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PAPER OF THE MONTH • AUGUST 2023

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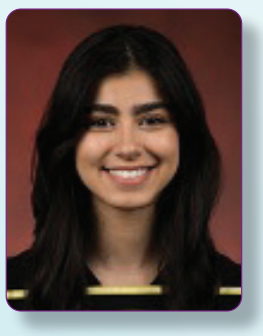

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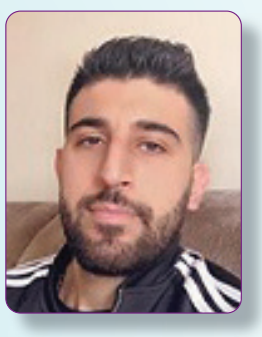

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THE EMBO JOURNAL

The EDC4-XRN1 interaction controls P-body dynamics to link mRNA decapping with decay

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Deadenylation-dependent mRNA decapping and decay is the major cytoplasmic mRNA turnover pathway in eukaryotes. Many mRNA decapping and decay factors are associated with each other via protein–protein interaction motifs. For example, the decapping enzyme DCP2 and the 5'–3' exonuclease XRN1 interact with the enhancer of mRNA-decapping protein 4 (EDC4), a large scaffold that has been reported to stimulate mRNA decapping. mRNA decapping and decay factors are also found in processing bodies (P-bodies), evolutionarily conserved ribonucleoprotein granules that are often enriched with mRNAs targeted for decay, yet paradoxically are not required for mRNA decay to occur.

The depletion of EDC4 has been linked to a loss of mRNA-decapping activity and decay. Therefore, we hypothesized that increasing cellular EDC4 levels might enhance the decay of a miRNA-targeted reporter.

In this study, we show that disrupting the EDC4-XRN1 interaction or altering their stoichiometry inhibits mRNA decapping, with microRNA-targeted mRNAs being stabilized in a translationally repressed state. Importantly, we demonstrate that this concomitantly leads to larger P-bodies that are responsible for preventing mRNA decapping. Taken together, these data demonstrate that the interaction between XRN1 and EDC4 regulates P-body dynamics to properly coordinate mRNA decapping with 5′–3′ decay in human cells.

In conclusion, our results show that P-bodies dynamically regulate mRNA decapping in response to changes in decapping complex stoichiometry and association. Moreover, our work suggests that P-bodies buffer stress granule formation and support cellular fitness in the absence of XRN1. Future research will be needed to understand how P-bodies can compensate for disrupted 5′ to 3′ decay to support cellular viability and when this may occur.

https://doi.org/10.15252/embj.2023113933