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# SnapShot: FMRP Interacting Proteins

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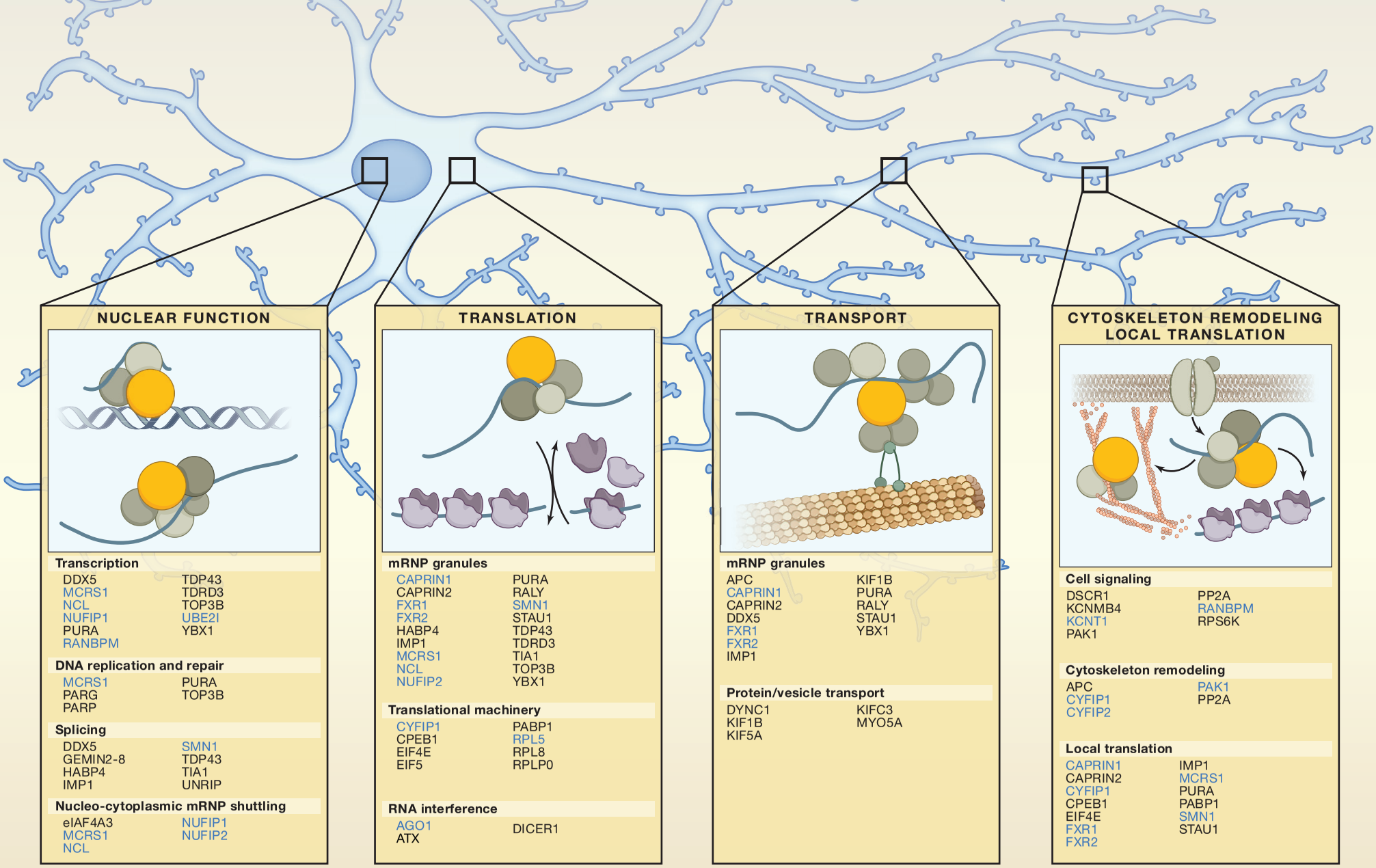
Cell



## NUCLEAR FUNCTION

**Transcription**

| | |
|---|---|
| DDX5 | TDP43 |
| MCRS1 | TDRD3 |
| NCL | TOP3B |
| NUFIP1 | UBE2I |
| PURA | YBX1 |
| RANBPM | |

**DNA replication and repair**

| | |
|---|---|
| MCRS1 | PURA |
| PARG | TOP3B |
| PARP | |

**Splicing**

| | |
|---|---|
| DDX5 | SMN1 |
| GEMIN2-8 | TDP43 |
| HABP4 | TIA1 |
| IMP1 | UNRIP |

**Nucleo-cytoplasmic mRNP shuttling**

| | |
|---|---|
| eIAF4A3 | NUFIP1 |
| MCRS1 | NUFIP2 |
| NCL | |

## TRANSLATION

**mRNP granules**

| | |
|---|---|
| CAPRIN1 | PURA |
| CAPRIN2 | RALY |
| FXR1 | SMN1 |
| FXR2 | STAU1 |
| HABP4 | TDP43 |
| IMP1 | TDRD3 |
| MCRS1 | TIA1 |
| NCL | TOP3B |
| NUFIP2 | YBX1 |

**Translational machinery**

| | |
|---|---|
| CYFIP1 | PABP1 |
| CPEB1 | RPL5 |
| EIF4E | RPL8 |
| EIF5 | RPLP0 |

**RNA interference**

| | |
|---|---|
| AGO1 | DICER1 |
| ATX | |

## TRANSPORT

**mRNP granules**

| | |
|---|---|
| APC | KIF1B |
| CAPRIN1 | PURA |
| CAPRIN2 | RALY |
| DDX5 | STAU1 |
| FXR1 | YBX1 |
| FXR2 | |
| IMP1 | |

**Protein/vesicle transport**

| | |
|---|---|
| DYNC1 | KIFC3 |
| KIF1B | MYO5A |
| KIF5A | |

## CYTOSKELETON REMODELING LOCAL TRANSLATION

**Cell signaling**

| | |
|---|---|
| DSCR1 | PP2A |
| KCNMB4 | RANBPM |
| KCNT1 | RPS6K |
| PAK1 | |

**Cytoskeleton remodeling**

| | |
|---|---|
| APC | PAK1 |
| CYFIP1 | PP2A |
| CYFIP2 | |

**Local translation**

| | |
|---|---|
| CAPRIN1 | IMP1 |
| CAPRIN2 | MCRS1 |
| CYFIP1 | PURA |
| CPEB1 | PABP1 |
| EIF4E | SMN1 |
| FXR1 | STAU1 |
| FXR2 | |

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The fragile X syndrome (FXS) is the most common identified cause of inherited intellectual disability and autism. It is due to the absence or mutation of the fragile X mental retardation protein, FMRP. The mRNA encoding FMRP is expressed in different tissues (https://www.genevestigator.com/gv/) suggesting a variety of functions according to the cell type and developmental stage.

FMRP has four RNA-binding domains necessary for the recognition of mRNA targets that also interact with a multitude of proteins involved in different cellular functions. This SnapShot surveys the known interactors of FMRP, focusing on the cellular pathways in which they are involved. Interacting proteins were identified by two-hybrid screens and/or coprecipitation of candidate proteins. In addition, FMRP was identified in unbiased characterization of other protein complexes; a thorough proteomic analysis of the FMRP interactome has not been reported so far. Some of the interactions have been mapped down to the FMRP-binding domain (in blue), while others are less well characterized and could also be indirect.

Many of the FMRP protein interactors are cytoplasmic RNA-binding proteins (RBPs) implicated in a number of cellular processes involving mRNA metabolism (Bagni and Klann, 2012), considered up to now the major contribution to FXS; others act in the nucleus, where they have been implicated in transcription, splicing, and DNA repair. Although FMRP interacts with several nuclear proteins, its function in the nucleus is still largely unknown. Very recently it was shown that FMRP binds chromatin and participates in the DNA damage response (Alpatov et al., 2014). Nuclear FMRP interacting RBPs also exhibit functions outside the nucleus, raising the possibility that FMRP mRNP granules assemble in the nucleus and translocate to the cytoplasm absolving different cellular functions.

Cytoplasmic FMRP interactors are involved in functions such as ribosome and spliceosome assembly, translational suppression, or alteration of RNA secondary structure. Other protein components of the FMRP mRNP complexes are part of heterogeneous RNA granules, including transport granules that deliver transcripts to dendrites while inhibiting RNA translational activity, stress granules sequestering RNA/mRNA under stressful conditions, processing bodies P-bodies (i.e., sites for mRNA storage and degradation), and mRNPs containing the miRNA machinery (Kanai et al., 2004; Doyle and Kiebler, 2011). FMRP mRNP granules travel along the microtubules via kinesin, myosin, and dynein motor proteins (Kanai et al., 2004; Bassell and Warren, 2008).

At the synapse, FMRP interacts with components of the signaling pathways like receptors, kinases, and phosphatases. Consistent with the presence of a translational machinery underneath the plasma membrane (Tcherkezian et al., 2010), FMRP regulates local translation. It is upon synaptic demand that specific mRNAs shuttle from storage granules to actively translating polysomes.

Finally FMRP, through its cytoplasmic interactor CYFIP1, links local protein synthesis to actin remodelling (De Rubeis et al., 2013; Schenck et al., 2003). Additional contacts with the cytoskeleton occur via the adenomatous polyposis coli (APC) tumor suppressor (Mili et al., 2008), CYFIP2 (Bagni and Klann 2012), and PAK1 (Hayashi et al., 2007).

## REFERENCE

Alpatov, R., Lesch, B.J., Nakamoto-Kinoshita, M., Blanco, A., Chen, S., Stützer, A., Armache, K.J., Simon, M.D., Xu, C., Ali, M., et al. (2014). Cell *157*, 869–881.

Bagni, C., and Klann, E. (2012). In The Autisms: Molecules to Model Systems, C.M. Powell and L.M. Monteggia, eds. (Oxford: Oxford University Press), pp. 126–146.

Bassell GJ, and Warren ST. (2008). Neuron *60*, 201-214.

De Rubeis, S., Pasciuto, E., Li, K.W., Fernández, E., Di Marino, D., Buzzi, A., Ostroff, L.E., Klann, E., Zwartkruis, F.J., Komiyama, N.H., et al. (2013). Neuron *79*, 1169–1182.

Doyle, M. and Kiebler, M.A. (2011). EMBO J. *30*, 3540–3552

Hayashi, M.L., Rao, B.S., Seo, J.S., Choi, H.S., Dolan, B.M., Choi, S.Y., Chattarji, S., and Tonegawa, S. (2007). Proc. Natl. Acad. Sci. USA *104*, 11489–11494.

Kanai, Y., Dohmae, N., and Hirokawa, N. (2004). Neuron *43*, 513–525.

Mili, S., Moissoglu, K., and Macara, I.G. (2008). Nature *453*, 115–119.

Schenck, A., Bardoni, B., Langmann, C., Harden, N., Mandel, J.L., and Giangrande, A. (2003). Neuron *38*, 887–898.

Tcherkezian, J., Brittis, P.A., Thomas, F., Roux, P.P., and Flanagan, J.G. (2010). Cell *141*, 632–644.

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