

A SYSTEMICS VIEW OF PURAS CELLULAR RNA-BINDING FUNCTION FROM OMICS DATA GIVES INSIGHTS INTO PURA RELATED DISEASES

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<https://biorxiv.org/cgi/content/short/2022.02.09.479353v1>

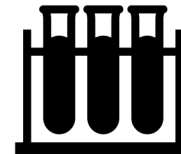
Collaboration



Buchmann Institute
for Molecular Life Sciences



Zarnack Group
me

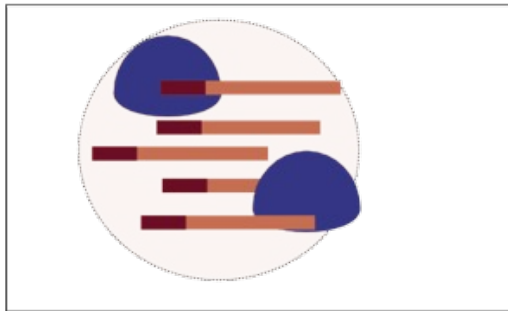


Niessing Group
Lena Molitor
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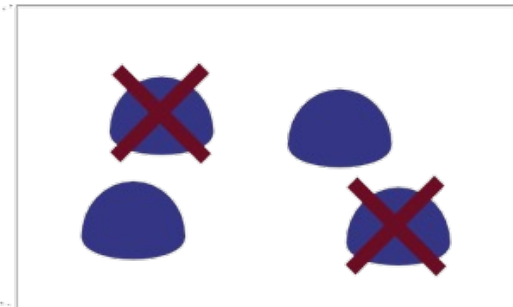
HelmholtzZentrum münchen
German Research Center for Environmental Health

PURA plays a role in several neuronal diseases

RNA repeat expansion disorders

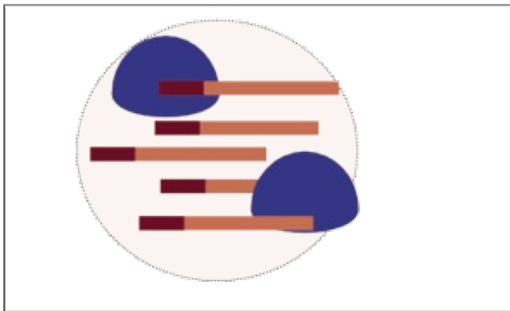


PURA Syndrome



PURA plays a role in several neuronal diseases

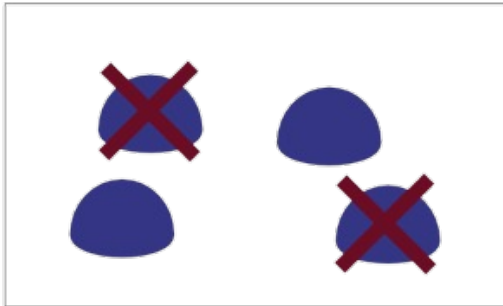
RNA repeat expansion disorders



- RNAs with expanded short repeats
- Form aggregates in the brain
- PURA was found in the aggregates

PURA plays a role in several neuronal diseases

PURA Syndrome

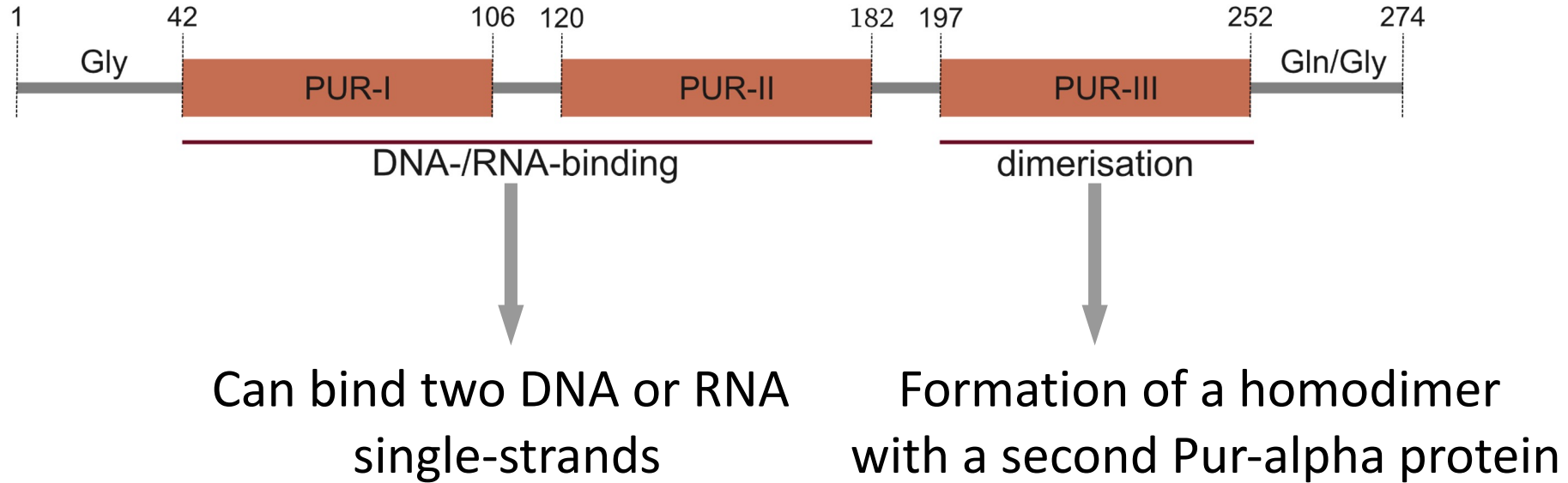


- Neurodevelopmental disease
- Rare (~300 cases described)
- Sporadic mutation of *PURA* gene
- Leads to heterogenous loss of functional PURA protein

Rejinders *et al* (2018): PURA syndrome: clinical delineation and genotype-phenotype study in 32 individuals with review of published literature *Journal of Medical Genetics* 55:104-113

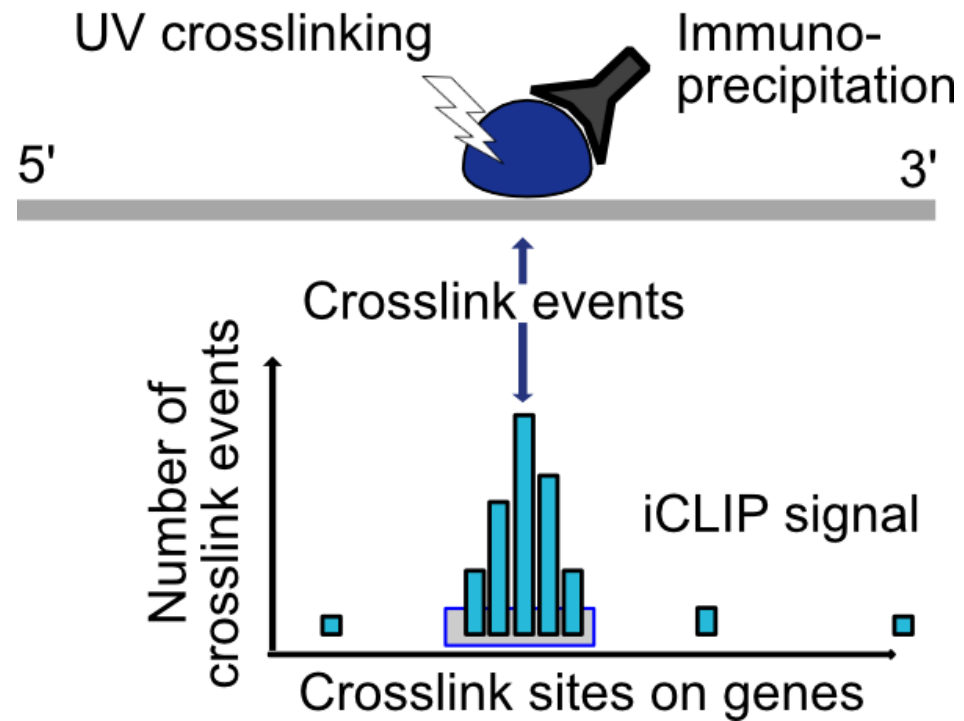
Structure of PURA protein

Pur-alpha protein (*Drosophila*)

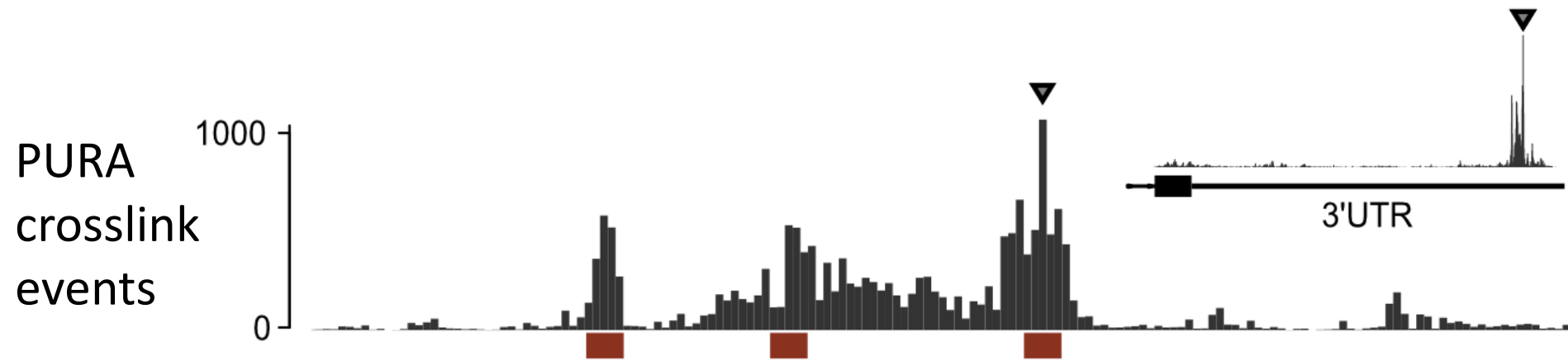


Weber et al (2016): Structural basis of nucleic-acid recognition and double-strand unwinding by the essential neuronal protein Pur-alpha. eLife, 5:e11297

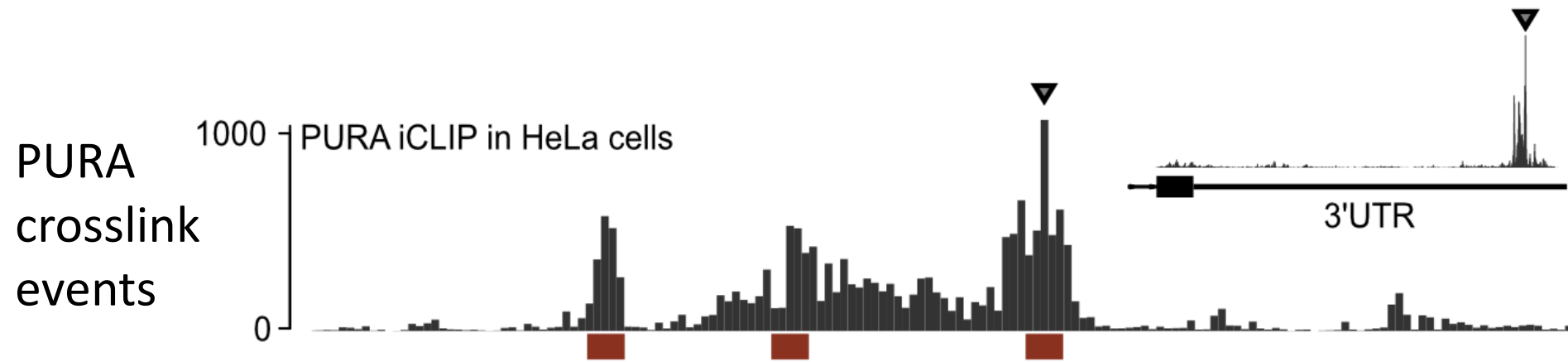
iCLIP can be used to assay all RNAs bound by an RNA-binding protein



We can extract PURA binding sites from crosslink peaks



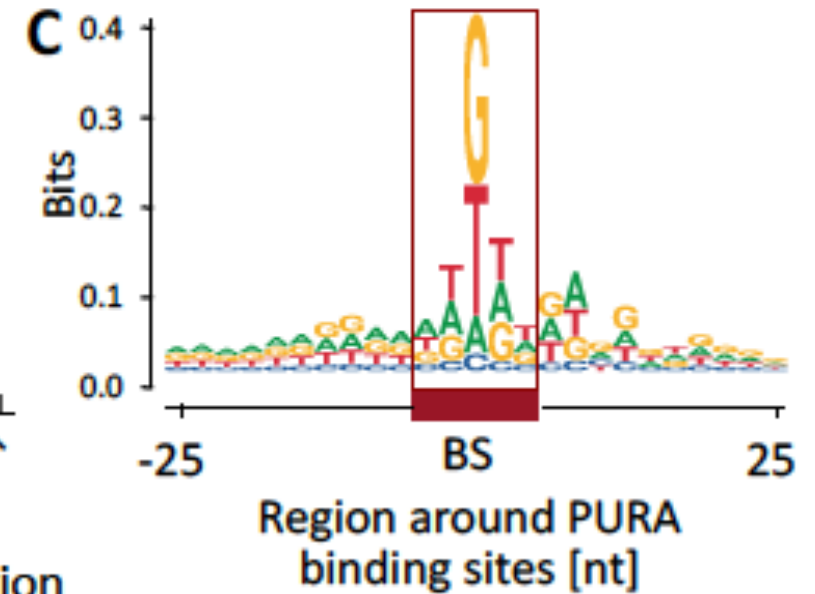
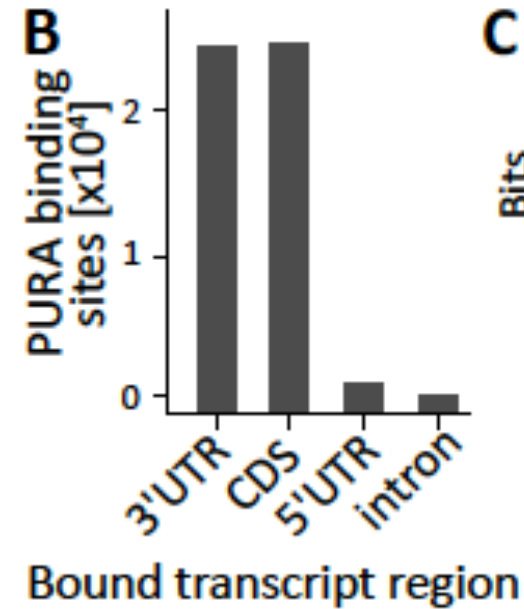
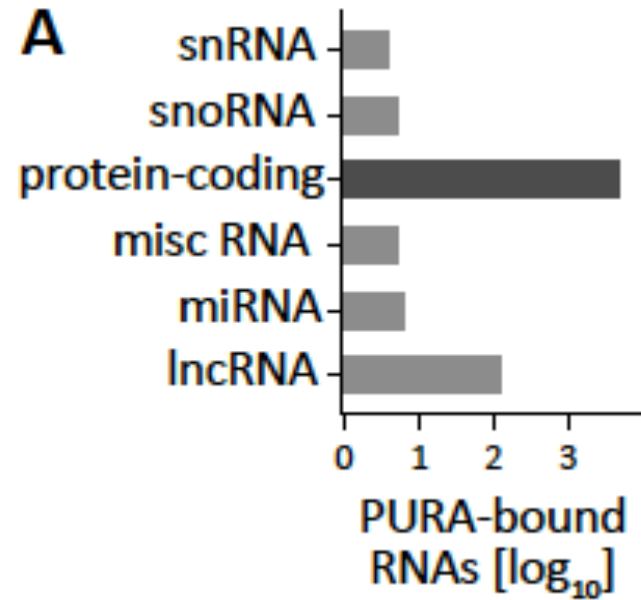
PURA is a global RNA binder



PURA binds throughout the transcriptome:

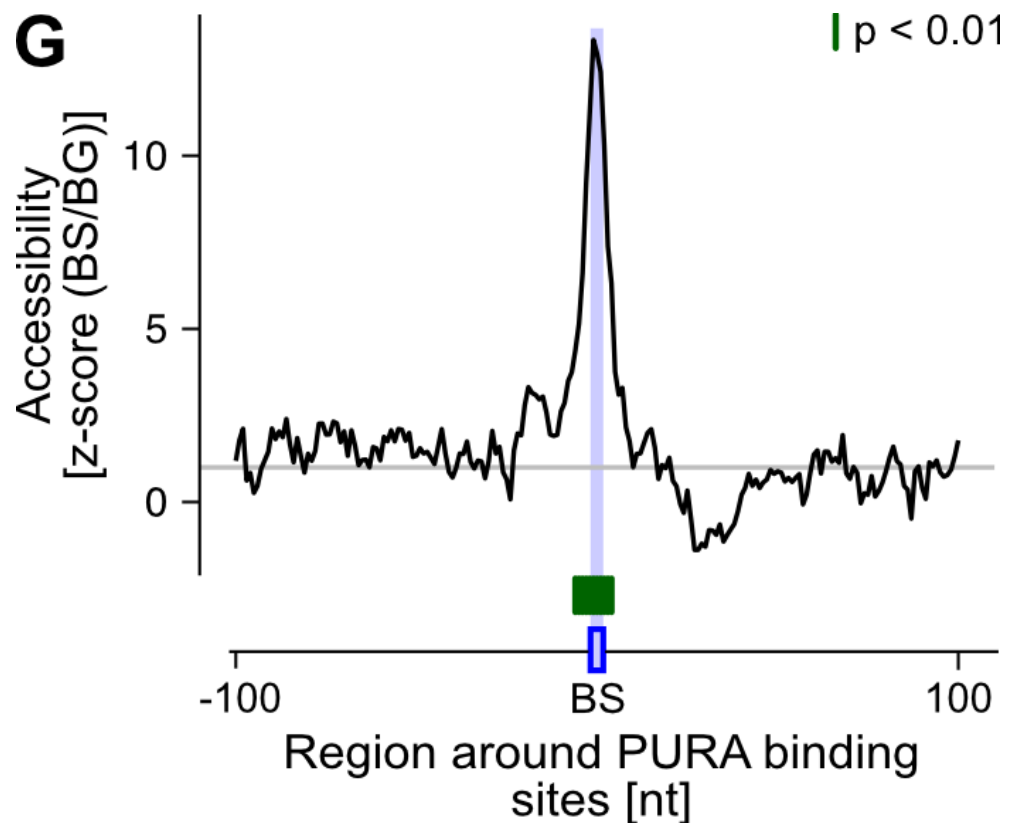
- 57,674 PURA binding sites
- on 4,880 RNAs

PURA preferentially binds in the 3'UTR and CDS of protein-coding genes

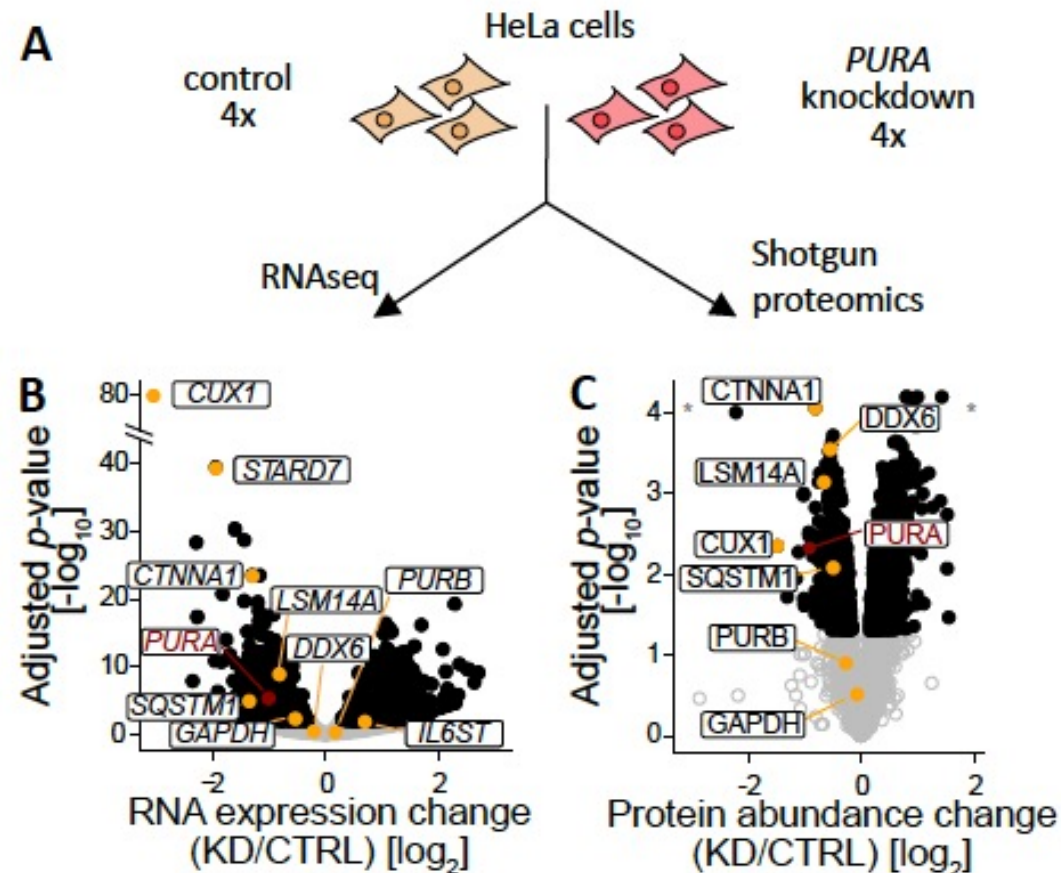


PURA binding sites are single stranded

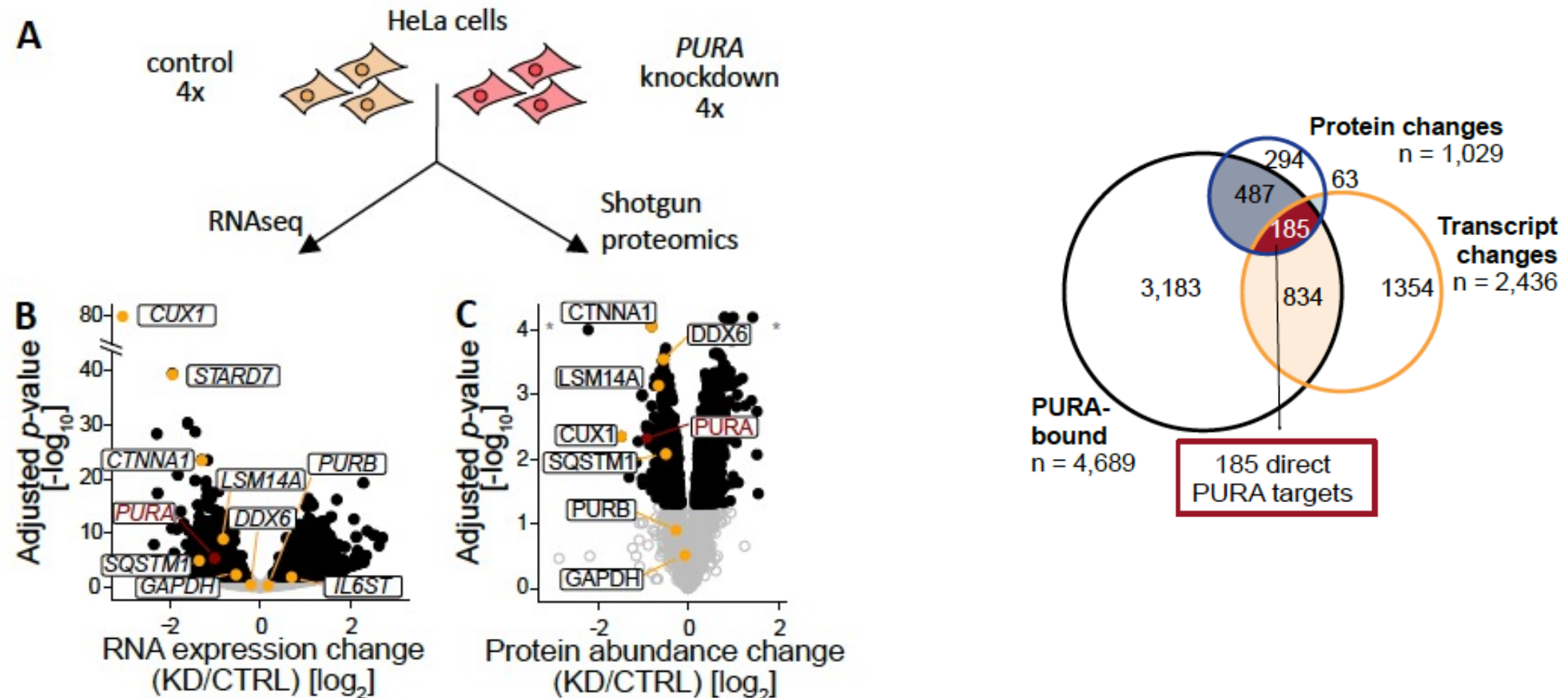
- RNAplfold
- Unpaired probability
- sliding window approach
- Z-score of bound sequence over random sequences



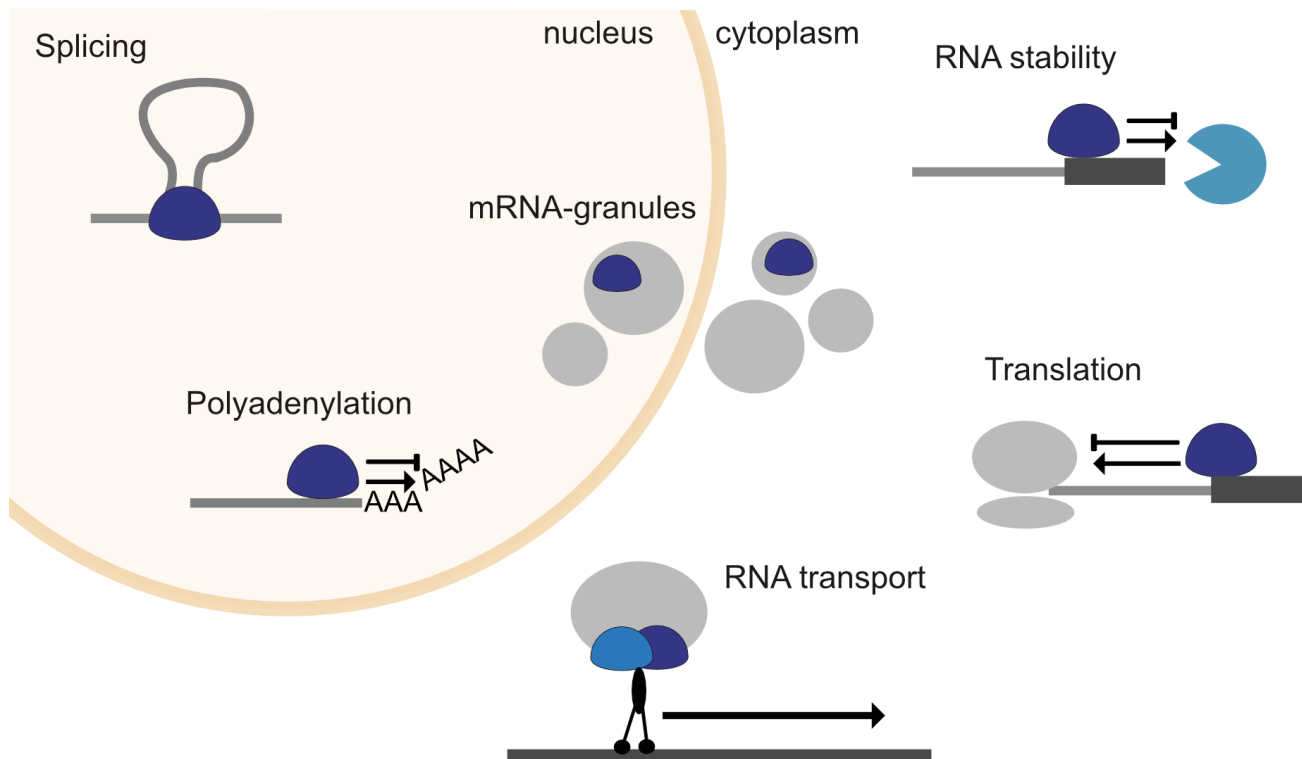
PURA binds and regulates 1019 target RNAs and 672 target proteins



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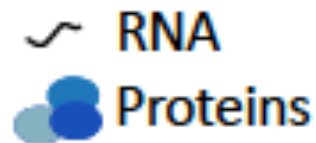
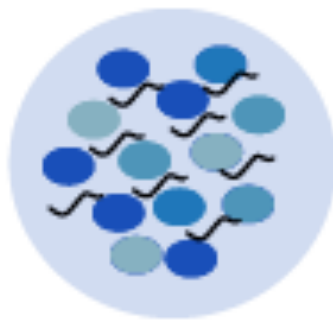


Cellular functions of RNA-binding proteins

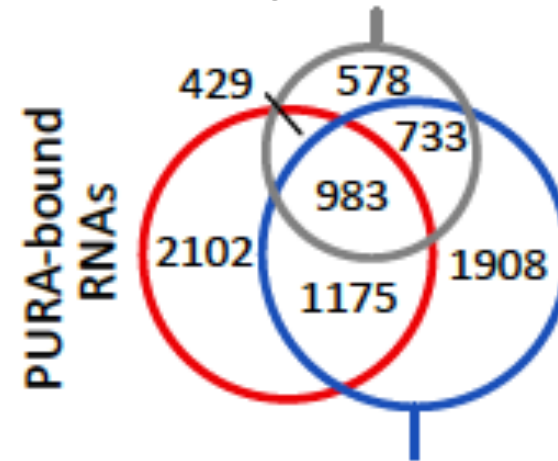


PURA bound targets are enriched in cytoplasmic granules

Cytoplasmic Granule



Stress granule transcriptome (Khong et al 2017)



Processing body transcriptome (Hubstenberger et al 2017)

Khong *et al* (2017): The stress granule transcriptome reveals principles of mRNA accumulation in stress granules.
Hubstenberger *et al* (2017): P-Body purification reveals the condensation of repressed mRNA regulons.

PURA localizes to P-bodies and these are depleted in PURA knockdown

