA sequences of human chromosomes 2 and 4. *Nature* **434**, 724–731.
- 76 Ciccarelli FD, von Mering C, Suyama M, Harrington ED, Izaurralde E & Bork P (2005) Complex genomic rearrangements lead to novel primate gene function. *Genome Res* **15**, 343–351.
- 77 Mao Y, Harvey WT, Porubsky D, Munson KM, Hoekzema K, Lewis AP, Audano PA, Rozanski A, Yang X, Zhang S, Gordon DS, Wei X, Logsdon GA, Haukness M, Dishuck PC, Jeong H, Rosario R del, Bauer VL, Fattor WT, Wilkerson GK, Lu Q, Paten B, Feng G, Sawyer SL, Warren WC, Carbone L & Eichler EE (2023) Structurally divergent and recurrently mutated regions of primate genomes. *bioRxiv*, 2023.03.07.531415.
- 78 Lynch M & Conery JS (2000) The evolutionary fate and consequences of duplicate genes. *Science* **290**, 1151–1155.
- 79 Parisi MA, Bennett CL, Eckert ML, Dobyms WB, Gleeson JG, Shaw DWW, McDonald R, Eddy A, Chance PF & Glass IA (2004) The NPHP1 gene deletion associated with juvenile nephronophthisis is present in a subset of individuals with Joubert syndrome. *Am J Hum Genet* **75**, 82–91.

- 80 Cai Y, Gao Y, Qi S, Miao S, Cui X, Wang L, Zong S & Koide SS (2002) Characterization and potential function of a novel testis-specific nucleoporin BS-63. *Mol Reprod Dev* **61**, 126–134.
- 81 Hutchins JRA, Toyoda Y, Hegemann B, Poser I, Hériché JK, Sykora MM, Augsburg M, Hudecz O, Buschhorn BA, Bulkescher J, Conrad C, Comartin D, Schleiffer A, Sarov M, Pozniakovskiy A, Slabicki MM, Schloissnig S, Steinmacher I, Leuschner M, Ssykor A, Lawo S, Pelletier L, Stark H, Nasmyth K, Ellenberg J, Durbin R, Buchholz F, Mechtler K, Hyman AA & Peters JM (2010) Systematic analysis of human protein complexes identifies chromosome segregation proteins. *Science* **328**, 593–599.
- 82 Sowa ME, Bennett EJ, Gygi SP & Harper JW (2009) Defining the human deubiquitinating enzyme interaction landscape. *Cell* **138**, 389–403.
- 83 Neilson DE, Adams MD, Orr CMD, Schelling DK, Eiben RM, Kerr DS, Anderson J, Bassuk AG, Bye AM, Childs AM, Clarke A, Crow YJ, Di Rocco M, Dohna-Schwake C, Dueckers G, Fasano AE, Gika AD, Giannis D, Gorman MP, Grattan-Smith PJ, Hackenberg A, Kuster A, Lentschig MG, Lopez-Laso E, Marco EJ, Mastroianni S, Perrier J, Schmitt-Mechelke T, Servidei S, Skardoutsou A, Uldall P, van der Knaap MS, Goglin KC, Tefft DL, Aubin C, de Jager P, Hafler D & Warman ML (2009) Infection-Triggered Familial or Recurrent Cases of Acute Necrotizing Encephalopathy Caused by Mutations in a Component of the Nuclear Pore, RANBP2. *Am J Hum Genet* **84**, 44–51.
- 84 Jiang J, Wang YE, Palazzo AF & Shen Q (2022) Roles of Nucleoporin RanBP2/Nup358 in Acute Necrotizing Encephalopathy Type 1 (ANE1) and Viral Infection. *International Journal of Molecular Sciences* 2022, Vol 23, Page 3548 **23**, 3548.
- 85 Levine JM, Ahsan N, Ho E & Santoro JD (2020) Genetic Acute Necrotizing Encephalopathy Associated with RANBP2: Clinical and Therapeutic Implications in Pediatrics. *Mult Scler Relat Disord* **43**, 102194.
- 86 Forest C, Laudisi M, Malaventura C, Tugnoli V, Pellino G, Marangoni E, Baldi E, Borgatti L, Pugliatti M & Suppiej A (2023) Pediatric recurrent acute necrotizing encephalomyelitis, RANBP2 genotype and Sars-CoV-2 infection: Diagnosis, pathogenesis and targeted treatments from a case study. *European Journal of Paediatric Neurology* **42**, 117–121.
- 87 Pongpitakmetha T, Hemachudha P, Rattanawong W, Thanapornsangsuth P, Viswanathan A & Hemachudha T (2022) COVID-19 related acute necrotizing encephalopathy with extremely high interleukin-6 and RANBP2 mutation in a patient with recently immunized inactivated virus vaccine and no pulmonary involvement. *BMC Infect Dis* **22**, 1–6.
- 88 Mizuguchi M, Abe J, Mikkaichi K, Noma S, Yoshida K, Yamanaka T & Kamoshita S (1995) Acute necrotizing encephalopathy of childhood: A new syndrome presenting with multifocal, symmetric brain lesions. *J Neurol Neurosurg Psychiatry* **58**, 555–561.
- 89 Denier C, Balu L, Husson B, Nasser G, Burglen L, Rodriguez D, Labauge P & Chevret L (2014) Familial acute necrotizing encephalopathy due to mutation in the RANBP2 gene. *J Neurol Sci* **345**, 236–238.
- 90 Sell K, Storch K, Hahn G, Lee-Kirsch MA, Ramantani G, Jackson S, Neilson D, von der Hagen M, Hehr U & Smitka M (2016) Variable clinical course in acute necrotizing encephalopathy and identification of a novel RANBP2 mutation. *Brain Dev* **38**, 777–780.
- 91 Chatur N, Yea C, Ertl-Wagner B & Yeh EA (2022) Outcomes in influenza and RANBP2 mutation-associated acute necrotizing encephalopathy of childhood. *Dev Med Child Neurol* **64**, 1008–1016.

- 92 Dale RC, Thomas T, Patel S, Han VX, Kothur K, Troedson C, Gupta S, Gill D, Malone S, Waak M, Calvert S, Subramanian G, Andrews PI, Kandula T, Menezes MP, Ardern-Holmes S, Mohammad S, Bandodkar S & Yan J (2023) CSF neopterin and quinolinic acid are biomarkers of neuroinflammation and neurotoxicity in FIRES and other infection-triggered encephalopathy syndromes. *Ann Clin Transl Neurol* **10**, 1417–1432.
- 93 Palazzo AF, Joseph J, Lim M & Thakur KT (2022) Workshop on RanBP2/Nup358 and acute necrotizing encephalopathy. *Nucleus* **13**, 154–169.
- 94 Neilson DE, Eiben RM, Waniewski S, Hoppel CL, Varnes ME, Bangert BA, Wiznitzer M, Warman ML & Kerr DS (2003) Autosomal dominant acute necrotizing encephalopathy. *Neurology* **61**, 226–230.
- 95 Marco EJ, Anderson JE, Neilson DE & Strober JB (2010) Acute Necrotizing Encephalopathy in 3 Brothers. *Pediatrics* **125**, e693–e698.
- 96 Aslanukov A, Bhowmick R, Guraju M, Oswald J, Raz D, Bush RA, Sieving PA, Lu X, Bock CB & Ferreira PA (2006) RanBP2 Modulates Cox11 and Hexokinase I Activities and Haploinsufficiency of RanBP2 Causes Deficits in Glucose Metabolism. *PLoS Genet* **2**, e177.
- 97 Shibata A, Kasai M, Hoshino A, Tanaka T & Mizuguchi M (2021) RANBP2 mutation causing autosomal dominant acute necrotizing encephalopathy attenuates its interaction with COX11. *Neurosci Lett* **763**, 136173.
- 98 Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR & Katze MG (2012) Into the Eye of the Cytokine Storm. *Microbiology and Molecular Biology Reviews* **76**, 16–32.
- 99 Pongpitakmetha T, Hemachudha P, Rattanawong W, Thanapornsangsuth P, Viswanathan A & Hemachudha T (2022) COVID-19 related acute necrotizing encephalopathy with extremely high interleukin-6 and RANBP2 mutation in a patient with recently immunized inactivated virus vaccine and no pulmonary involvement. *BMC Infect Dis* **22**, 640.
- 100 Campbell IL, Abraham CR, Masliah E, Kemper P, Inglis JD, Oldstone MBA & Mucke L (1993) Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6. *Proc Natl Acad Sci U S A* **90**, 10061–10065.
- 101 Kim DH, Kwon S, Byun S, Xiao Z, Park S, Wu SY, Chiang CM, Kemper B & Kemper JK (2016) Critical role of RanBP2-mediated SUMOylation of Small Heterodimer Partner in maintaining bile acid homeostasis. *Nature Communications* **2016 7:1** **7**, 1–12.
- 102 Yang J, Liu Y, Wang B, Lan H, Liu Y, Chen F, Zhang J & Luo J (2017) Sumoylation in p27kip1 via RanBP2 promotes cancer cell growth in cholangiocarcinoma cell line QBC939. *BMC Mol Biol* **18**, 1–9.
- 103 Wang H, Luo Q, Kang J, Wei Q, Yang Y, Yang D, Liu X, Liu T & Yi P (2021) YTHDF1 Aggravates the Progression of Cervical Cancer Through m6A-Mediated Up-Regulation of RANBP2. *Front Oncol* **11**, 650383.
- 104 Liu X, Chen X, Xiao M, Zhu Y, Gong R, Liu J, Zeng Q, Xu C, Chen X, Wang F & Cao K (2021) RANBP2 Activates O-GlcNAcylation through Inducing CEBP $\alpha$ -Dependent OGA Downregulation to Promote Hepatocellular Carcinoma Malignant Phenotypes. *Cancers (Basel)* **13**, 3475.
- 105 Köhler A & Hurt E (2010) Gene Regulation by Nucleoporins and Links to Cancer. *Mol Cell* **38**, 6–15.
- 106 Satow R, Shitashige M, Jigami T, Fukami K, Honda K, Kitabayashi I & Yamada T (2012)  $\beta$ -Catenin Inhibits Promyelocytic Leukemia Protein Tumor Suppressor Function in Colorectal Cancer Cells. *Gastroenterology* **142**, 572–581.

- 107 Shimura H, Hattori N, Kubo SI, Mizuno Y, Asakawa S, Minoshima S, Shimizu N, Iwai K, Chiba T, Tanaka K & Suzuki T (2000) Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. *Nat Genet* **25**, 302–305.
- 108 Um JW, Min DS, Hyewhon R, Kim J, Paik SR & Chung KC (2006) Parkin ubiquitinates and promotes the degradation of RanBP2. *J Biol Chem* **281**, 3595–3603.
- 109 Cho KI, Searle K, Webb M, Yi H & Ferreira PA (2012) Ranbp2 haploinsufficiency mediates distinct cellular and biochemical phenotypes in brain and retinal dopaminergic and glia cells elicited by the Parkinsonian neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Cell Mol Life Sci* **69**, 3511–3527.
- 110 Narendra D, Tanaka A, Suen DF & Youle RJ (2008) Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J Cell Biol* **183**, 795.
- 111 Eftekharzadeh B, Daigle JG, Kapinos LE, Coyne A, Schiantarelli J, Carlomagno Y, Cook C, Miller SJ, Dujardin S, Amaral AS, Grima JC, Bennett RE, Tepper K, DeTure M, Vanderburgh CR, Corjuc BT, DeVos SL, Gonzalez JA, Chew J, Vidensky S, Gage FH, Mertens J, Troncoso J, Mandelkow E, Salvatella X, Lim RYH, Petrucelli L, Wegmann S, Rothstein JD & Hyman BT (2018) Tau Protein Disrupts Nucleocytoplasmic Transport in Alzheimer’s Disease. *Neuron* **99**, 925-940.e7.
- 112 Bitetto G & Di Fonzo A (2020) Nucleo–cytoplasmic transport defects and protein aggregates in neurodegeneration. *Translational Neurodegeneration* **2020 9:1** **9**, 1–16.
- 113 Sheffield LG, Miskiewicz HB, Tannenbaum LB & Mirra SS (2006) Nuclear Pore Complex Proteins in Alzheimer Disease. *J Neuropathol Exp Neurol* **65**, 45–54.
- 114 Nag N & Tripathi T (2023) Tau–FG-nucleoporin98 interaction and impaired nucleocytoplasmic transport in Alzheimer’s disease. *Brief Funct Genomics* **22**, 161–167.
- 115 Dickson JR, Frosch MP & Hyman BT (2023) Altered localization of nucleoporin 98 in primary tauopathies. *Brain Commun* **5**, fcac334.
- 116 Mastroeni D, Chouliaras L, Grover A, Liang WS, Hauns K, Rogers J & Coleman PD (2013) Reduced RAN Expression and Disrupted Transport between Cytoplasm and Nucleus; A Key Event in Alzheimer’s Disease Pathophysiology. *PLoS One* **8**, e53349.
- 117 Neufeldt CJ, Joyce MA, Levin A, Steenbergen RH, Pang D, Shields J, Tyrrell DLJ & Wozniak RW (2013) Hepatitis C Virus-Induced Cytoplasmic Organelles Use the Nuclear Transport Machinery to Establish an Environment Conducive to Virus Replication. *PLoS Pathog* **9**, e1003744.
- 118 Khuperkar D, Kamble A, Singh A, Ghate A, Nawadkar R, Sahu A & Joseph J (2017) Selective recruitment of nucleoporins on vaccinia virus factories and the role of Nup358 in viral infection. *Virology* **512**, 151–160.
- 119 Hampoelz B, Schwarz A, Ronchi P, Bragulat-Teixidor H, Tischer C, Gaspar I, Ephrussi A, Schwab Y & Beck M (2019) Nuclear Pores Assemble from Nucleoporin Condensates During Oogenesis. *Cell* **179**, 671-686.e17.
- 120 Flather D, Nguyen JHC, Semler BL & Gershon PD (2018) Exploitation of nuclear functions by human rhinovirus, a cytoplasmic RNA virus. *PLoS Pathog* **14**, e1007277.
- 121 Carlon-Andres I, Lagadec F, Pied N, Rayne F, Lafon M-E, Kehlenbach RH & Wodrich H (2020) Nup358 and Transportin 1 Cooperate in Adenoviral Genome Import. *J Virol* **94**, e00164-20.
- 122 Bjerke SL & Roller RJ (2006) Roles for herpes simplex virus type 1 UL34 and US3 proteins in disrupting the nuclear lamina during herpes simplex virus type 1 egress. *Virology* **347**, 261–276.

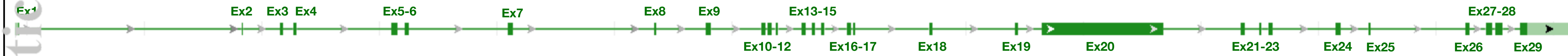
- 123 Reynolds AE, Liang L & Baines JD (2004) Conformational Changes in the Nuclear Lamina Induced by Herpes Simplex Virus Type 1 Require Genes U L 31 and U L 34 . *J Virol* **78**, 5564–5575.
- 124 Simpson-Holley M, Colgrove RC, Nalepa G, Harper JW & Knipe DM (2005) Identification and Functional Evaluation of Cellular and Viral Factors Involved in the Alteration of Nuclear Architecture during Herpes Simplex Virus 1 Infection. *J Virol* **79**, 12840–12851.
- 125 Hofemeister H & O’Hare P (2008) Nuclear Pore Composition and Gating in Herpes Simplex Virus-Infected Cells. *J Virol* **82**, 8392–8399.
- 126 Copeland AM, Newcomb WW & Brown JC (2009) Herpes simplex virus replication: roles of viral proteins and nucleoporins in capsid-nucleus attachment. *J Virol* **83**, 1660–1668.
- 127 Schaller T, Ocwieja KE, Rasaiyaah J, Price AJ, Brady TL, Roth SL, Hué S, Fletcher AJ, Lee K, KewalRamani VN, Noursadeghi M, Jenner RG, James LC, Bushman FD & Towers GJ (2011) HIV-1 Capsid-Cyclophilin Interactions Determine Nuclear Import Pathway, Integration Targeting and Replication Efficiency. *PLoS Pathog* **7**, e1002439.
- 128 Di Nunzio F, Danckaert A, Fricke T, Perez P, Fernandez J, Perret E, Roux P, Shorte S, Charneau P, Diaz-Griffero F & Arhel NJ (2012) Human Nucleoporins Promote HIV-1 Docking at the Nuclear Pore, Nuclear Import and Integration. *PLoS One* **7**, e46037.
- 129 Bichel K, Price AJ, Schaller T, Towers GJ, Freund SMV & James LC (2013) HIV-1 capsid undergoes coupled binding and isomerization by the nuclear pore protein NUP358. *Retrovirology* **10**, 81.
- 130 Zhang R, Mehla R & Chauhan A (2010) Perturbation of Host Nuclear Membrane Component RanBP2 Impairs the Nuclear Import of Human Immunodeficiency Virus -1 Preintegration Complex (DNA). *PLoS One* **5**, e15620.
- 131 Strunze S, Engelke MF, Wang IH, Puntener D, Boucke K, Schleich S, Way M, Schoenenberger P, Burckhardt CJ & Greber UF (2011) Kinesin-1-mediated capsid disassembly and disruption of the nuclear pore complex promote virus infection. *Cell Host Microbe* **10**, 210–223.
- 132 McCormick C & Khaperskyy DA (2017) Translation inhibition and stress granules in the antiviral immune response. *Nat Rev Immunol* **17**, 647–660.
- 133 Zhang LK, Chai F, Li HY, Xiao G & Guo L (2013) Identification of host proteins involved in japanese encephalitis virus infection by quantitative proteomics analysis. *J Proteome Res* **12**, 2666–2678.
- 134 Dutrieux J, Portilho DM, Arhel NJ, Hazan U & Nisole S (2015) TRIM5 $\alpha$  is a SUMO substrate. *Retrovirology* **12**, 1–6.
- 135 Portilho DM, Fernandez J, Ringiard M, Machado AK, Boulay A, Mayer M, Müller-Trutwin M, Beignon AS, Kirchhoff F, Nisole S & Arhel NJ (2016) Endogenous TRIM5 $\alpha$  Function Is Regulated by SUMOylation and Nuclear Sequestration for Efficient Innate Sensing in Dendritic Cells. *Cell Rep* **14**, 355–369.



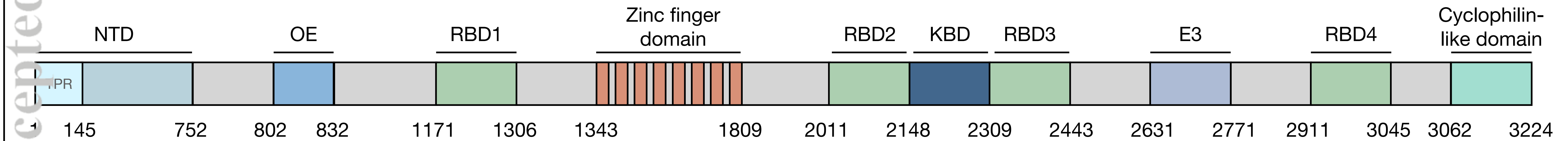
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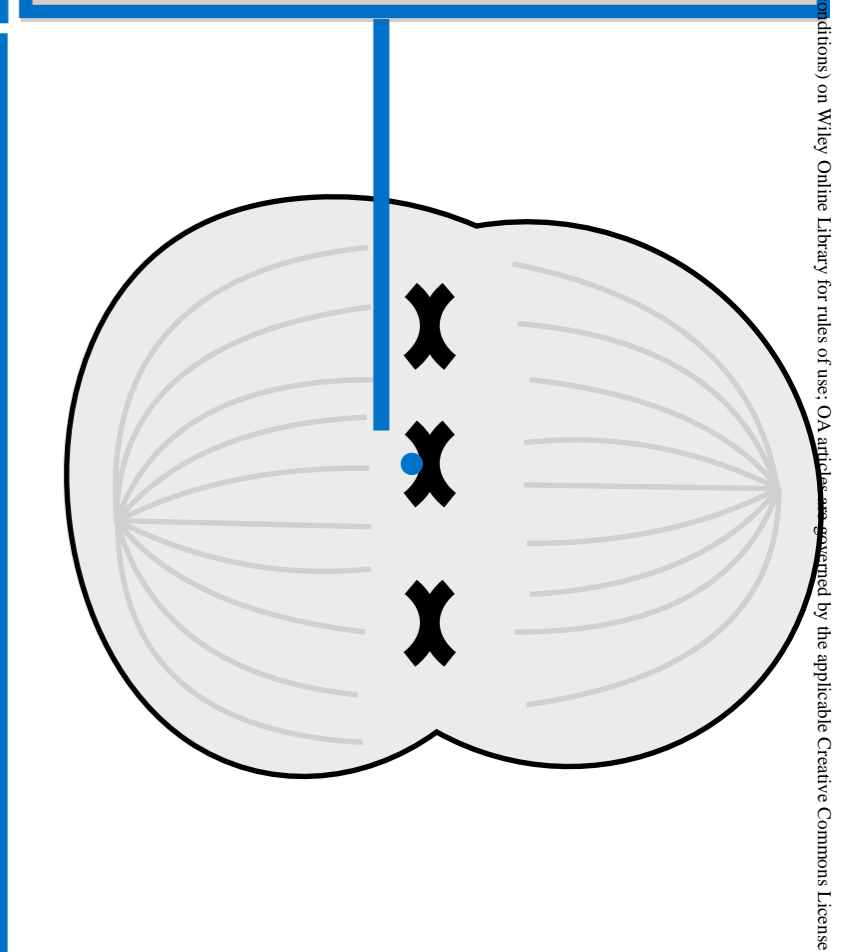
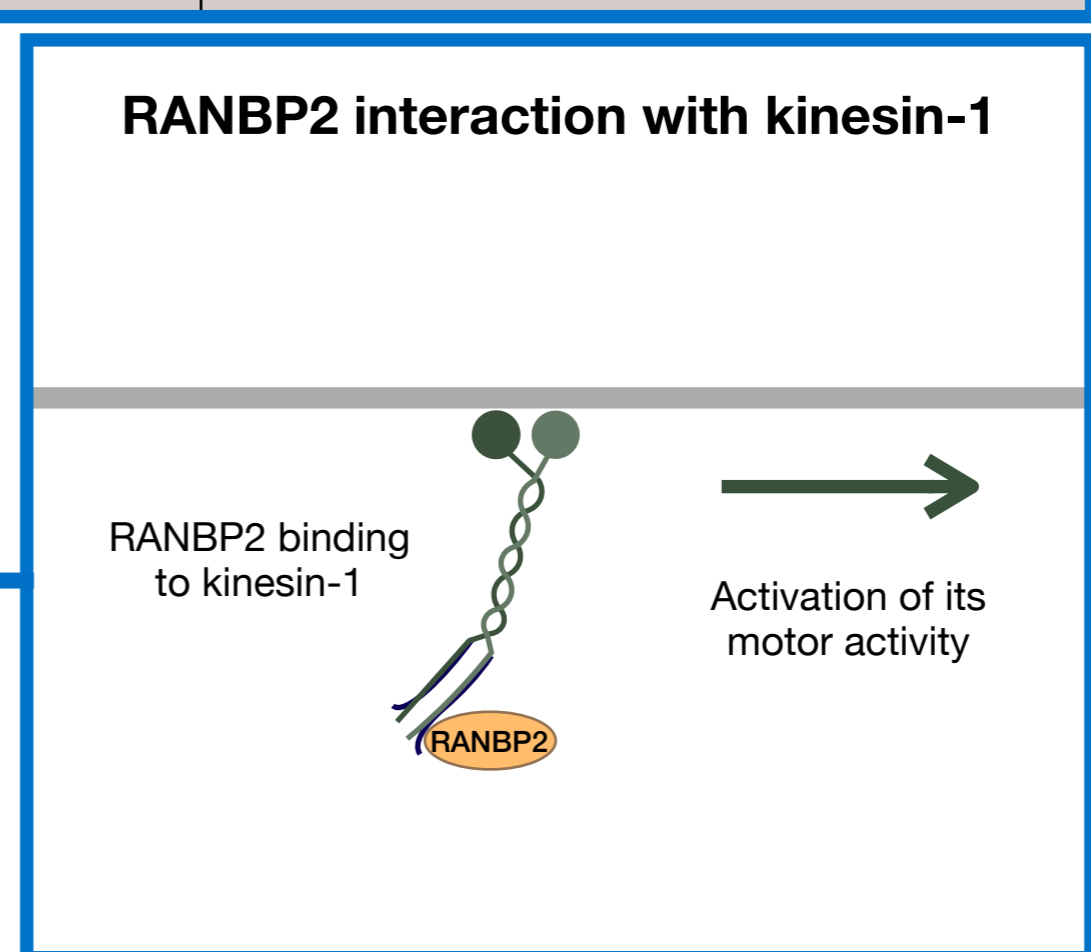
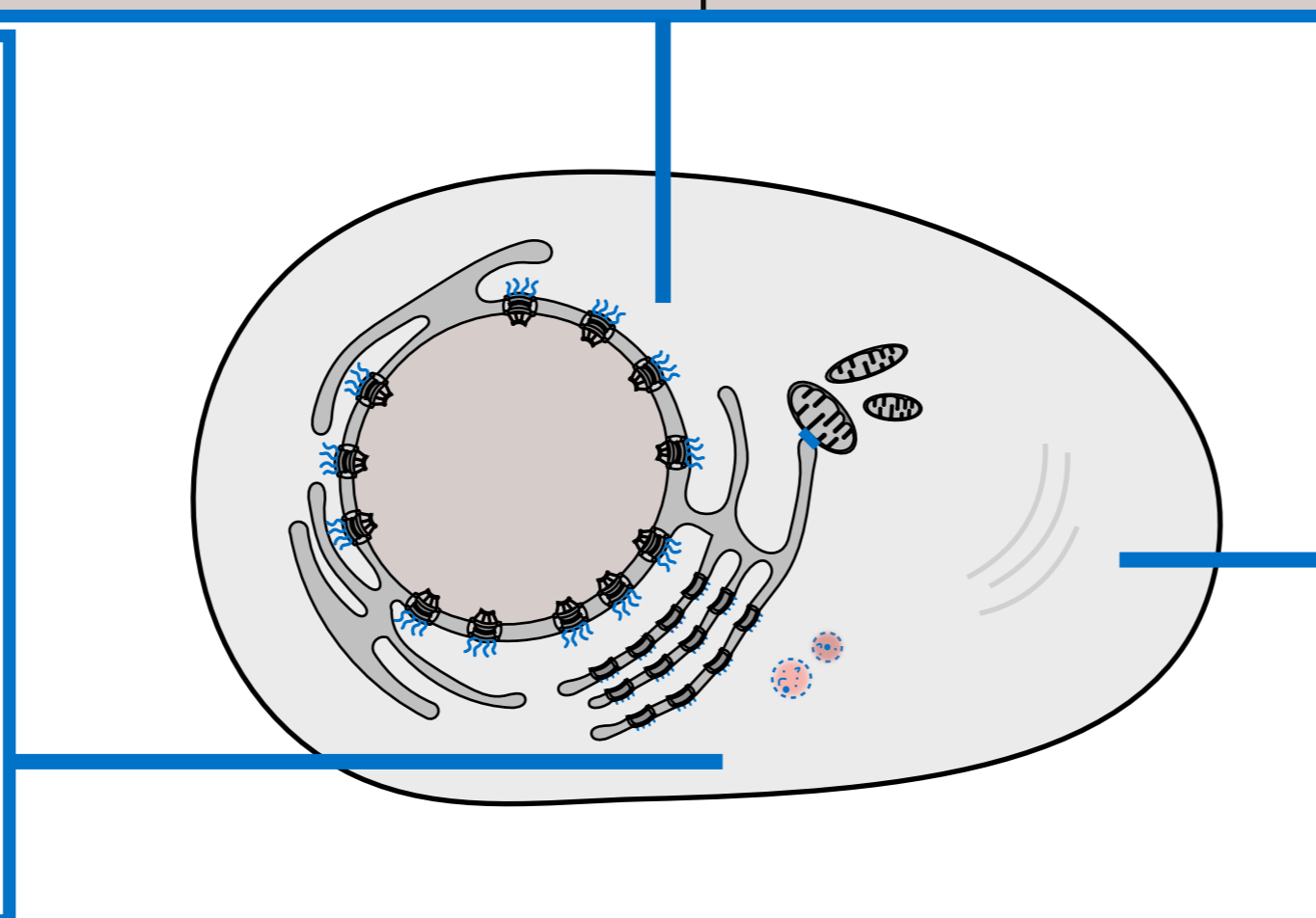
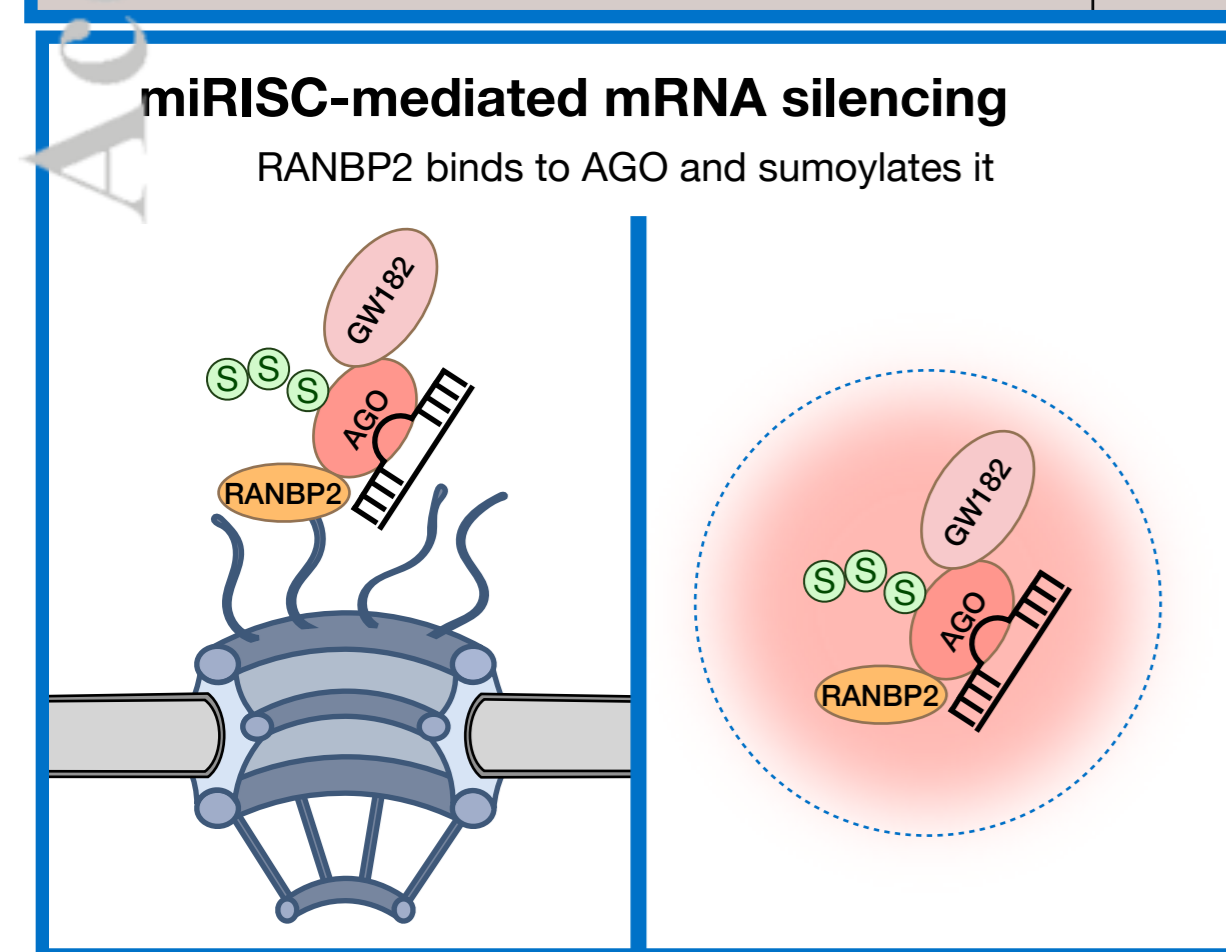
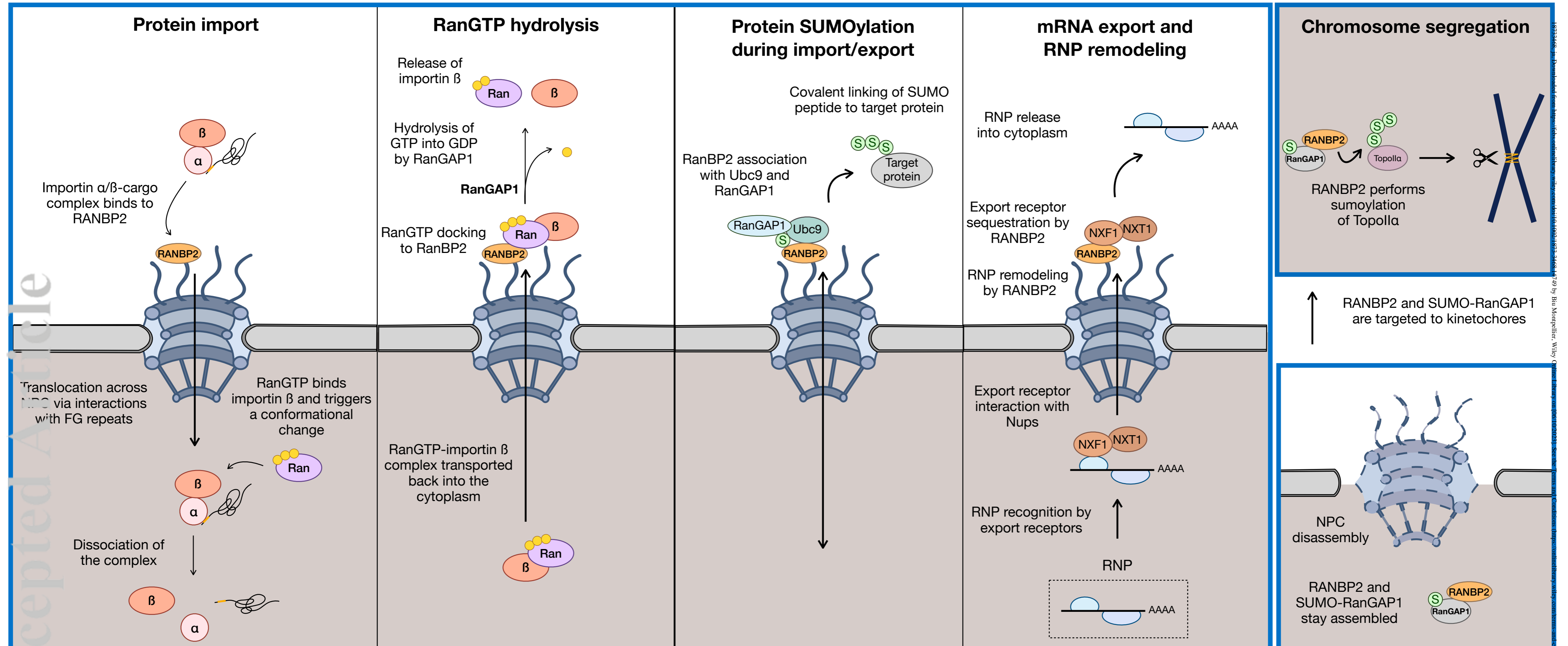


### Protein



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