


ADVANCED REVIEW

Unwinding the roles of RNA helicase MOV10

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Abstract

MOV10 is an RNA helicase that associates with the RNA-induced silencing complex component Argonaute (AGO), likely resolving RNA secondary structures. MOV10 also binds the Fragile X mental retardation protein to block AGO2 binding at some sites and associates with UPF1, a principal component of the nonsense-mediated RNA decay pathway. MOV10 is widely expressed and has a key role in the cellular response to viral infection and in suppressing retrotransposition. Posttranslational modifications of MOV10 include ubiquitination, which leads to stimulation-dependent degradation, and phosphorylation, which has an unknown function. MOV10 localizes to the nucleus and/or cytoplasm in a cell type-specific and developmental stage-specific manner. Knockout of *Mov10* leads to embryonic lethality, underscoring an important role in development where it is required for the completion of gastrulation. MOV10 is expressed throughout the organism; however, most studies have focused on germline cells and neurons. In the testes, the knockdown of *Mov10* disrupts proliferation of spermatogonial progenitor cells. In brain, MOV10 is significantly elevated postnatally and binds mRNAs encoding cytoskeleton and neuron projection proteins, suggesting an important role in neuronal architecture. Heterozygous *Mov10* mutant mice are hyperactive and anxious and their cultured hippocampal neurons have reduced dendritic arborization. Zygotic knockdown of *Mov10* in *Xenopus laevis* causes abnormal head and eye development and mislocalization of neuronal precursors in the brain. Thus, MOV10 plays a vital role during development, defense against viral infection and in neuronal development and function: its many roles and regulation are only beginning to be unraveled.

This article is categorized under:

RNA Interactions with Proteins and Other Molecules > RNA-Protein Complexes

RNA Interactions with Proteins and Other Molecules > Protein-RNA Interactions: Functional Implications

KEYWORDS

RNA-binding proteins, MOV10, RNA helicase, translation regulation

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1 | INTRODUCTION

The *Mov10* gene was first identified in a screen of mouse lines derived by infecting embryos with the murine Moloney leukemia virus (Mu-MLV) to query virus expression at random chromosomal locations. Mice with Mu-MLV inserted into germ cells were derived into 13 substrains, named accordingly (*Mov-1* through *Mov-13*), each with a single Mu-MLV genome at a different chromosomal position in its germline. The *Mov10* line did not develop viremia at any point during its lifespan and was shown to be heterozygous for the insertion of Mu-MLV (Jaenisch et al., 1981). Later, this mouse line was used to clone the *Mov10* gene. The predicted amino acid sequence of MOV10 had motifs found in proteins from the Guanosine Triphosphate (GTP)-binding family. The *Mov10* gene was also found to be differentially expressed depending on the developmental stage of the mouse embryo, the differentiation state of an embryonal carcinoma cell (F9), and the cell cycle stage of NIH 3T3 fibroblasts, suggesting its importance during development and cell proliferation (Mooslehner et al., 1990). Subsequent studies showed that the provirus had integrated into Intron 1 of a transcription unit, which was identified as a protein with a molecular weight of 110 kDa and comprising a putative GTP-binding motif (Mooslehner et al., 1991). Consequently, the gene was called *gb110* and was found to be regulated developmentally and in a cell cycle-specific manner. However, the knockdown of both alleles of *gb110* gene in mouse embryonic stem (ES) cells did not affect the proliferation or differentiation in vitro and no further studies on MOV10 were published for over a decade (Hamann et al., 1993). Interest in MOV10 was revived in 2005 when it was identified as a novel player in the rising field of miRNA-mediated translational regulation of mRNA targets as an interactor of Argonaute 2 (AGO2; Meister et al., 2005).

2 | GENE STRUCTURE, HOMOLOGS, AND PROTEIN DOMAINS

The *MOV10* gene is encoded on human Chromosome 1 and murine Chromosome 3. It is 23,792 nucleotides long and has 21 exons and 20 introns. There are 17 splicing variants of the gene and 2 protein isoforms (Yates et al., 2020). The first isoform (a) includes all of the exons and codes for a 1077-amino acid-long protein. The other isoform (b) does not include Exon 1 and codes for a 1004-amino acid-long protein (NCBI Resource Coordinators, 2018).

MOV10 has orthologs in 280 species according to Ensembl (Yates et al., 2020). Most notable are the *Arabidopsis thaliana* (SDE3), *Drosophila melanogaster* (dMOV10/CG6967; Takemura et al., 2021), and *Caenorhabditis elegans* (ERI-6/7). Like MOV10, these proteins were found to participate in the RNAi pathway and protect the host organism from exogenous viruses and endogenous retroviral elements. Here, we have aligned the entire MOV10 protein sequence from Human, Rhesus, Mouse, Xenopus, and Zebrafish and highlighted multiple conserved histidine and cysteine residues (Figure 1, cysteine highlighted in yellow, histidine in green). Based on the conserved residues across Human and mouse, the proposed cysteine histidine (CH) domain of MOV10 has a consensus of *Cys-X₁₅-Cys-X₁₀-His-X₂-Cys*. In addition, the MOV10 consensus CH domain does not exactly match with the UPF1 consensus CH domain sequence (*Cys-X₂-Cys-X₉-His-X₃-Cys*; Applequist et al., 1997), which is proposed to form a Zinc-finger binding domain based on the NCBI Conserved Domain Database (Marchler-Bauer et al., 2017). It remains to be tested if the proposed MOV10 CH domain folds in a Zinc-dependent manner or not.

The alignment between multiple species in Figure 1 also shows that certain stretches of the N-terminus encompassing the histidines and cysteines that form the proposed CH domain are conserved between Human, Rhesus, and Mouse but differ from other species. These sequences could have important roles in interacting with other proteins as shown for the HIV-1 protein (Abudu et al., 2012). The C-terminal core of MOV10, however, is well conserved, especially the helicase motifs (Motifs I, II, V, and VI have complete conservation) compared to the N-terminus across the different species (Figure 1).

2.1 | Polymorphisms in MOV10

No mutations in the *MOV10* gene or other aberrations have been demonstrated to directly cause disease, but several studies identified in ClinVar, a public database that reports relationships among human variations (Landrum et al., 2018), showed that the *MOV10* gene is present in copy number variants (CNVs) identified in individuals with intellectual and developmental delay (Coe et al., 2014; Cooper et al., 2011; Kaminsky et al., 2011). Also, according to ClinVar *MOV10* was among genes present in CNVs observed in at least seven pathogenic cases of individuals with intellectual disability; however, it should be noted that there are hundreds to thousands of other genes in the CNVs. Four



□ 0 % similarity * 40 % similarity * 60 % similarity * 80 % similarity ! 100 % similarity

FIGURE 1 Evolutionary conservation of MOV10. Amino acid alignment of human (NM_020963.4), rhesus monkey (NM_001261223.1), mouse (NM_008619.2), *Xenopus* (XM_018246602.1), and zebrafish (NM_001044342.2) are shown beginning at amino acid 83 in *Homo sapiens*. The conserved cysteine and histidine residues between human, rhesus and mouse that form a consensus CH domain are highlighted in yellow and green, respectively. The helicase motifs are presented in red and annotated according to Fairman-Williams et al. (2010), Rocak and Linder (2004), X. Wang et al. (2010). Gag-binding domain is presented based on findings of Abudu et al. (2012). Red exclamation marks represent complete conservation across all five genera, green asterisks indicate strongly similar group conservation; asterisk of blue shades indicate weakly similar group conservation and blanks are regions of no conservation. Alignment was done using ClustalW function in msa package (Bodenhofer et al., 2015)

CNVs that include *MOV10* and are smaller than 5 Mb are classified as likely benign or of uncertain significance. In addition, genome-wide association studies (GWAS) have shown that SNP rs2932538 in the intron of *MOV10* is associated with blood pressure and hypertension (Ehret et al., 2011; Hong et al., 2013; X. Lu et al., 2015). A recent study elaborated on this result showing a potential link between this SNP and preeclampsia (Tang et al., 2020).

With regard to participating in normal variation, *MOV10* is implicated in the cortical surface area in humans (Shin et al., 2020). Meta-analysis of GWAS of size and thickness of 34 cortical regions from 23,684 individuals and replicated in 25,746 individuals revealed 8 SNPs in the *MOV10* intron that are significantly associated with cortical surface area in the visual cortex. Although such SNPs could affect splicing, they may also act at the DNA level to modulate chromatin and affect transcription, ultimately, affecting cortical development.

2.2 | Protein domains in MOV10

MOV10 was predicted to be a GTP-binding protein, thus the name gb110 was coined (Mooslehner et al., 1991). In addition, *MOV10* has a (aspartic acid (D)-glutamic acid (E)-alanine (A)-glycine (G) (DEAG) amino acid region instead of the more common DEAD/H box, hence it was recognized as a Superfamily1 (SF1) helicase in 1992 when Koonin et al. described a new group of helicases (Koonin, 1992). Helicases are enzymes that unwind nucleic acid (NA) duplexes in an Adenosine Triphosphate (ATP) ATP-dependent manner. Superfamily II (SF2) or DEAD/H superfamily contains a large number of DNA and RNA helicases and is characterized by a DEAD in Motif II of the helicase core domain of its protein members (Fairman-Williams et al., 2010; Putnam & Jankowsky, 2013). SF1 family of helicases shares many features with SF2, including the seven conserved motifs of two RecA-like helicase core domains. Domain 1 consists of Motifs I, Ia, II, and III, while Domain II consists of Motifs IV, V, and VI. Two of the most well-described motifs of helicases are Motif I (*Walker A*) and Motif II (*Walker B*) (Figures 1 and 2(a); Koonin, 1992). *Walker A* is a phosphate-binding loop or “P” loop, and *Walker B* has a Mg^{2+} -binding aspartic acid. *Walker A* has sequence GxxxxGK(T/S) where the T/S residues offer their hydroxyl group to bind the Mg^{2+} ions of the ATP and the K residue binds the phosphate of the ATP. *Walker B* has the consensus sequence of DExx, where D binds Mg^{2+} and E is involved in ATP hydrolysis, which provides energy for helicase activity (Figure 2). Motifs Ia and IV interact with the backbone of oligonucleotides, and Motifs III and V are responsible for coordination between NTP and NA binding (Bourgeois et al., 2016; Caruthers & McKay, 2002; Gregersen et al., 2014).

Initially predicted to be a helicase, *MOV10* was shown to be an ATP-dependent helicase, unwinding 5' overhang duplex RNAs (Gregersen et al., 2014; Kenny et al., 2020). All of the helicase motifs are located near the C-terminus between residues 524–911 (Figure 1). Both the C- and N-termini of helicases also serve as accessory domains and contribute to various functions like NA binding, nuclease activity and protein–protein interactions. A study done to explore

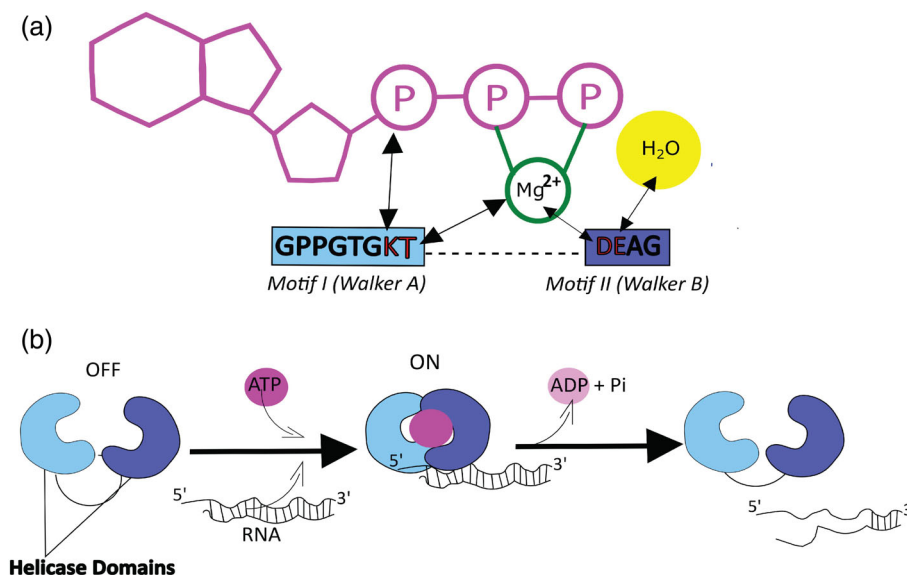


FIGURE 2 ATP-dependent helicase activity of *MOV10*. *MOV10* has Walker A and Walker B motifs which allow it to interact and hydrolyze ATP molecules to yield energy for RNA helicase activity. (a) ATP hydrolysis by interactions of the residues with the phosphate group (P) and magnesium ion (Mg^{2+}) are shown (see the text for detail; Caruthers & McKay, 2002). (b) The helicase domains of *MOV10* are in OFF configuration. Upon ATP hydrolysis, the domains are in ON configuration and the helicase translocates along the 5' to 3' direction to unwind the RNA duplex (Bourgeois et al., 2016)

the binding and packaging of MOV10 in the HIV-1 virions showed that the N-terminal amino acid residues 261–305 of MOV10 are required for interacting with the basic linker region of the Gag protein but are not sufficient for the packaging in the virions (Abudu et al., 2012). All but Motif V of the helicase motifs in the C-terminal are also required for MOV10 packaging in the HIV1-virions.

MOV10 shares 40% homology with fellow SF1 family member UPF1 including the CH domain in its N-terminus. UPF1 was shown to bind UPF2 through its CH domain (Kadlec et al., 2006). The CH domains were described as highly conserved with a range of functions including protein–protein interactions. Heise and colleagues showed that these domains require Zn^{2+} ions to interact with other proteins and for maintaining their structure in plant defense signaling pathways (Heise et al., 2007). MOV10 has four cysteines and nine histidines between residues 93 and 305, which includes the Gag-binding domain (261–305, refer to Figure 1). However, the role of the putative CH domain in MOV10 is yet to be studied.

The role of the MOV10 helicase domains has been linked to resolving the secondary structures in the 3' untranslated regions (UTRs) of the target mRNAs to render them accessible for degradation or transportation. Gregersen and colleagues showed that MOV10 translocates on target mRNAs in a 5' to 3' direction using its helicase domains, presumably to pave the way for UPF1 binding which is an integral component of the nonsense-mediated decay (NMD) pathway. Another important mechanistic insight was provided by a study that showed that MOV10 uses its helicase activity to resolve G-quadruplexes (rG4s) in the 3' UTRs of target mRNAs (Kenny et al., 2014, 2020). rG4s are highly stable NA structures formed by hydrogen bonding-mediated stacking of G-quartets in the guanine rich regions of NAs. In mRNAs, rG4s in the 5' UTR are shown to suppress translation (Agarwala et al., 2015; Beaudoin & Perreault, 2010). However, their presence in the 3' UTR blocks miRNA binding to the miRNA recognition elements (MREs) in the 3' UTR of mRNAs (Rouleau et al., 2017). Kenny and coworkers showed that MOV10 resolves the rG4s to expose MREs to the RNA-induced silencing complex (RISC) for translation suppression (Kenny et al., 2020). However, the same study showed that MOV10 also protects a subset of mRNAs from AGO binding by associating with the Fragile X mental retardation protein (FMRP) (Kenny et al., 2014, 2020) as discussed below. The C-terminus of MOV10 also binds many proteins in the cell including core RISC component AGO (C. Lu et al., 2012; Figure 3). Here, MOV10 was identified as an essential AGO cofactor, being required for suppression of a reporter by miR-21. Another study showed that AGO interaction with MOV10 is in competition with APOBEC3G (A3G), whose binding site overlaps with the AGO2 binding site in the MOV10 C-terminus (C. Liu et al., 2012). Importantly, by inhibiting the interaction of AGO2 and MOV10, A3G inhibits translation repression.

The N-terminus of MOV10 also plays a vital role in the interaction with FMRP. In 2014 Kenny and colleagues found that MOV10 binds a shared subset of target mRNAs with FMRP and facilitates AGO-mediated translation inhibition as discussed earlier. However, if the RNA binding sites of MOV10 overlapped with the binding sites of FMRP, the target mRNAs are protected from AGO2-mediated degradation. Thus, MOV10 has a bifunctional role in translation regulation of cobound mRNAs—facilitating AGO2 suppression of some RNAs while blocking AGO2 association with other RNAs (Kenny & Ceman, 2016). Similarly, FMRP is an RNA binding protein that binds brain mRNAs and regulates their translation positively and negatively (Brown et al., 2001). The N-terminus of MOV10 binds the KH1 domain of FMRP to alter its conformation such that there is increased binding to rG4s through FMRP's 20–25 amino acid arginine–glycine–glycine region (RGG box). Functionally intact rG4s are required to protect mRNAs by the MOV10-FMRP complex (Kenny et al., 2020). In addition to FMRP, MOV10 binds other RGG box-containing proteins like DHX9, an RNA/DNA helicase that controls transcription and translation and Fused in sarcoma (FUS) protein (Gregersen et al., 2014; Kenny et al., 2014; Lee & Pelletier, 2016). Overexpression of the N-terminus of MOV10 reduced the ability of AGO2 to bind rG4-rich mRNAs like MAZ, likely by stabilizing the FMRP-rG4 complex that protects the MRE. MOV10 also interacts with LINE1 protein ORF2P through its N-terminus to restrict retrotransposition of L1 in the nucleus (Skariah et al., 2017). A summary of MOV10 protein interactors is shown in Figure 3.

2.3 | Post-translational modifications

Posttranslational modifications (PTMs) can change the functionality of a protein and many MOV10 PTMs have been reported. MOV10 is ubiquitinated and proteosomally degraded in rodent hippocampal neurons, following NMDA stimulation (Banerjee et al., 2009). MOV10 phosphorylated residues have also been identified in human cell lines in a large proteomic analysis. Dephore and colleagues used HeLa cells to identify the phosphoproteins, whose phosphorylation states are changed depending on the cell cycle stage (Dephore et al., 2008). Mass spectrometry identified that

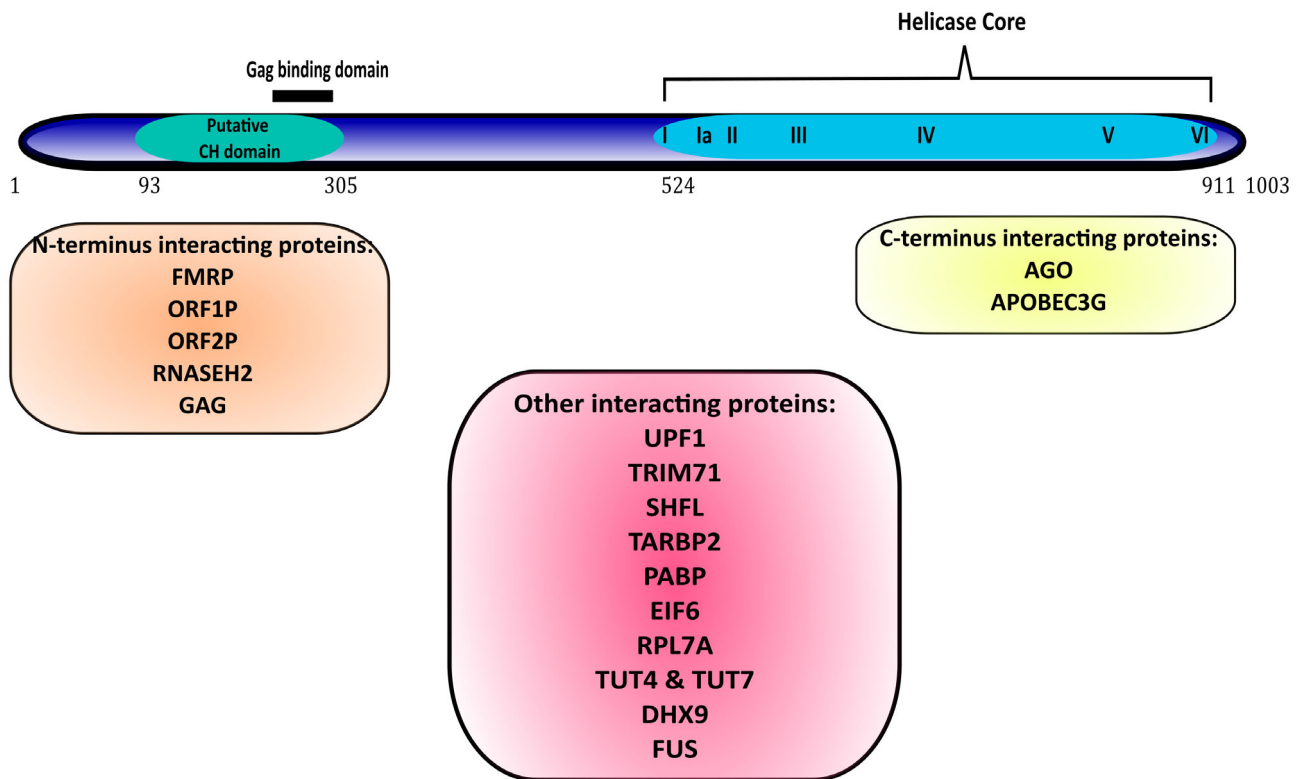


FIGURE 3 MOV10 structure and protein interactors: MOV10 has a putative CH domain near its N-terminal. The helicase core consisting of seven motifs, is near the C-terminus. Most known protein interactions occur through the N-terminus. The MOV10 sequences for interaction with most of the shown proteins are yet to be discovered AGO (Meister et al., 2005); APOBEC3G (C. Liu et al., 2012); TARBP, EIF6, RPL7A, DICER (Chendrimada et al., 2007); UPF1, PABP, ZCCH3, DHX9 (Gregersen et al., 2014); TUT 4 & TUT 7 (Warkocki et al., 2018); ZAP (Taylor et al., 2013); GAG (Abudu et al., 2012); FMRP, FUS (P. J. Kenny et al., 2014, 2020); SHFL (Balinsky et al., 2016); L1 ORF proteins (Goodier et al., 2013; Skariah et al., 2017); RNASEH2 (Choi et al., 2018, p. 20)

phosphorylated MOV10 residues T160 and T164 are enriched in cells arrested in G1 phase, while T254 is phosphorylated in M phase of the cell cycle. An independent global quantitative phosphoproteomics study in HeLa cells identified MOV10 residues T254 and S969 as being phosphorylated (Olsen et al., 2010). MOV10 was also reported as containing the consensus sequence recognized by DNA damage response kinases ataxia telangiectasia mutated (ATM) and ATM and Rad3 related (ATR) and was found to be phosphorylated at T160 in response to DNA damage in HEK 293 cells (Matsuoka et al., 2007). Acetylation of lysine residues mitigates the positive charge on a protein and changes its function, including but not limited to modulating chromatin architecture. Choudhary and colleagues found that MOV10 is acetylated at K148 using high resolution mass spectrometry (Choudhary et al., 2009).

3 | CELLULAR ROLES OF MOV10

MOV10 is mostly known to be a part of processing bodies (PBs) where it suppresses mRNA translation together with AGO2 and FMRP (Kenny et al., 2014; Meister et al., 2005). In addition, MOV10 associates with APOBEC3G in PBs and stress granules (SGs), functioning as an antiviral agent (Gallois-Montbrun et al., 2007). Apart from PBs and SGs, MOV10 was found to associate with polysomes where it presumably controls the translation of the target mRNAs (Kenny et al., 2014; Kute et al., 2019). Zappulo and colleagues found that MOV10 is enriched in neurites (Zappulo et al., 2017). This result confirmed the initial localization of MOV10 in punctate structures in dendrites of hippocampal neurons observed with fluorescent microscopy (Wulczyn et al., 2007). In addition, MOV10 is present at the synapses where it controls local translation of the target mRNAs (Banerjee et al., 2009; Kute et al., 2019).

The evidence for a nuclear role for MOV10 came from its association with the Polycomb group of proteins (PRC1), which are responsible for gene silencing by inducing histone methylation on the cis-regulatory regions of target genes.

MOV10 interacts with PRC1 members CBX7 and CBX8 and bound chromatin (Messaoudi-Aubert et al., 2010). This interaction enhanced recruitment of PRC1 complex to the target loci, as the knockdown of MOV10 resulted in an upregulation of INK4a tumor suppressor. Reduced MOV10 also resulted in less occupancy of the INK4a promoter by PRC1 components and Histone 3 Lysine 27 trimethylation (H3K27me3), which is a known marker for silenced genes, suggesting a role for MOV10 in regulating gene expression. This study also suggested that MOV10 is primarily nuclear, contrary to the previous notion that MOV10 is primarily cytoplasmic due to its association with polyribosomes and the RNAi pathway (Kenny et al., 2014). However, MOV10's localization may be cell type specific and/or developmental stage specific because MOV10 was identified in the nucleus of neurons in P2 brain but was cytoplasmic in both cultured neurons (Banerjee et al., 2009) and in the hippocampus of adult brain (Skariah et al., 2017). MOV10 may be nuclear in developing brain to suppress retrotransposition, as its reduction leads to increased L1 content in the DNA (Skariah et al., 2017). MOV10 was also found in the nuclei of spermatogonia of developing mouse pups and 293T cells (Fu et al., 2019; Messaoudi-Aubert et al., 2010).

3.1 | Role of MOV10 in mRNA decay and storage

MicroRNA (miRNA)-mediated gene silencing is integral to all biological processes including cell growth, differentiation, and division. MiRNAs are posttranscriptional regulators that are transcribed from the intergenic regions, introns or occasionally UTRs of endogenous genes by RNA polymerase II. They are processed by the nuclear microprocessor complex containing the RNase III-type enzyme DROSHA to yield ~70 nucleotide long hairpin structures called precursor miRNAs. Once exported to the cytoplasm, they are further processed to 20–22 nucleotide long duplexes by another protein complex containing a RNase III-type enzyme DICER. The mature single-stranded miRNAs are loaded into protein complexes called miRNA-induced silencing complexes (miRISCs). The miRISC ribonucleoprotein complex includes catalytic unit AGO2 and GW182 (TNRC6 in mammals) family members. Canonically, miRISCs recognize and bind their target MREs in mRNAs, which are typically located in the 3' UTRs. GW182 proteins recruit poly(A)-binding protein which in turn recruits deadenylase complexes that cleave the poly A tail, leading to mRNA degradation. In addition to the canonical mRNA decay pathway, miRISCs also repress translation by other means such as inhibiting the binding of eukaryotic initiation factor 4F (eIF4F) complex, which is required to initiate translation in cells (Gebert & MacRae, 2019; Jonas & Izaurralde, 2015; O'Carroll & Schaefer, 2013).

MOV10 was found as an interacting partner of miRISCs, where it colocalizes in PBs with AGO proteins and trinucleotide repeat containing gene 6 (*TNRC6*) (Meister et al., 2005). PBs are sites in cells of translational control where repressed mRNAs are either destroyed or stored temporarily so they can reenter translation at a more feasible state. Although storage has typically been associated with early development and oogenesis (Ross Buchan, 2014), even somatic cells have PBs where mRNAs have opposite fates between storage or decay (Aizer et al., 2014; Hubstenberger et al., 2017). MOV10 is involved in miRNA-mediated decay of miR-21 target mRNAs in HeLa cells (Meister et al., 2005). Further reports gave deeper insight about the role of MOV10 in miRNA-mediated translation inhibition, where it was found to be an interactor of minimal RISC complex DICER-AGO-TRBP (HIV-tar RNA binding protein), along with the translation repressor eukaryotic translational Initiation factor 6 (eIF6) (Landthaler et al., 2008). eIF6 inhibits translation by blocking the binding of 60S and 40S ribosomal subunits to form the functional 80S subunit. eIF6 and MOV10 both associated in let-7 miRNA-mediated repression of target mRNA (Chendrimada et al., 2007). Later, it was shown that MOV10 interacts with these complexes independent of DICER binding, suggesting that MOV10 works downstream of DICER-mediated miRNA processing in the RISC pathway (Frohn et al., 2012).

As RISC pathway protein interactions occur in an RNA-dependent manner, it could be proposed that MOV10 deploys its helicase activity to unfold RNA secondary structures to expose the MREs so they can be targeted for degradation or translational suppression. Indeed, this hypothesis was validated when Kenny and coworkers showed that MOV10 knockdown leads to an increase in its target mRNAs while MOV10 overexpression leads to a decrease in its target mRNAs (Kenny et al., 2014). However, in this same study, a subgroup of mRNAs was identified that were cobound by FMRP and MOV10 on rG4s, which blocked AGO2 association. Thus, MOV10 is able to either facilitate AGO2 association or block AGO2 association, depending on associated proteins like FMRP and secondary structures like rG4s (Kenny et al., 2020). This was further supported by Kute et al., where N-Methyl-D-Aspartate Receptor (NMDAR) stimulation in rat neurons led to phosphorylation of FMRP which led to increase in translation possibly due to dissociation of AGO2 from the mRNAs (Kute et al., 2019). This switch between MOV10-FMRP-AGO2 association is vital for local

translation of proteins where mRNAs are transported from the soma to the distant parts like axon and dendrites via kinesin transporters (Kiebler & Bassell, 2006; Nalavadi et al., 2012; Zeitelhofer et al., 2008).

In addition, MOV10 associates with PBs and SGs. SGs and PBs are membraneless structures consisting of mRNAs and proteins condensed together in response to stress or mRNA decay. PBs are mainly enriched in mRNA decay machinery, with mRNA-decapping enzyme subunit 1 (DCP1) and GW182 as the characteristic proteins (Riggs et al., 2020). However, isolation of PBs from human cell line followed by mass spectrometry revealed that MOV10 is enriched in PBs, where translationally suppressed mRNAs are accumulated and are protected from decay (Hubstenberger et al., 2017). In addition, MOV10 also associates with proteins involved in SGs such as Ras-GTPase-Activating Protein SH3-Domain-Binding Protein (G3BP1), FMRP and Poly-A binding protein (PABP). (Gregersen et al., 2014). It is not clear what role is played by MOV10 in these RNA condensates. It is possible that MOV10 performs its RNA helicase function to reveal binding sites of proteins to allow formation of these condensates; however, this requires further investigation (Tauber et al., 2020). Figure 4 shows the role of MOV10 in regulation of mRNA metabolism, PB and SG formation and local translation in dendrites.

MOV10 also assists in mRNA degradation in the NMD pathway. Gregersen and colleagues showed that while the wildtype MOV10 translocated on mRNAs in 5' to 3' direction, the helicase domain mutants failed to do so (Gregersen

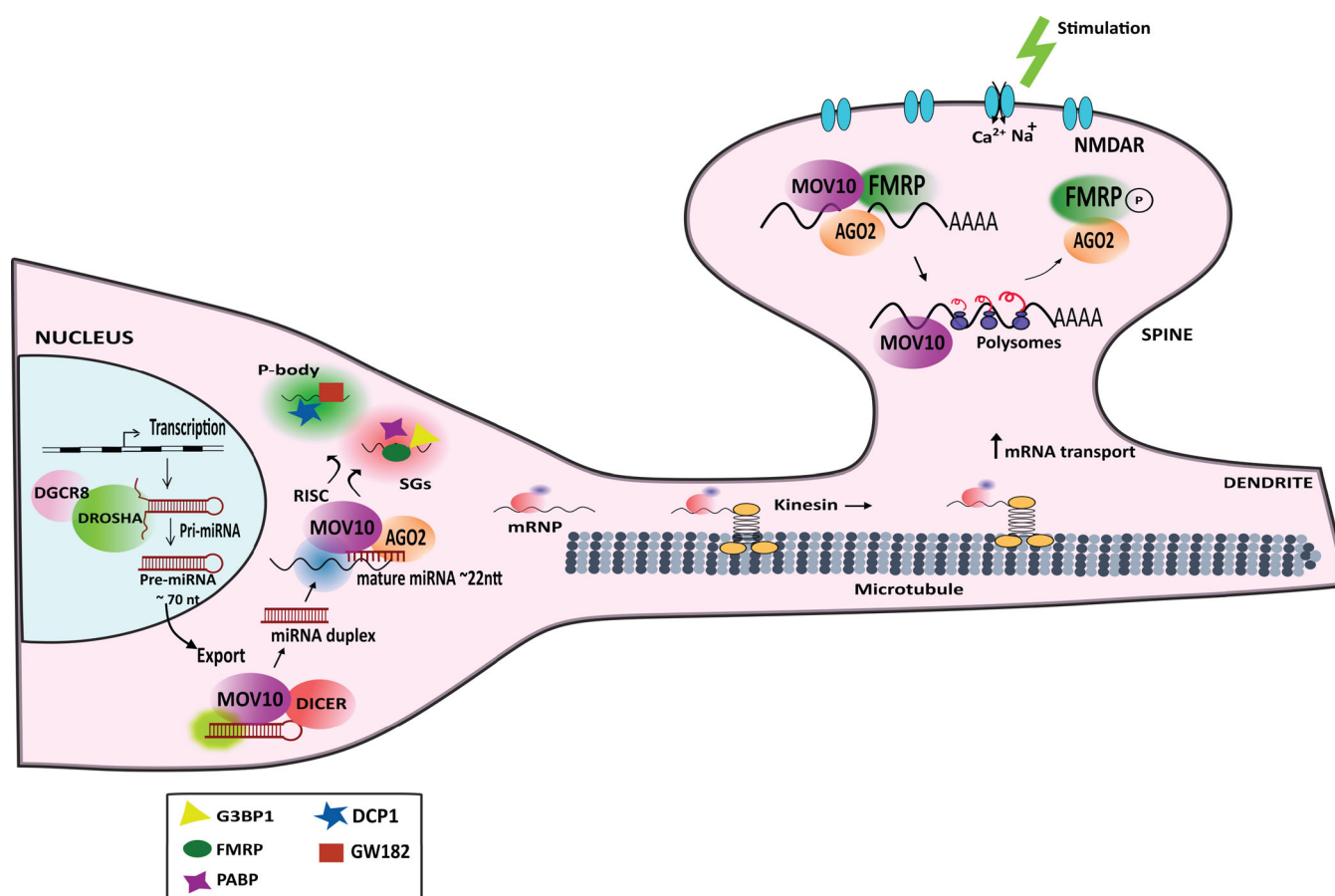


FIGURE 4 Role of MOV10 in miRISC pathway and translation regulation in neurons: General biogenesis of miRNA for miRNA-mediated regulation of target mRNAs. miRNAs are transcribed from the genome after which they are processed through the DROSHA microprocessor complex. After being exported to the cytoplasm, the pre-miRNA is further processed to remove the hairpin loop structure and yield a double-stranded miRNA. The miRNA strand gets cleaved, and one strand is loaded onto AGO to form the RISC. RISC-bound mRNAs are either translationally suppressed by decay or by inhibition. Both the processes involve MOV10 (O'Carroll & Schaefer, 2013). RISC-bound mRNAs can be transported to RNA condensates like SGs or PBs (Riggs et al., 2020). MOV10 associates with proteins associated with both SGs (G3BP1, FMRP and PABP) and PBs (DCP1 and GW182). In the neurons, mRNAs are stabilized to form mRNPs which are transported along microtubules to the dendritic regions (Zeitelhofer et al., 2008). Here, MOV10 associates with AGO2 and FMRP to regulate mRNA translation. Upon NMDAR stimulation, FMRP is phosphorylated which dissociates AGO2 from the mRNAs to allow local translation (Kenny et al., 2020, 2019). AGO2, Argonaute 2; FMRP, Fragile X mental retardation protein; PBs, processing bodies; RISC, RNA-induced silencing complex; SGs, stress granules

et al., 2014). In addition, while looking for MOV10 interactors, it was found that UPF1 associates with MOV10 in an RNA-dependent manner. UPF1 is an integral component of the NMD pathway, which results in degradation of mRNAs with premature termination codons (Schweingruber et al., 2013). Photoactivable RNA crosslinking immunoprecipitation showed that MOV10 initially binds near the UPF1 binding sites and then translocates in a 5' to 3' direction suggesting that MOV10 works downstream of UPF1 and clears its way by disassembling mRNPs and unfolding the secondary structures in the mRNAs to allow UPF1-mediated accelerated mRNA decay (Gregersen et al., 2014). Another study showed that MOV10 interacts with Stau2 (Stau 2), along with UPF1. Stau is a double-stranded RNA binding protein, which localizes in the somatodendritic compartments of neurons and associates with RNA granules (Miki et al., 2011). Although this work focused on the interaction between UPF1 and Stau2, the interaction of MOV10 with these proteins hints at its involvement in RNA regulation in neurons in addition to the canonical miRNA-mediated translational suppression shown earlier (Banerjee et al., 2009).

Another mechanism through which MOV10 might be involved in mRNA regulation is by associating with tripartite motif (TRIM) family member TRIM 71. TRIM 71 is also known as LIN 41 and is an ubiquitin ligase (Slack & Ruvkun, 1998) which is involved in E3 ubiquitin ligation of target proteins, leading to their degradation. Rybak and colleagues showed that TRIM-71 co-localized to PBs along with miRISC pathway components AGO2, TNRC6, and MOV10, both in HeLa cells and hippocampal neurons (Rybak et al., 2009). Further interaction studies showed that Lin-41 binds AGO2 through its coiled-coil domain and results in ubiquitin-mediated turnover of AGO2, relieving translational suppression. However, Loedige and colleagues showed that while TRIM 71 ubiquitinates AGO2, it does not affect its stability (Loedige et al., 2013). More importantly, it was shown that TRIM 71 binds 3' UTRs through its RNA binding domain NHL and causes their accelerated decay in human cells as well as mouse ES cells, which require TRIM 71 for viability. Although TRIM 71 shares common targets with miRISC components, the decay of mRNAs occurs independently (Loedige et al., 2013). Association of TRIM 71 with MOV10 and common targets could unravel another mechanism of mRNA decay.

3.2 | Inhibition of retrotransposition

Retrotransposons are mobile genomic elements found in all eukaryotes. LINEs (L1s) make up about 17% of the human genome and are known to be active, particularly in germ cells (Kazazian, 2004) (Adams, 2017). L1s mobilize by a “copy and paste” mechanism where they are transcribed from their genomic locus by RNA polymerase to produce two proteins: ORF1P and ORF2P. The two proteins along with their parent mRNA are imported back into the nucleus. ORF1P mainly works as a chaperone for its parent mRNA, while ORF2P has endonuclease and reverse transcription (RT) activities.

While L1 retrotransposition is high in germ cells and sometimes in somatic cells, particularly, neuronal precursor cells (Adams, 2017; Upton et al., 2015), host genomes have developed strategies to suppress retrotransposition as it can pose deleterious effects on host genome structure and function (Babushok & Kazazian, 2007; Cordaux & Batzer, 2009; Muotri et al., 2005). These strategies include DNA methylation of the L1 intrinsic promoter for transcriptional silencing, as well as P-element-induced wimpy testis-mediated L1 suppression in mouse germ line cells (Carmell et al., 2007) and modification by APOBEC3G (Goila-Gaur & Strebler, 2008). MOV10 also strongly inhibits retrotransposition in cells where it directly associates with L1—either suppressing its activities or targeting for its degradation (Arjan-Odedra et al., 2012; Goodier et al., 2012; Figure 4). Li and colleagues showed that inhibition of endogenous MOV10 increased RNA levels of L1 while exogenously expressed Intracisternal A-type Particle (IAPs) were reduced by MOV10 overexpression (X. Li et al., 2013). However, in another study, Lu et al. found that MOV10 only reduced IAP RT products and not its RNA or protein levels (C. Lu et al., 2012). MOV10 was found in the L1 RNP in an affinity proteomics study, showing that it interacted with ORF1P (Goodier et al., 2013). Later, Skariah and coworkers showed that the N-terminus of MOV10 binds directly to ORF2P and that addition of purified MOV10 to an RT reaction blocked RT activity (Skariah et al., 2017). In cells, MOV10-bound L1 RNPs are recruited to PBs that are enriched with MOV10 interactors of RISC, suggesting that MOV10 inhibits L1 through RNAi. UPF1 also associates with L1 transcript and the Open Reading Frame (ORF) proteins, both in the nucleus and cytoplasm, likely mediating degradation. Interestingly, UPF1 depletion reduced retrotransposition in cells, suggesting that it also somehow participates in retrotransposition (Taylor et al., 2013). Other protein interactors of MOV10-L1 RNPs include PABP, zinc-finger CCHC domain containing protein 3 and zinc-finger antiviral protein (ZAP), where ZAP also negatively regulates L1 retrotransposition (Goodier, 2016; Moldovan & Moran, 2015; Taylor et al., 2013, 2018). Ribonuclease H2 (RNASEH2) may be recruited to degrade L1

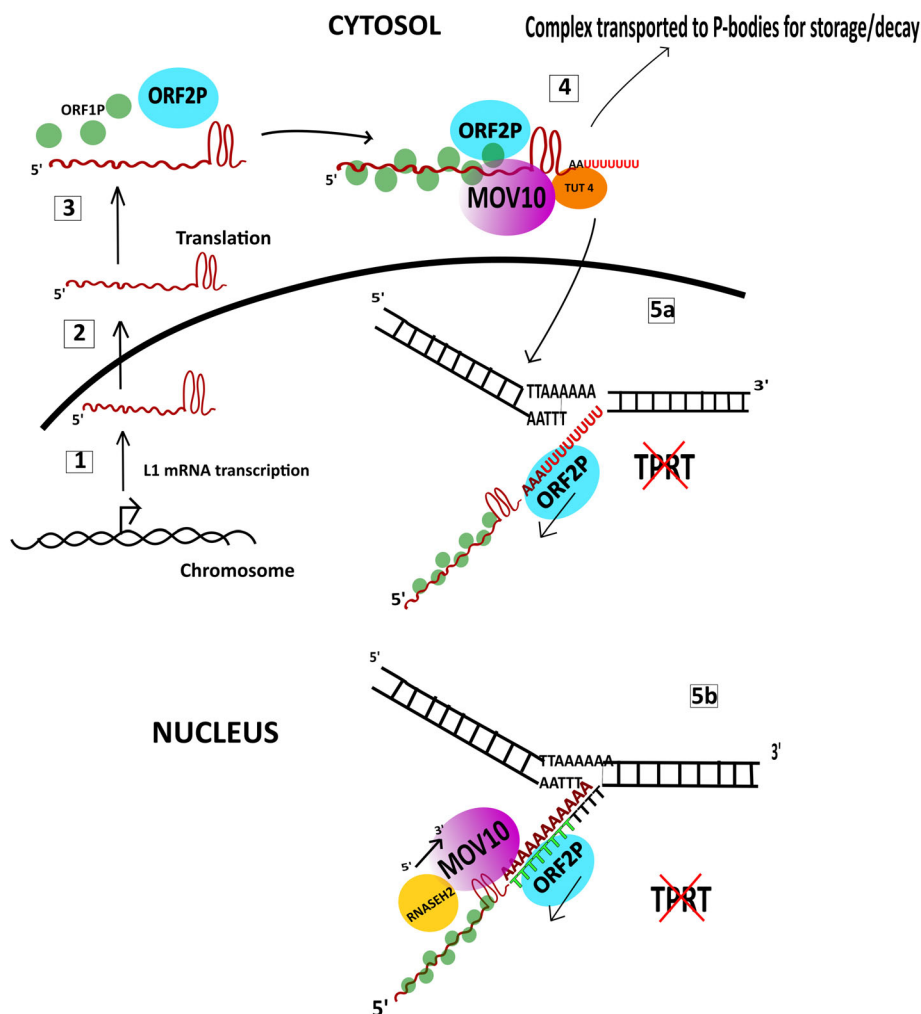


FIGURE 5 Proposed models for the role of MOV10 in inhibition of L1 retrotransposition: (1) L1 mRNA is transcribed by RNA polymerase and the transcript is exported to the cytosol. (2) The L1 mRNA is translated into ORF1P chaperone protein and ORF2P endonuclease/reverse transcriptase and assembled into the L1 RNP. (3) MOV10 binds at the rG4 present in the L1 3' UTR. TUT4 binds MOV10 and adds U residues at the 3' end. (4) The complex is taken to the PBs for storage or decay or exported back into the nucleus where L1 retrotransposition suppression is proposed to occur in two ways: (5) at the insertion site, the U residues are not complementary to the target site which results in failure of TPRT (Warkocki et al., 2018). (6) A second model proposed that at the site of insertion, ORF2p which binds to the polyA tail of the L1 mRNA attempts to reverse transcribe the L1 mRNA into cDNA and encounters steric hindrance from MOV10 which is moving in the 5' to 3' direction to unwind the rG4 or the DNA:RNA heteroduplexes in association with RNASEH2 (Choi et al., 2018; Skariah et al., 2017). TPRT, target-primed reverse transcription; UTR, untranslated region

RNA, too. RNASEH2 interacts with MOV10 in an RNA-dependent manner and together they resolve the heteroduplexes formed during L1 retrotransposition, by degrading the L1 RNA bound to the DNA at a target insertion site. Hence, MOV10 helicase activity is indispensable for RNASEH2-mediated retrotransposition inhibition (Choi et al., 2018). Thus, MOV10 overexpression reduces L1 retrotransposition through a number of potential mechanisms (Figure 5) (Bartsch et al., 2017; Pokatayev et al., 2016).

A more recent report showed that MOV10 associates with terminal uridylyltransferases (TUTases) 4/7 to inhibit retrotransposition. TUTases add uridine residues to the 3' ends of the mRNAs which leads to their decay (Lim et al., 2014; Warkocki et al., 2018). This study proposed a model where upon binding the L1 RNA, MOV10 translocates in the 5' to 3' direction due to its ATP-dependent helicase activity and aids in 3' uridylation by TUT 7 and TUT4 which can lead to mRNA degradation or storage in the cytoplasm. Interestingly, in the nucleus blocking L1 RT leads to inhibition of retrotransposition. As L1 Target Primed Reverse Transcription (TRPT) requires complementarity with AT-rich insertion target sites during transposition, its U-rich 3' end is not able to bind to the target sites resulting in inhibition of RT (Warkocki et al., 2018).

L1 retrotransposition has also been implicated in cancers and not surprisingly, MOV10 is also perturbed in diseases associated with elevated L1 transposition. A study done in cancers of the digestive tract showed that esophageal cancer-specific L1 insertion in Exon 20 of MOV10 resulted in MOV10 degradation presumably through NMD (Jung et al., 2018). Additional evidence of control of MOV10-mediated L1 retrotransposition inhibition came from the study of Kaposi's sarcoma (KS) which is caused by KS-associated herpesvirus (KSHV) that is a common malignancy in HIV patients. During the KSHV latent cycle, viral FLICE-inhibitory protein (vFLIP) is upregulated in nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B)-dependent manner, which in turn upregulates intracellular adhesion molecule-1. This physiological change in the primary effusion lymphoma cells, which are closely associated with KSHV, leads to downregulation of MOV10 giving rise to L1 retrotransposition during KSHV latent infection (Nakayama et al., 2019).

4 | TISSUE EXPRESSION OF MOV10 AND ITS ANTIVIRAL ACTIVITY

In one of the pioneer studies on MOV10, Mooslehner and colleagues identified that *MOV10* mRNA is expressed in all the tissues in adult mice except for muscle and skin. The highest expression of MOV10 was found in the thymus and testes. In pups, the predominant expression was in the fetal liver (Mooslehner et al., 1991). Northern blotting experiments on human samples showed similar results—the highest expression was found in the testis and ovary, and some expression in the placenta and liver (Nakano et al., 2009). Genome-wide transcriptomics analysis of 27 human tissue samples showed that *MOV10* has relatively high expression in the testis, placenta, skin, spleen, and organs of digestive system—colon, duodenum, and small intestine (Fagerberg et al., 2014). In a large-scale study to discover new genes expressed in human adult and fetal brain, *MOV10* was identified as one of the new genes (referred to as KIAA1631) found to be differentially expressed in various adult brain regions and moderately expressed in whole fetal brain (Nagase et al., 2000). Additionally, according to the Allen Mouse Brain Atlas (2004), *Mov10* transcript shows low expression in the olfactory bulb and cortical subplate in adult brain but its expression has not been examined across development in the mouse brain (Allen Developing Mouse Brain Atlas, 2008). Skariah et al. found that although there is almost no MOV10 protein expression in the adult mouse brain, there are high levels of MOV10 protein in the brain of the developing pups. The highest expression was found in the P0-P3 pups, after which protein levels steadily decline as the mouse approaches sexual maturity (Skariah et al., 2017). MOV10 expression in the testes was recently confirmed in the developing pups, where MOV10 was mainly expressed in spermatogonia and its localization was both nuclear as well as cytoplasmic (Fu et al., 2019). Interestingly, MOV10 shares very low C-terminal homology with another protein MOV10-Like1 (MOV10L1), which is germline specific and functions in the piRNA pathway (Zheng et al., 2010). MOV10L1 was also shown to inhibit retrotransposons during spermatogenesis (Frost et al., 2010; Zhu et al., 2015), a function shared by MOV10 in brain and cell culture (Goodier et al., 2012; Skariah et al., 2017).

We discuss the antiviral properties of MOV10 against HIV1, Influenza, Hepatitis B and C viruses (HBV and HCV) below.

4.1 | Human Immunodeficiency Virus-1 (HIV-1)

MOV10's wide-spread expression in tissues is compatible with its role as a viral restriction factor. MOV10 likely acquired relatively minor adaptations of existing cellular activities that had the potential to inhibit viral replication (Blanco-Melo et al., 2012). In general, MOV10 has an antiviral effect; however, there is also evidence for the viruses recruiting MOV10 for some of proviral activities (Furtak et al., 2010; X. Wang et al., 2010). In line with its antiviral activity, multiple groups have reported that MOV10 incorporates into the HIV-1 virions and reduces late transcription events. Overexpression of MOV10 consistently reduces infectivity of HIV-1 and extracellular concentration of HIV-1 proteins. However, there are conflicting data regarding MOV10's involvement in the early transcription events (Burdick et al., 2010; Furtak et al., 2010; X. Wang et al., 2010), processing of Gag (Arjan-Odedra et al., 2012; Burdick et al., 2010; Izumi et al., 2013; X. Wang et al., 2010) and the role of endogenous MOV10 versus overexpression. Huang and colleagues have tried to explain the inconsistency between the antiviral properties of overexpressed MOV10 and the proviral properties of endogenous MOV10 by showing that endogenous MOV10 is required for the synthesis of HIV-1 but that overexpression of MOV10 inhibits the budding of HIV-1 (Huang et al., 2015). MOV10 is able to bind HIV mRNA

(Burdick et al., 2010; Chen et al., 2017) but it is unclear if this property of MOV10 is required for HIV-1 reduction. There are additional MOV10-mediated mechanisms for viral inhibition, as described (Yu et al., 2003).

4.2 | Influenza

MOV10 also has antiviral properties against Influenza A virus (IAV). The initial discovery was made by Zhang and colleagues when they identified MOV10 associated with Polymerase basic protein 2 (PB2) through mass spectrometry (Zhang et al., 2016). Then, through overexpression and knockdown experiments, they showed that MOV10 respectively either protects cells or makes them more susceptible to IAV in a dose-dependent manner. Zhang and colleagues also showed that MOV10 interacts with nucleoprotein (NP) in an RNA-dependent manner. According to their data, MOV10 disrupts the nucleocytoplasmic distribution of NP by blocking its nuclear import. MOV10 has regions in both its N- and C-termini that bind NP, and these regions inhibit viral RdRp activity. The inhibition of IAV by MOV10 was validated by Li and colleagues (J. Li et al., 2019). They also repeated the RNA-dependent interaction of MOV10 with NP. They showed that MOV10 sequesters IAV RNPs in the PBs in the cells, and that helicase activity is not needed for IAV inhibition. Lastly, Li and colleagues showed that interaction between MOV10 and NS1 leads to MOV10 degradation through the lysosomal pathway.

4.3 | Hepatitis B virus

The consensus is that MOV10 has anti-HBV effects although the mechanism is unclear. Song and colleagues showed that MOV10 changes extracellular levels of HBsAg and HBeAg, as well as intracellular levels of HBV mRNA in a dose-dependent manner but has no effect on HBV DNA (Song et al., 2014). In contrast, Liu et al. found that MOV10 had no effect on HBeAg levels, production and encapsidation of HBV RNA, but reduced viral DNA levels through inhibition of RT (T. Liu et al., 2019). Similarly, Puray-Chavez et al. showed that HBV DNA and pregenomic RNA (pgRNA) levels increase with MOV10 knockdown and reduce with MOV10 overexpression (Puray-Chavez et al., 2019). Both Liu et al. and Puray-Chavez et al. found that MOV10 interacts with HBV RNA but does not cause its degradation.

4.4 | Hepatitis C virus

MOV10 has anti-HCV activity similar to that against HIV-1 and HBV (D. Liu et al., 2020). Liu and colleagues showed that MOV10 localization in the cytoplasm changes from scattered to foci upon HCV infection. Overexpression of MOV10 significantly reduces the infectivity of HCV and protects cells from the virus in a dose-dependent manner. However, the knockout and knockdown of MOV10 counterintuitively reduce HCV infectivity. Helicase activity of MOV10 is not required for anti-HCV activity. Thus, perhaps similar to its multipronged defense against retrotransposition, MOV10 inhibits viral infection through a number of different intracellular strategies.

4.5 | Antiviral response through interferon-mediated immunity

MOV10 is also associated with interferon (IFN)-mediated immunity against viral pathogens. Viral NAs bind cellular receptors like retinoic acid-inducible gene I (RIG-I)-like receptors and Toll-like receptors. These receptors induce IFNs and IFN-stimulated genes to trigger immunity (Goubau et al., 2013). A study to identify novel antiviral effectors in the type I IFN system found that MOV10 elicited an IFN response specifically against HCV (Schoggins et al., 2011). Similarly, Mov10 plays a role in the IFN-mediated defense response against viral infection by interacting with the IFN-regulated viral gene (IRAV) called Shiftless antiviral inhibitor of ribosomal frameshifting protein (SHFL). This protein was shown to be upregulated in response to IFNs released during many viral infections including Influenza and Ebola and it colocalized to the PBs along with UPF1 and MOV10. In addition, IRAV and MOV10 localized to the viral replication complex and restricted viral replication, possibly by destabilizing viral DNA (Balinsky et al., 2016). MOV10 also triggers IFN-mediated antiviral activity against RNA viruses like picornavirus family EMCV, which did not require its helicase activity. Since MOV10 retains its RNA binding ability even when the helicase domains are mutated, MOV10

might elicit immune response simply by binding the viral RNAs and interfering with their assembly (Cuevas et al., 2016; Gregersen et al., 2014). In fact, MOV10 also binds the N protein of the Thrombocytopenia syndrome virus and inhibits its polymerization with viral RNA thus inhibiting viral replication independent of MOV10 helicase activity (Mo et al., 2020).

MOV10 may also participate in human infections by corona viruses. Publicly available RNA-seq data from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), SARS-CoV, and Middle East respiratory syndrome (MERS)-CoV-infected cell lines and patient samples were subjected to differential expression analyses and a weighted gene co-expression network analysis (Salgado-Albarrán et al., 2021). One of the goals was to identify unique and shared central epigenetic players in the three infections. Among the changed genes, *MOV10* mRNA, which they describe as an “epigene,” was upregulated in infected cells. The authors note that MOV10—among other proteins—appears to be a driver of SARS-CoV-2 infection. Thus, the infected cell may upregulate MOV10 in response to the infection but the virus has co-opted MOV10 for its own production. Based on its large number of roles in the cell, MOV10 likely has different cellular functions based on the proteins it interacts with and the compartment (nucleus or cytoplasm) in which it is located.

5 | MOV10'S ROLE IN ORGANISMS AND DURING DEVELOPMENT

A critical role for MOV10 in development was first discovered by the embryonic lethality of a full body *Mov10* knockout mouse (Skariah et al., 2017). To identify the developmental step where MOV10 was required, the authors turned to *Xenopus laevis* (Skariah et al., 2018). They used morpholinos to block the maternal *Mov10* mRNA in *X. laevis* embryos and found that they failed to complete gastrulation. RNA sequencing of these embryos revealed significantly increased mRNAs, suggesting that MOV10 was required for the maternal to zygotic transition in which the maternal RNAs are degraded to enable zygotic transcription. They hypothesized that MOV10 was functioning as an AGO2 cofactor to facilitate this transition, which has been reported in mice (Lykke-Andersen et al., 2008).

Skariah and coworkers showed that MOV10 has an important role in neuronal development, as well. MOV10 protein levels showed a developmental increase in mouse whole brain and was about 40-fold higher than in the adult brain at postnatal stages P0–P2 (Skariah et al., 2017). This is an extremely important stage in brain development where a host of important events like neuronal differentiation, synaptogenesis, and synaptic pruning occurs to influence brain structure and circuitry (Rice & Barone, 2000). The pattern of MOV10 distribution in whole brain showed a transition from being ubiquitous in P0 brain to becoming restricted to the hippocampus in adult brain. As mentioned earlier, MOV10 also showed a change in cellular localization from nucleocytoplasmic at P0–P2 to predominantly cytoplasmic in the adult brain. This developmentally timed increase and nuclear localization of MOV10 at postnatal stages was shown to be important for regulating L1s that become active during neuronal differentiation (Kuwabara et al., 2009).

In addition to its nuclear role, cytoplasmic MOV10 also bound cytoskeletal mRNAs in postnatal brain and regulated neurite outgrowth in a knockout neuroblastoma, reminiscent of its function in cytoskeletal remodeling during embryogenesis. The preference of MOV10 for binding cytoskeletal RNAs is reminiscent of FMRP, which also preferentially binds RNAs involved in neuron projection (Darnell et al., 2011). Because FMRP binds mRNAs before MOV10 does (Kenny et al., 2014), this could serve as an initial selection for MOV10 to preferentially bind actin/cytoskeletal/neuron projection RNAs.

Interestingly, the *Mov10* heterozygous knockout mice showed increased genomic L1 content, decreased hippocampal dendritic arborization as well as behavioral deficits suggesting an important role for MOV10 in the formation of normal brain circuitry. The importance of MOV10 in the development of CNS was also demonstrated in *X. laevis* (Skariah et al., 2018). MOV10's absence in tadpoles led to shorter body length and smaller eyes. In addition, there was an expanded ventricular compartment in the embryonic brain and abnormal localization of neuronal precursors, suggesting an important role for MOV10 in brain development.

MOV10 was shown to regulate gene expression in neuronal synapses. Kute and colleagues showed that upon NMDA signaling, MOV10 localization shifts from being associated with AGO2 to being associated with polysomes, resulting in a subset of MOV10-regulated mRNAs being actively translated (Kute et al., 2019). In addition, Banerjee and coworkers showed that NMDA stimulation of cultured hippocampal neurons causes ubiquitination of MOV10 and its subsequent degradation, releasing its bound mRNAs for translated (Banerjee et al., 2009). This result was elaborated later by Jarome et al. (2011) who showed that MOV10 was being degraded by the ubiquitin-proteasome system upon

formation and retrieval of memory after auditory and context fear conditioning. Taken together, MOV10 has a critical role in brain development and function.

MOV10 also has an important role in spermatogonial progenitor cells (SPCs; Fu et al., 2019). There, MOV10 knockdown was shown to reduce proliferation of the cultured SPCs and migration into the seminiferous tubes in vivo. MOV10 knockdown also caused a shift in gene expression and overall reduction in miRNA levels. Interestingly, miRNA-processing enzymes Droscha, DCGR8, and Dicer were not changed upon MOV10 knockdown. Analysis of RNA-seq data confirmed that MOV10 regulated gene expression through the 3' UTR and revealed the potential involvement in RNA splicing, which is supported by association of MOV10 with splicing factors.

6 | MOV10'S ROLE IN CANCER

MOV10 may participate in cancer emergence and progression. Nakano and colleagues showed that the expression of MOV10 in a cancerous cell line HeLa is three times higher than in TIG-3 normal fibroblast cells (Nakano et al., 2009), suggesting increased MOV10 levels correlated with tumorigenicity. MOV10 also participates in the downregulation of tumor suppressor *INK4a* through interaction with the PRC1 complex (Messaoudi-Aubert et al., 2010). The pro-cancerous properties of MOV10 were demonstrated in pancreatic cancer (PC) cells by Yang et al. 2019). When MOV10 was shown to bind and stabilize the mRNA of Integrin-1 (ITGB1). ITGB1 was shown to be upregulated in PC cells and antagonizes the anticancerous effects of miR-760 that targets MOV10. Similarly, a study showed that MOV10 interacts with breast cancer antiestrogen resistance protein 1, which is associated with lung adenocarcinoma, potentially to play carcinogenic roles (Mao et al., 2020). In a study of the development of gliomas, He and colleagues showed that MOV10 suppresses circ-DICER from downregulating angiogenesis factor ZIC4, acting to facilitate angiogenesis, necessary for tumor growth. There is evidence for MOV10 having an anti-tumor effect whereby decreased MOV10 expression promotes cell invasion and Wnt5a secretion (W. Wang et al., 2015).

7 | CONCLUSIONS

MOV10 is an RNA helicase that has orthologs in other species and is required for embryonic viability and normal development. It is widely expressed and has roles in the nucleus and cytoplasm. In addition to participating in normal mRNA metabolism and translation, it has anti-viral and retrotransposition-blocking activities. MOV10 also regulates cell growth, thus, has been implicated in tumorigenesis. Future directions will be to create a conditional knockout mouse that can be used in studies of neuronal function, including neuronal stimulation and electrophysiology. In addition, brain development, as well as MOV10's role in behavior, particularly in learning and memory can be explored.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Aatiqa Nawaz: Conceptualization; writing-original draft; writing-review & editing. **Temirlan Shilikbay:** Investigation; writing-original draft. **Geena Skariah:** Writing-original draft; writing-review & editing. **Stephanie Ceman:** Conceptualization; funding acquisition; supervision; writing-review & editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study

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- Su, F., Liu, X., & Jiang, Y. (2020). Roles of MOV10 in animal RNA virus infection. *Frontiers in Veterinary Science*, *7*, 569737.

REFERENCES

- Abudu, A., Wang, X., Dang, Y., Zhou, T., Xiang, S.-H., & Zheng, Y.-H. (2012). Identification of molecular determinants from Moloney leukemia virus 10 homolog (MOV10) protein for virion packaging and anti-HIV-1 activity. *The Journal of Biological Chemistry*, *287*(2), 1220–1228. <https://doi.org/10.1074/jbc.M111.309831>
- Adams, I. (2017). Retrotransposons and the mammalian germline. In G. Cristofari (Ed.), *Human retrotransposons in health and disease*. Springer.
- Agarwala, P., Pandey, S., & Maiti, S. (2015). The tale of RNA G-quadruplex. *Organic and Biomolecular Chemistry*, *13*(20), 5570–5585. <https://doi.org/10.1039/c4ob02681k>
- Aizer, A., Kalo, A., Kafri, P., Shraga, A., Ben-Yishay, R., Jacob, A., Kinor, N., & Shav-Tal, Y. (2014). Quantifying mRNA targeting to P-bodies in living human cells reveals their dual role in mRNA decay and storage. *Journal of Cell Science*, *127*(20), 4443–4456. <https://doi.org/10.1242/jcs.152975>
- Allen Institute for Brain Science. Allen Mouse Brain Atlas. 2004. Available from: <http://mouse.brain-map.org/>.
- Allen Institute for Brain Science. Allen developing Mouse Brain Atlas. 2008. Available from: <http://developingmouse.brain-map.org/>.
- Applequist, S. E., Selg, M., Raman, C., & Jäck, H.-M. (1997). Cloning and characterization of HUPF1, a human homolog of the *Saccharomyces cerevisiae* nonsense mRNA-reducing UPF1 protein. *Nucleic Acids Research*, *25*(4), 814–821. <https://doi.org/10.1093/nar/25.4.814>
- Arjan-Odedra, S., Swanson, C. M., Sherer, N. M., Wolinsky, S. M., & Malim, M. H. (2012). Endogenous MOV10 inhibits the retrotransposition of endogenous retroelements but not the replication of exogenous retroviruses. *Retrovirology*, *9*, 53. <https://doi.org/10.1186/1742-4690-9-53>
- Babushok, D. V., & Kazazian, H. H. (2007). Progress in understanding the biology of the human mutagen LINE-1. *Human Mutation*, *28*(6), 527–539. <https://doi.org/10.1002/humu.20486>
- Balinsky, C. A., Schmeisser, H., Wells, A. I., Ganesan, S., Jin, T., Singh, K., & Zoon, K. C. (2017). IRAV (FLJ11286), an Interferon-Stimulated Gene with Antiviral Activity against Dengue Virus, Interacts with MOV10. *Journal of Virology*, *91*(5), e01606–e01616. <https://doi.org/10.1128/jvi.01606-16>.
- Banerjee, S., Neveu, P., & Kosik, K. S. (2009). A coordinated local translational control point at the synapse involving relief from silencing and MOV10 degradation. *Neuron*, *64*(6), 871–884. <https://doi.org/10.1016/j.neuron.2009.11.023>
- Bartsch, K., Knittler, K., Borowski, C., Rudnik, S., Damme, M., Aden, K., Spehlmann, M. E., Frey, N., Saftig, P., Chalaris, A., & Rabe, B. (2017). Absence of RNase H2 triggers generation of immunogenic micronuclei removed by autophagy. *Human Molecular Genetics*, *26*(20), 3960–3972. <https://doi.org/10.1093/hmg/ddx283>
- Beaudoin, J. D., & Perreault, J. P. (2010). 5'-UTR G-quadruplex structures acting as translational repressors. *Nucleic Acids Research*, *38*(20), 7022–7036. <https://doi.org/10.1093/nar/gkq557>
- Blanco-Melo, D., Venkatesh, S., & Bieniasz, P. D. (2012). Intrinsic cellular defenses against human immunodeficiency viruses. *Immunity*, *37*(3), 399–411. <https://doi.org/10.1016/j.immuni.2012.08.013>
- Bodenhofer, U., Bonatesta, E., Horejš-Kainrath, C., & Hochreiter, S. (2015). msa: An R package for multiple sequence alignment. *Bioinformatics*, *31*(24), 3997–3999. <https://doi.org/10.1093/bioinformatics/btv494>
- Bourgeois, C. F., Mortreux, F., & Auboeuf, D. (2016). The multiple functions of RNA helicases as drivers and regulators of gene expression. *Nature Reviews Molecular Cell Biology*, *17*(7), 426–438. <https://doi.org/10.1038/nrm.2016.50>
- Brown, V., Jin, P., Ceman, S., Darnell, J. C., O'Donnell, W. T., Tenenbaum, S. A., Jin, X., Feng, Y., Wilkinson, K. D., Keene, J. D., Darnell, R. B., & Warren, S. T. (2001). Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome. *Cell*, *107*(4), 477–487. [https://doi.org/10.1016/S0092-8674\(01\)00568-2](https://doi.org/10.1016/S0092-8674(01)00568-2)
- Burdick, R., Smith, J., Chaipan, C., Friew, Y., Venkatachari, J. J., Venkatachari, N. J., Delviks-Frankenberry, K. A., Hu, W.-S., & Pathak, V. (2010). P body-associated protein Mov10 inhibits HIV-1 replication at multiple stages. *Journal of Virology*, *84*(19), 10241–10253. <https://doi.org/10.1128/jvi.00585-10>
- Carmell, M. A., Girard, A., van de Kant, H. J. G., Bourc'his, D., Bestor, T. H., de Rooij, D. G., & Hannon, G. J. (2007). MIWI2 is essential for spermatogenesis and repression of transposons in the mouse male germline. *Developmental Cell*, *12*(4), 503–514. <https://doi.org/10.1016/j.devcel.2007.03.001>
- Caruthers, J. M., & McKay, D. B. (2002). Helicase structure and mechanism. *Current Opinion in Structural Biology*, *12*(1), 123–133. [https://doi.org/10.1016/S0959-440X\(02\)00298-1](https://doi.org/10.1016/S0959-440X(02)00298-1)
- Chen, C., Ma, X., Hu, Q., Li, X., Huang, F., Zhang, J., Pan, T., Xia, J., Liu, C., & Zhang, H. (2017). Moloney leukemia virus 10 (MOV10) inhibits the degradation of APOBEC3G through interference with the Vif-mediated ubiquitin–proteasome pathway. *Retrovirology*, *14*(1), 56. <https://doi.org/10.1186/s12977-017-0382-1>
- Chendrimada, T. P., Finn, K. J., Ji, X., Baillat, D., Gregory, R. I., Liebhaber, S. A., Pasquinelli, A. E., & Shiekhattar, R. (2007). MicroRNA silencing through RISC recruitment of eIF6. *Nature*, *447*(7146), 823–828. <https://doi.org/10.1038/nature05841>

- Choi, J., Hwang, S.-Y., & Ahn, K. (2018). Interplay between RNASEH2 and MOV10 controls LINE-1 retrotransposition. *Nucleic Acids Research*, *46*(4), 1912–1926. <https://doi.org/10.1093/nar/gkx1312>
- Choudhary, C., Kumar, C., Gnad, F., Nielsen, M. L., Rehman, M., Walther, T. C., Olsen, J. V., & Mann, M. (2009). Lysine acetylation targets protein complexes and co-regulates major cellular functions. *Science*, *325*(5942), 834–840. <https://doi.org/10.1126/science.1175371>
- Coe, B. P., Witherspoon, K., Rosenfeld, J. A., van Bon, B. W. M., Vulto-van Silfhout, A. T., Bosco, P., Friend, K. L., Baker, C., Buono, S., Vissers, L. E. L. M., Schuurs-Hoeijmakers, J. H., Hoischen, A., Pfundt, R., Krumm, N., Carvill, G. L., Li, D., Amaral, D., Brown, N., Lockhart, P. J., ... Eichler, E. E. (2014). Refining analyses of copy number variation identifies specific genes associated with developmental delay. *Nature Genetics*, *46*(10), 1063–1071. <https://doi.org/10.1038/ng.3092>
- Cooper, G. M., Coe, B. P., Girirajan, S., Rosenfeld, J. A., Vu, T. H., Baker, C., Williams, C., Stalker, H., Hamid, R., Hannig, V., Abdel-Hamid, H., Bader, P., McCracken, E., Niyazov, D., Leppig, K., Thiese, H., Hummel, M., Alexander, N., Gorski, J., ... Eichler, E. E. (2011). A copy number variation morbidity map of developmental delay. *Nature Genetics*, *43*(9), 838–846. <https://doi.org/10.1038/ng.909>
- Cordaux, R., & Batzer, M. A. (2009). The impact of retrotransposons on human genome evolution. *Nature Reviews Genetics*, *10*(10), 691–703. <https://doi.org/10.1038/nrg2640>
- Cuevas, R. A., Ghosh, A., Wallerath, C., Hornung, V., Coyne, C. B., & Sarkar, S. N. (2016). MOV10 provides antiviral activity against RNA viruses by enhancing RIG-I–MAVS-independent IFN induction. *The Journal of Immunology*, *196*(9), 3877–3886. <https://doi.org/10.4049/jimmunol.1501359>
- Darnell, J. C., Van Driesche, S. J., Zhang, C., Hung, K. Y. S., Mele, A., Fraser, C. E., Stone, E. F., Chen, C., Fak, J. J., Chi, S. W., Licatalosi, D. D., Richter, J. D., & Darnell, R. B. (2011). FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. *Cell*, *146*(2), 247–261. <https://doi.org/10.1016/j.cell.2011.06.013>
- Dephoure, N., Zhou, C., Villén, J., Beausoleil, S. A., Bakalarski, C. E., Elledge, S. J., & Gygi, S. P. (2008). A quantitative atlas of mitotic phosphorylation. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(31), 10762–10767. <https://doi.org/10.1073/pnas.0805139105>
- Ehret, G. B., Munroe, P. B., Rice, K. M., Bochud, M., Johnson, A. D., Chasman, D. I., Smith, A. V., Tobin, M. D., Verwoert, G. C., Hwang, S.-J., Pihur, V., Vollenweider, P., O'Reilly, P. F., Amin, N., Bragg-Gresham, J. L., Teumer, A., Glazer, N. L., Launer, L., Hua Zhao, J., ... CHARGE-HF consortium. (2011). Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*, *478*(7367), 103–109. <https://doi.org/10.1038/nature10405>
- Fagerberg, L., Hallström, B. M., Oksvold, P., Kampf, C., Djureinovic, D., Odeberg, J., Habuka, M., Tahmasebpoor, S., Danielsson, A., Edlund, K., Asplund, A., Sjöstedt, E., Lundberg, E., Szilyarto, C. A.-K., Skogs, M., Takanan, J. O., Berling, H., Tegel, H., Mulder, J., ... Uhlén, M. (2014). Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Molecular & Cellular Proteomics: MCP*, *13*(2), 397–406. <https://doi.org/10.1074/mcp.M113.035600>
- Fairman-Williams, M. E., Guenther, U.-P., & Jankowsky, E. (2010). SF1 and SF2 helicases: Family matters. *Current Opinion in Structural Biology*, *20*(3), 313–324. <https://doi.org/10.1016/j.sbi.2010.03.011>
- Frohn, A., Eberl, H. C., Stöhr, J., Glasmacher, E., Rüdél, S., Heissmeyer, V., Mann, M., & Meister, G. (2012). Dicer-dependent and -independent argonaute 2 protein interaction networks in mammalian cells. *Molecular and Cellular Proteomics*, *11*(11), 1442–1456. <https://doi.org/10.1074/mcp.M112.017756>
- Frost, R. J. A., Hamra, F. K., Richardson, J. A., Qi, X., Bassel-Duby, R., & Olson, E. N. (2010). MOV10L1 is necessary for protection of spermatocytes against retrotransposons by Piwi-interacting RNAs. *Proceedings of the National Academy of Sciences*, *107*(26), 11847–11852. <https://doi.org/10.1073/pnas.1007158107>
- Fu, K., Tian, S., Tan, H., Wang, C., Wang, H., Wang, M., Wang, Y., Chen, Z., Wang, Y., Yue, Q., Xu, Q., Zhang, S., Li, H., Xie, J., Lin, M., Luo, M., Chen, F., Ye, L., & Zheng, K. (2019). Biological and RNA regulatory function of MOV10 in mammalian germ cells. *BMC Biology*, *17*(1), 1–24. <https://doi.org/10.1186/s12915-019-0659-z>
- Furtak, V., Mulky, A., Rawlings, S. A., Kozhaya, L., Lee, K., KewalRamani, V. N., & Unutmaz, D. (2010). Perturbation of the P-body component Mov10 inhibits HIV-1 infectivity. *PLoS One*, *5*(2), e9081. <https://doi.org/10.1371/journal.pone.0009081>
- Gallois-Montbrun, S., Kramer, B., Swanson, C. M., Byers, H., Lynham, S., Ward, M., & Malim, M. H. (2007). Antiviral protein APOBEC3G localizes to ribonucleoprotein complexes found in P bodies and stress granules. *Journal of Virology*, *81*(5), 2165–2178. <https://doi.org/10.1128/JVI.02287-06>
- Gebert, L. F. R., & MacRae, I. J. (2019). Regulation of microRNA function in animals. *Nature Reviews Molecular Cell Biology*, *20*(1), 21–37. <https://doi.org/10.1038/s41580-018-0045-7>
- Goila-Gaur, R., & Strebler, K. (2008). HIV-1 Vif, APOBEC, and intrinsic immunity. *Retrovirology*, *5*. <https://doi.org/10.1186/1742-4690-5-51>
- Goodier, J. L. (2016). Restricting retrotransposons: A review. *Mobile DNA*, *7*(1), 1–30. <https://doi.org/10.1186/s13100-016-0070-z>
- Goodier, J. L., Cheung, L. E., & Kazazian, H. H. (2012). MOV10 RNA helicase is a potent inhibitor of Retrotransposition in cells. *PLoS Genetics*, *8*(10), e1002941. <https://doi.org/10.1371/journal.pgen.1002941>
- Goodier, J. L., Cheung, L. E., & Kazazian, H. H. (2013). Mapping the LINE1 ORF1 protein interactome reveals associated inhibitors of human retrotransposition. *Nucleic Acids Research*, *41*(15), 7401–7419. <https://doi.org/10.1093/nar/gkt512>
- Goubau, D., Deddouche, S., & Reis e Sousa, C. (2013). Cytosolic sensing of viruses. *Immunity*, *38*(5), 855–869. <https://doi.org/10.1016/j.immuni.2013.05.007>
- Gregersen, L. H., Schueler, M., Munschauer, M., Mastrobuoni, G., Chen, W., Kempa, S., Dieterich, C., & Landthaler, M. (2014). MOV10 is a 5' to 3' RNA helicase contributing to UPF1 mRNA target degradation by translocation along 3' UTRs. *Molecular Cell*, *54*(4), 573–585. <https://doi.org/10.1016/j.molcel.2014.03.017>

- Hamann, L., Jensen, K., & Harbers, K. (1993). Consecutive inactivation of both alleles of the *gbl10* gene has no effect on the proliferation and differentiation of mouse embryonic stem cells. *Gene*, *126*, 279–284.
- Heise, C. T., Le Duff, C. S., Boter, M., Casais, C., Airey, J. E., Leech, A. P., Amigues, B., Guerois, R., Moore, G. R., Shirasu, K., & Kleanthous, C. (2007). Biochemical characterization of RAR1 cysteine- and histidine-rich domains (CHORDs): A novel class of zinc-dependent protein-protein interaction modules. *Biochemistry*, *46*(6), 1612–1623. <https://doi.org/10.1021/bi062174k>
- Hong, G. L., Chen, X. Z., Liu, Y., Liu, Y. H., Fu, X., Lin, S. B., & Zhu, Q. (2013). Genetic variations in *MOV10* and *CACNB2* are associated with hypertension in a Chinese Han population. *Genetics and Molecular Research*, *12*(4), 6220–6227. <https://doi.org/10.4238/2013.December.4.9>
- Huang, F., Zhang, J., Zhang, Y., Geng, G., Liang, J., Li, Y., Chen, J., Liu, C., & Zhang, H. (2015). RNA helicase *MOV10* functions as a co-factor of HIV-1 Rev to facilitate Rev/RRE-dependent nuclear export of viral mRNAs. *Virology*, *486*, 15–26. <https://doi.org/10.1016/j.virol.2015.08.026>
- Hubstenberger, A., Courel, M., Mozziconacci, J., Kress, M., & Weil, D. (2017). P-body purification reveals the condensation of repressed mRNA regulons. *Molecular Cell*, *68*, 144–157.e5. <https://doi.org/10.1016/j.molcel.2017.09.003>
- Izumi, T., Burdick, R., Shigemi, M., Plisov, S., Hu, W.-S., & Pathak, V. K. (2013). *Mov10* and *APOBEC3G* localization to processing bodies is not required for *Virion* incorporation and antiviral activity. *Journal of Virology*, *87*(20), 11047–11062. <https://doi.org/10.1128/JVI.02070-13>
- Jaenisch, R., Jähner, D., Nobis, P., Simon, I., Löhler, J., Harbers, K., & Grotkopp, D. (1981). Chromosomal position and activation of retroviral genomes inserted into the germ line of mice. *Cell*, *24*(2), 519–529. [https://doi.org/10.1016/0092-8674\(81\)90343-3](https://doi.org/10.1016/0092-8674(81)90343-3)
- Jonas, S., & Izaurralde, E. (2015). Towards a molecular understanding of microRNA-mediated gene silencing. *Nature Reviews Genetics*, *16*(7), 421–433. <https://doi.org/10.1038/nrg3965>
- Jung, H., Choi, J. K., & Lee, E. A. (2018). Immune signatures correlate with L1 retrotransposition in gastrointestinal cancers. *Genome Research*, *28*(8), 1136–1146. <https://doi.org/10.1101/gr.231837.117>
- Kadlec, J., Guilligay, D., Ravelli, R. B., & Cusack, S. (2006). Crystal structure of the UPF2-interacting domain of nonsense-mediated mRNA decay factor UPF1. *RNA*, *12*(10), 1817–1824. <https://doi.org/10.1261/rna.177606>
- Kaminsky, E. B., Kaul, V., Paschall, J., Church, D. M., Bunke, B., Kunig, D., Moreno-De-Luca, D., Moreno-De-Luca, A., Mülle, J. G., Warren, S. T., Richard, G., Compton, J. G., Fuller, A. E., Gliem, T. J., Huang, S., Collinson, M. N., Beal, S. J., Ackley, T., Pickering, D. L., ... Martin, C. L. (2011). An evidence-based approach to establish the functional and clinical significance of copy number variants in intellectual and developmental disabilities. *Genetics in Medicine*, *13*(9), 777–784. <https://doi.org/10.1097/GIM.0b013e31822c79f9>
- Kazazian, H. H. (2004). Mobile elements: Drivers of genome evolution. *Science*, *303*(5664), 1626–1632. <https://doi.org/10.1126/science.1089670>
- Kenny, P. J., & Ceman, S. (2016). RNA secondary structure modulates FMRP's bi-functional role in the microRNA pathway. *International Journal of Molecular Sciences*, *17*(6), 985–998. <https://doi.org/10.3390/ijms17060985>
- Kenny, P. J., Kim, M., Skariah, G., Nielsen, J., Lannom, M. C., & Ceman, S. (2020). The FMRP–*MOV10* complex: A translational regulatory switch modulated by G-quadruplexes. *Nucleic Acids Research*, *48*(2), 862–878. <https://doi.org/10.1093/nar/gkz1092>
- Kenny, P. J., Zhou, H., Kim, M., Skariah, G., Khetani, R. S., Drnevich, J., Arcila, M. L., Kosik, K. S., & Ceman, S. (2014). *MOV10* and FMRP regulate *AGO2* association with MicroRNA recognition elements. *Cell Reports*, *9*(5), 1729–1741. <https://doi.org/10.1016/j.celrep.2014.10.054>
- Kiebler, M. A., & Bassell, G. J. (2006). Neuronal RNA Granules: Movers and Makers. *Neuron*, *51*(6), 685–690. <https://doi.org/10.1016/j.neuron.2006.08.021>
- Koonin, E. V. (1992). A new group of putative RNA helicases. *Trends in Biochemical Sciences*, *17*(12), 495–497. [https://doi.org/10.1016/0968-0004\(92\)90338-A](https://doi.org/10.1016/0968-0004(92)90338-A)
- Kute, P. M., Ramakrishna, S., Neelagandan, N., Chattarji, S., & Muddashetty, R. S. (2019). NMDAR mediated translation at the synapse is regulated by *MOV10* and FMRP. *Molecular Brain*, *12*(1). <https://doi.org/10.1186/s13041-019-0473-0>
- Kuwabara, T., Hsieh, J., Muotri, A., Yeo, G., Warashina, M., Lie, D. C., Moore, L., Nakashima, K., Asashima, M., & Gage, F. H. (2009). Wnt-mediated activation of *NeuroD1* and retro-elements during adult neurogenesis. *Nature Neuroscience*, *12*(9), 1097–1105. <https://doi.org/10.1038/nn.2360>
- Landrum, M. J., Lee, J. M., Benson, M., Brown, G. R., Chao, C., Chitipiralla, S., Gu, B., Hart, J., Hoffman, D., Jang, W., Karapetyan, K., Katz, K., Liu, C., Maddipatla, Z., Malheiro, A., McDaniel, K., Ovetsky, M., Riley, G., Zhou, G., ... Maglott, D. R. (2018). ClinVar: Improving access to variant interpretations and supporting evidence. *Nucleic Acids Research*, *46*(D1), D1062–D1067. <https://doi.org/10.1093/nar/gkx1153>
- Landthaler, M., Gaidatzis, D., Rothballer, A., Chen, P. Y., Soll, S. J., Dinic, L., Ojo, T., Hafner, M., Zavolan, M., & Tuschl, T. (2008). Molecular characterization of human Argonaute-containing ribonucleoprotein complexes and their bound target mRNAs. *RNA*, *14*(12), 2580–2596. <https://doi.org/10.1261/rna.1351608>
- Lee, T., & Pelletier, J. (2016). The biology of *DHX9* and its potential as a therapeutic target. *Oncotarget*, *7*(27), 42716–42739. <https://doi.org/10.18632/oncotarget.8446>
- Lein, E. S., Hawrylycz, M. J., Ao, N., Ayres, M., Bensinger, A., Bernard, A., Boe, A. F., Boguski, M. S., Brockway, K. S., Byrnes, E. J., Chen, L., Chen, L., Chen, T.M., Chi Chin, M., Chong, J., Crook, B. E., Czaplinska, A., Dang, C. N., Datta, S., ... Jones, A. R. (2007). Genome-wide atlas of gene expression in the adult mouse brain. *Nature*, *445*(7124), 168–176. <https://doi.org/10.1038/nature05453>

- Li, J., Hu, S., Xu, F., Mei, S., Liu, X., Yin, L., Zhao, F., Zhao, X., Sun, H., Xiong, Z., Zhang, D., Cen, S., Wang, J., Liang, C., & Guo, F. (2019). MOV10 sequesters the RNP of influenza A virus in the cytoplasm and is antagonized by viral NS1 protein. *Biochemical Journal*, 476(3), 467–481. <https://doi.org/10.1042/BCJ20180754>
- Li, X., Zhang, J., Jia, R., Cheng, V., Xu, X., Qiao, W., Guo, F., Liang, C., & Cen, S. (2013). The MOV10 Helicase Inhibits LINE-1 Mobility. *Journal of Biological Chemistry*, 288(29), 21148–21160. <https://doi.org/10.1074/jbc.m113.465856>
- Lim, J., Ha, M., Chang, H., Kwon, S. C., Simanshu, D. K., Patel, D. J., & Kim, V. N. (2014). Uridylation by TUT4 and TUT7 marks mRNA for degradation. *Cell*, 159(6), 1365–1376. <https://doi.org/10.1016/j.cell.2014.10.055>
- Liu, C., Zhang, X., Huang, F., Yang, B., Li, J., Liu, B., Luo, H., Zhang, P., & Zhang, H. (2012). APOBEC3G inhibits microRNA-mediated repression of translation by interfering with the interaction between Argonaute-2 and MOV10. *Journal of Biological Chemistry*, 287(35), 29373–29383. <https://doi.org/10.1074/jbc.M112.354001>
- Liu, D., Ndongwe, T. P., Puray-Chavez, M., Casey, M. C., Izumi, T., Pathak, V. K., Tedbury, P. R., & Sarafianos, S. G. (2020). Effect of P-body component Mov10 on HCV virus production and infectivity. *The FASEB Journal*, 34(7), 9433–9449. <https://doi.org/10.1096/fj.201800641R>
- Liu, T., Sun, Q., Liu, Y., Cen, S., & Zhang, Q. (2019). The MOV10 helicase restricts hepatitis B virus replication by inhibiting viral reverse transcription. *The Journal of Biological Chemistry*, 294(51), 19804–19813. <https://doi.org/10.1074/jbc.ra119.009435>
- Loedige, I., Gaidatzis, D., Sack, R., Meister, G., & Filipowicz, W. (2013). The mammalian TRIM-NHL protein TRIM71/LIN-41 is a repressor of mRNA function. *Nucleic Acids Research*, 41(1), 518–532. <https://doi.org/10.1093/nar/gks1032>
- Lu, C., Luo, Z., Jager, S., Krogan, N. J., & Peterlin, B. M. (2012). Moloney leukemia virus type 10 inhibits reverse transcription and retrotransposition of intracisternal particles. *Journal of Virology*, 86(19), 10517–10523. <https://doi.org/10.1128/jvi.00868-12>
- Lu, X., Wang, L., Lin, X., Huang, J., Charles Gu, C., He, M., Shen, H., He, J., Zhu, J., Li, H., Hixson, J. E., Wu, T., Dai, J., Lu, L., Shen, C., Chen, S., He, L., Mo, Z., Hao, Y., ... Gu, D. (2015). Genome-wide association study in Chinese identifies novel loci for blood pressure and hypertension. *Human Molecular Genetics*, 24(3), 865–874. <https://doi.org/10.1093/hmg/ddu478>
- Lykke-Andersen, K., Gilchrist, M. J., Grabarek, J. B., Das, P., Miska, E., & Zernicka-Goetz, M. (2008). Maternal Argonaute 2 is essential for early mouse development at the maternal-zygotic transition. *Molecular Biology of the Cell*, 19(10), 4383–4392. <https://doi.org/10.1091/mbc.e08-02-0219>
- Mao, C., Jiang, S., Shen, C., Long, T., Jin, H., Tan, Q., & Deng, B. (2020). BCAR1 promotes proliferation and cell growth in lung adenocarcinoma via upregulation of POLR2A. *Thoracic Cancer*, 11(11), 3326–3336. <https://doi.org/10.1111/1759-7714.13676>
- Marchler-Bauer, A., Bo, Y., Han, L., He, J., Lanczycki, C. J., Lu, S., Chitsaz, F., Derbyshire, M. K., Geer, R. C., Gonzales, N. R., Gwadz, M., Hurwitz, D. I., Lu, F., Marchler, G. H., Song, J. S., Thanki, N., Wang, Z., Yamashita, R. A., Zhang, D., ... Bryant, S. H. (2017). CDD/SPARCLE: Functional classification of proteins via subfamily domain architectures. *Nucleic Acids Research*, 45(D1), D200–D203. <https://doi.org/10.1093/nar/gkw1129>
- Matsuoka, S., Ballif, B. A., Smogorzewska, A., McDonald, E. R., Hurov, K. E., Luo, J., Bakalarski, C. E., Zhao, Z., Solimini, N., Lerenthal, Y., Shiloh, Y., Gygi, S. P., & Elledge, S. J. (2007). ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. *Science*, 316(5828), 1160–1166. <https://doi.org/10.1126/science.1140321>
- Meister, G., Landthaler, M., Peters, L., Chen, P. Y., Urlaub, H., Lührmann, R., & Tuschl, T. (2005). Identification of novel argonaute-associated proteins. *Current Biology*, 15(23), 2149–2155. <https://doi.org/10.1016/j.cub.2005.10.048>
- Messaoudi-Aubert, S. E., Nicholls, J., Maertens, G. N., Brookes, S., Bernstein, E., & Peters, G. (2010). Role for the MOV10 RNA helicase in Polycomb-mediated repression of the INK4a tumor suppressor. *Nature Structural & Molecular Biology*, 17(7), 862–868. <https://doi.org/10.1038/nsmb.1824>
- Miki, T., Kamikawa, Y., Kurono, S., Kaneko, Y., Katahira, J., & Yoneda, Y. (2011). Cell type-dependent gene regulation by Staufen2 in conjunction with Upf1. *BMC Molecular Biology*, 12(1), 48–48. <https://doi.org/10.1186/1471-2199-12-48>
- Mo, Q., Xu, Z., Deng, F., Wang, H., & Ning, Y.-J. (2020). Host restriction of emerging high-pathogenic bunyaviruses via MOV10 by targeting viral nucleoprotein and blocking ribonucleoprotein assembly. *PLoS Pathogens*, 16(12), e1009129. <https://doi.org/10.1371/journal.ppat.1009129>
- Moldovan, J. B., & Moran, J. V. (2015). The zinc-finger antiviral protein ZAP inhibits LINE and Alu retrotransposition. *PLoS Genetics*, 11(5), e1005121. <https://doi.org/10.1371/journal.pgen.1005121>
- Mooslehner, K., Karls, U., & Harbers, K. (1990). Retroviral integration sites in transgenic Mov mice frequently map in the vicinity of transcribed DNA regions. *Journal of Virology*, 64(6), 3056–3058.
- Mooslehner, K., Müller, U., Karls, U., Hamann, L., & Harbers, K. (1991). Structure and expression of a gene encoding a putative GTP-binding protein identified by provirus integration in a transgenic mouse strain. *Molecular and Cellular Biology*, 11(2), 886–893. <https://doi.org/10.1128/MCB.11.2.886>
- Muotri, A. R., Chu, V. T., Marchetto, M. C. N., Deng, W., Moran, J. V., & Gage, F. H. (2005). Somatic mosaicism in neuronal precursor cells mediated by L1 retrotransposition. *Nature*, 435(7044), 903–910. <https://doi.org/10.1038/nature03663>
- Nagase, T., Kikuno, R., Hattori, A., Kondo, Y., Okumura, K., & Ohara, O. (2000). Prediction of the coding sequences of unidentified human genes. XIX. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. *DNA Research*, 7(6), 347–355. <https://doi.org/10.1093/dnares/7.6.347>
- Nakano, M., Kakiuchi, Y., Shimada, Y., Ohyama, M., Ogiwara, Y., Sasaki-Higashiyama, N., Yano, N., Ikeda, F., Yamada, E., Iwamatsu, A., Kobayashi, K., Nishiyama, K., Ichikawa, S., Kaji, K., Ide, T., Murofushi, H., & Murakami-Murofushi, K. (2009). MOV10 as a novel

- telomerase-associated protein. *Biochemical and Biophysical Research Communications*, 388(2), 328–332. <https://doi.org/10.1016/j.bbrc.2009.08.002>
- Nakayama, R., Ueno, Y., Ueda, K., & Honda, T. (2019). Latent infection with Kaposi's sarcoma-associated herpesvirus enhances retrotransposition of long interspersed element-1. *Oncogene*, 38(22), 4340–4351. <https://doi.org/10.1038/s41388-019-0726-5>
- Nalavadi, V. C., Griffin, L. E., Picard-Fraser, P., Swanson, A. M., Takumi, T., & Bassell, G. J. (2012). Regulation of Zipcode Binding Protein 1 Transport Dynamics in Axons by Myosin Va. *Journal of Neuroscience*, 32(43), 15133–15141. <https://doi.org/10.1523/jneurosci.2006-12.2012>
- NCBI Resource Coordinators. (2018). Database resources of the National Center for Biotechnology Information. *Nucleic Acids Research*, 46(D1), D8–D13. <https://doi.org/10.1093/nar/gkx1095>
- O'Carroll, D., & Schaefer, A. (2013). General principals of miRNA biogenesis and regulation in the brain. *Neuropsychopharmacology*, 38(1), 39–54. <https://doi.org/10.1038/npp.2012.87>
- Olsen, J. V., Vermeulen, M., Santamaria, A., Kumar, C., Miller, M. L., Jensen, L. J., Gnad, F., Cox, J., Jensen, T. S., Nigg, E. A., Brunak, S., & Mann, M. (2010). Quantitative phosphoproteomics reveals widespread full phosphorylation site occupancy during mitosis. *Science Signaling*, 3(104), rA3. <https://doi.org/10.1126/scisignal.2000475>
- Pokatajev, V., Hasin, N., Chon, H., Cerritelli, S. M., Sakhujia, K., Ward, J. M., Douglas Morris, H., Yan, N., & Crouch, R. J. (2016). RNase H2 catalytic core Aicardi-Goutières syndrome-related mutant invokes cGAS-STING innate immunosensing pathway in mice. *Journal of Experimental Medicine*, 213(3), 329–336. <https://doi.org/10.1084/jem.20151464>
- Puray-Chavez, M. N., Farghali, M. H., Yapo, V., Huber, A. D., Liu, D., Ndongwe, T. P., Casey, M. C., Laughlin, T. G., Hannink, M., Tedbury, P. R., & Sarafianos, S. G. (2019). Effects of Moloney leukemia virus 10 protein on hepatitis B virus infection and viral replication. *Viruses*, 11(7), 651. <https://doi.org/10.3390/v11070651>
- Putnam, A. A., & Jankowsky, E. (2013). DEAD-box helicases as integrators of RNA, nucleotide and protein binding. *Biochimica et Biophysica Acta (BBA)—Gene Regulatory Mechanisms*, 1829(8), 884–893. <https://doi.org/10.1016/j.bbagr.2013.02.002>
- Rice, D., & Barone, S. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives*, 108(Suppl 3), 511–533. <https://doi.org/10.1289/ehp.00108s3511>
- Riggs, C. L., Kedersha, N., Ivanov, P., & Anderson, P. (2020). Mammalian stress granules and P bodies at a glance. *Journal of Cell Science*, 133(16).
- Rocak, S., & Linder, P. (2004). DEAD-box proteins: The driving forces behind RNA metabolism. *Nature Reviews Molecular Cell Biology*, 5(3), 232–241. <https://doi.org/10.1038/nrm1335>
- Ross Buchan, J. (2014). MRNP granules assembly, function, and connections with disease. *RNA Biology*, 11(8), 1019–1030. <https://doi.org/10.4161/15476286.2014.972208>
- Rouleau, S., Glouzon, J. P. S., Brumwell, A., Bisailon, M., & Perreault, J. P. (2017). 3' UTR G-quadruplexes regulate miRNA binding. *RNA*, 23(8), 1172–1179. <https://doi.org/10.1261/rna.060962.117>
- Rybak, A., Fuchs, H., Hadian, K., Smirnova, L., Wulczyn, E. A., Michel, G., Nitsch, R., Krappmann, D., & Wulczyn, F. G. (2009). The let-7 target gene mouse lin-41 is a stem cell specific E3 ubiquitin ligase for the miRNA pathway protein Ago2. *Nature Cell Biology*, 11(12), 1411–1420. <https://doi.org/10.1038/ncb1987>
- Salgado-Albarrán, M., Navarro-Delgado, E. I., Del Moral-Morales, A., Alcaraz, N., Baumbach, J., González-Barrios, R., & Soto-Reyes, E. (2021). Comparative transcriptome analysis reveals key epigenetic targets in SARS-CoV-2 infection. *NPI Systems Biology and Applications*, 7(1), 21–21.
- Schoggins, J. W., Wilson, S. J., Panis, M., Murphy, M. Y., Jones, C. T., Bieniasz, P., & Rice, C. M. (2011). A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature*, 472(7344), 481–485. <https://doi.org/10.1038/nature09907>
- Schweingruber, C., Rufener, S. C., Zünd, D., Yamashita, A., & Mühlemann, O. (2013). Nonsense-mediated mRNA decay—Mechanisms of substrate mRNA recognition and degradation in mammalian cells. *Biochimica et Biophysica Acta—Gene Regulatory Mechanisms*, 1829(6–7), 612–623. <https://doi.org/10.1016/j.bbagr.2013.02.005>
- Shin, J., Ma, S., Hofer, E., Patel, Y., Vosberg, D. E., Tilley, S., Roshchupkin, G. V., Sousa, A. M. M., Jian, X., Gottesman, R., Mosley, T. H., Fornage, M., Saba, Y., Pirpamer, L., Schmidt, R., Schmidt, H., Carrion-Castillo, A., Crivello, F., Mazoyer, B., ... neuroCHARGE Working Group. (2020). Global and regional development of the human cerebral cortex: Molecular architecture and occupational aptitudes. *Cerebral Cortex*, 30(7), 4121–4139. <https://doi.org/10.1093/cercor/bhaa035>
- Skariah, G., Perry, K. J., Drnevich, J., Henry, J. J., & Ceman, S. (2018). RNA helicase Mov10 is essential for gastrulation and central nervous system development. *Developmental Dynamics*, 247(4), 660–671. <https://doi.org/10.1002/dvdy.24615>
- Skariah, G., Seimetz, J., Norsworthy, M., Lannom, M. C., Kenny, P. J., Elrakhawy, M., Forsthoefel, C., Drnevich, J., Kalsotra, A., & Ceman, S. (2017). Mov10 suppresses retroelements and regulates neuronal development and function in the developing brain. *BMC Biology*, 15(1). <https://doi.org/10.1186/s12915-017-0387-1>
- Slack, F. J., & Ruvkun, G. (1998). A novel repeat domain that is often associated with RING finger and B-box motifs. *Trends in Biochemical Sciences*, 23(12), 474–475. [https://doi.org/10.1016/S0968-0004\(98\)01299-7](https://doi.org/10.1016/S0968-0004(98)01299-7)
- Song, Z.-W., Ma, Y.-X., Fu, B., Teng, X., Chen, S.-J., Xu, W.-Z., Gu, H.-X., & Antibiotic Resistance Surveillance Program in Portugal (ARSIP) Participants. (2014). Altered mRNA levels of MOV10, A3G, and IFN- α in patients with chronic hepatitis B. *Journal of Microbiology*, 52(6), 510–514. <https://doi.org/10.1007/s12275-014-3467-8>
- Takemura, M., Bowden, N., Lu, Y.-S., Nakato, E., O'Connor, M. B., & Nakato, H. (2021). Drosophila MOV10 regulates the termination of midgut regeneration. *Genetics*, 218(iyab031). <https://doi.org/10.1093/genetics/iyab031>

- Tang, Q., Wang, L., Cai, R., Zhang, L., Zhang, X., Liu, X., & Liu, S. (2020). The association of MOV10 polymorphism and expression levels with preeclampsia in the Chinese Han population. *Molecular Genetics & Genomic Medicine*, 9(1), e1564. <https://doi.org/10.1002/mgg3.1564>
- Tauber, D., Tauber, G., Khong, A., Van Treeck, B., Pelletier, J., & Parker, R. (2020). Modulation of RNA Condensation by the DEAD-Box Protein eIF4A. *Cell*, 180(3), 411–426.e16. <https://doi.org/10.1016/j.cell.2019.12.031>
- Taylor, M. S., Altukhov, I., Molloy, K. R., Mita, P., Jiang, H., Adney, E. M., Wudzinska, A., Badri, S., Ischenko, D., Eng, G., Burns, K. H., Fenyő, D., Chait, B. T., Alexeev, D., Rout, M. P., Boeke, J. D., & LaCava, J. (2018). Dissection of affinity captured LINE-1 macromolecular complexes. *ELife*, 7. <https://doi.org/10.7554/eLife.30094>
- Taylor, M. S., LaCava, J., Mita, P., Molloy, K. R., Huang, C. R. L., Li, D., Adney, E. M., Jiang, H., Burns, K. H., Chait, B. T., Rout, M. P., Boeke, J. D., & Dai, L. (2013). Affinity proteomics reveals human host factors implicated in discrete stages of LINE-1 retrotransposition. *Cell*, 155(5), 1034–1048. <https://doi.org/10.1016/j.cell.2013.10.021>
- Upton, K. R., Gerhardt, D. J., Jesuadian, J. S., Richardson, S. R., Sánchez-Luque, F. J., Bodea, G. O., Ewing, A. D., Salvador-Palomeque, C., van der Knaap, M. S., Brennan, P. M., Vanderver, A., & Faulkner, G. J. (2015). Ubiquitous L1 mosaicism in hippocampal neurons. *Cell*, 161(2), 228–239.
- Wang, W., Snyder, N., Worth, A. J., Blair, I. A., & Witze, E. S. (2015). Regulation of lipid synthesis by the RNA helicase Mov10 controls Wnt5a production. *Oncogene*, 4(6), e154–e154. <https://doi.org/10.1038/oncsis.2015.15>
- Wang, X., Han, Y., Dang, Y., Fu, W., Zhou, T., Ptak, R. G., & Zheng, Y.-H. (2010). Moloney leukemia virus 10 (MOV10) protein inhibits retrovirus replication. *The Journal of Biological Chemistry*, 285(19), 14346–14355. <https://doi.org/10.1074/jbc.M110.109314>
- Warkocki, Z., Krawczyk, P. S., Adamska, D., Bijata, K., Garcia-Perez, J. L., & Dziembowski, A. (2018). Uridylation by TUT4/7 restricts retrotransposition of human LINE-1s. *Cell*, 174(6), 1537–1548.e29. <https://doi.org/10.1016/j.cell.2018.07.022>
- Wulczyn, F. G., Smirnova, L., Rybak, A., Brandt, C., Kwidzinski, E., Ninnemann, O., Strehle, M., Seiler, A., Schumacher, S., & Nitsch, R. (2007). Post-transcriptional regulation of the let-7 microRNA during neural cell specification. *The FASEB Journal*, 21(2), 415–426. <https://doi.org/10.1096/fj.06-6130com>
- Yang, D., Hu, Z., Xu, J., Tang, Y., Wang, Y., Cai, Q., & Zhu, Z. (2019). MiR-760 enhances sensitivity of pancreatic cancer cells to gemcitabine through modulating Integrin β 1. *Bioscience Reports*, 39(11), BSR20192358. <https://doi.org/10.1042/BSR20192358>
- Yates, A. D., Achuthan, P., Akanni, W., Allen, J., Allen, J., Alvarez-Jarreta, J., Amode, M. R., Armean, I. M., Azov, A. G., Bennett, R., Bhai, J., Billis, K., Boddu, S., Marugán, J. C., Cummins, C., Davidson, C., Dodiya, K., Fatima, R., Gall, A., ... Flicek, P. (2020). Ensembl 2020. *Nucleic Acids Research*, 48(D1), D682–D688. <https://doi.org/10.1093/nar/gkz966>
- Yu, X., Yu, Y., Liu, B., Luo, K., Kong, W., Mao, P., & Yu, X.-F. (2003). Induction of APOBEC3G ubiquitination and degradation by an HIV-1 Vif-Cul5-SCF complex. *Science*, 302(5647), 1056–1060. <https://doi.org/10.1126/science.1089591>
- Zappulo, A., van den Bruck, D., Ciolli Mattioli, C., Franke, V., Imami, K., McShane, E., Moreno-Estelles, M., Calviello, L., Filipchuk, A., Peguero-Sanchez, E., Müller, T., Woehler, A., Birchmeier, C., Merino, E., Rajewsky, N., Ohler, U., Mazzoni, E. O., Selbach, M., Akalin, A., & Chekulaeva, M. (2017). RNA localization is a key determinant of neurite-enriched proteome. *Nature Communications*, 8(1), 583. <https://doi.org/10.1038/s41467-017-00690-6>
- Zeitelhofer, M., Karra, D., Macchi, P., Tolino, M., Thomas, S., Schwarz, M., Kiebler, M., & Dahm, R. (2008). Dynamic interaction between P-bodies and transport ribonucleoprotein particles in dendrites of mature hippocampal neurons. *The Journal of Neuroscience*, 28(30), 7555.
- Zhang, J., Huang, F., Tan, L., Bai, C., Chen, B., Liu, J., Liang, J., Liu, C., Zhang, S., Lu, G., Chen, Y., & Zhang, H. (2016). Host protein Moloney leukemia virus 10 (MOV10) acts as a restriction factor of influenza A virus by inhibiting the nuclear import of the viral nucleoprotein. *Journal of Virology*, 90(8), 3966–3980. <https://doi.org/10.1128/JVI.03137-15>
- Zheng, K., Xiol, J., Reuter, M., Eckardt, S., Leu, N. L., McLaughlin, K. J., Stark, A., Sachidanandam, R., Pillai, R. S., & Wang, P. J. (2010). Mouse MOV10L1 associates with Piwi proteins and is an essential component of the Piwi-interacting RNA (piRNA) pathway. *Proceedings of the National Academy of Sciences of the United States of America*, 107(26), 11841–11846. <https://doi.org/10.1073/pnas.1003953107>
- Zhu, X., Zhi, E., & Li, Z. (2015). MOV10L1 in piRNA processing and gene silencing of retrotransposons during spermatogenesis. *Reproduction*, 149(5), R229–R235. <https://doi.org/10.1530/REP-14-0569>

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