Cell
Leading Edge

CellPress

Preview

UTR-ly unexpected: RNA chaperones tame intrinsically disordered proteins

Miriam Linsenmeier[1] and James Shorter[1,*]
[1]Department of Biochemistry and Biophysics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
*Correspondence: jshorter@pennmedicine.upenn.edu
https://doi.org/10.1016/j.cell.2026.06.023

How do cells ensure that complex, multidomain proteins fold correctly? Luo et al. reveal a self-contained solution. The 3′ UTR of an mRNA co-translationally chaperones the protein it encodes, preventing intrinsically disordered regions from making inappropriate contacts. This functionality, localized to mesh-like condensates, challenges Anfinsen's dogma and opens therapeutic possibilities.

Proteins must navigate complex conformational energy landscapes, progressing through ordered native-like intermediates to achieve stable, functional structures.[1] Molecular chaperones are highly conserved (HC) proteins that assist this process co- and post-translationally by preventing kinetic trapping of polypeptide chains in misfolded, nonfunctional states.[2] Yet, ~70% of human proteins contain intrinsically disordered regions (IDRs) of 30 or more residues, which present a very different challenge.[3] Rather than converging on a single stable structure, IDRs occupy heterogeneous, dynamic conformational ensembles governed by shallower energy landscapes with many local minima.[3] How cells safeguard the folding of complex, multidomain proteins containing long IDRs has remained poorly understood. Now, in a landmark study in this issue of *Cell*, Luo et al. reveal that the 3′ untranslated region (UTR) of an mRNA co-translationally chaperones the protein encoded by that same transcript, guiding folding to enable full biological activity.[4]

Luo et al. begin with a striking observation.[4] Among the ~2,700 human mRNAs with HC 3′ UTRs, the encoded proteins are strongly enriched for long IDRs bearing short regions of clustered hydrophobic residues, termed hydrophobic clusters (HPCs). These mRNAs predominantly encode transcription factors and chromatin regulators, including MYC, UTX, and JMJD3. When expressed from mRNA lacking the native 3′ UTR, these proteins are produced at normal levels and localize correctly yet show markedly reduced activity. Conversely, restoring the 3′ UTR in the mRNA restores full activity without any change in protein abundance. Thus, primary sequence alone, as enshrined in Anfinsen's dogma,[1,2] is insufficient for the biogenesis of fully active versions of these proteins in human cells.

Mechanistically, Luo et al. scrutinize JMJD3, an H3K27me3 demethylase composed of a long N-terminal IDR and a structured C-terminal JmjC catalytic domain. In-cell crosslinking followed by mass spectrometry reveals a remarkable 3′ UTR-dependent difference in JMJD3 conformation. When translated from a 3′ UTR-containing mRNA, two-thirds of unique intramolecular crosslinks involve IDR-IDR contacts, whereas translation from a 3′ UTR-lacking template alters this pattern toward IDR-folded domain contacts. A small regulatory region within the IDR containing a positively charged RNA-binding region flanked by HPCs accounts for the majority of crosslinks. When HPCs are mutated or the IDR is deleted entirely, JMJD3 becomes fully active even without the 3′ UTR, pinpointing HPCs as the culprit driving misfolding. Biochemical reconstitution confirms that RNA-IDR binding is necessary and sufficient to shift domain interaction preference from IDR-folded domains toward IDR-IDR contacts, recapitulating the cellular data. The 3′ UTR shifts JMJD3 nascent chains from disome-associated states toward monosomal ones, providing evidence that these conformational effects arise during translation. Notably, the 3′ UTR-mediated chaperoning of JMJD3 is critical for proper differentiation of cardiomyocytes.[4]

Where does this chaperone activity operate? HC 3′ UTRs are adenine-uracil (AU)-rich, conferring high RNA valency that drives enrichment of their mRNAs in mesh-like cytoplasmic condensates.[5,6] Strikingly, 91% of HC 3′ UTR-containing mRNAs localize to these condensates, compared with only 60% of mRNAs with non-conserved 3′ UTRs. The condensate-enriched RNA-binding protein TIAL1 is required for full 3′ UTR-dependent chaperone activity, suggesting the mesh-like condensate environment is an active folding compartment.[4] Thus, the mRNA multitasks. The coding sequence encodes the protein, and the 3′ UTR draws the transcript into a folding compartment and chaperones the IDR so the JmjC domain folds correctly (Figure 1).

These findings add to a growing body of evidence that RNA plays surprisingly active roles in proteostasis beyond canonical functions in transcript stability, localization, and translation. For example, G-quadruplex-containing small RNAs catalyze protein folding by reshaping the energetic landscape of folding intermediates, likely by stabilizing on-pathway conformations.[7] The long non-coding RNA MALAT1, induced during hypoxia, assembles splicing factors and RNA polymerase II near nuclear speckles to facilitate alternative splicing, illustrating how RNAs can organize entire molecular machines within condensate-like environments.[8] Together with the 3′ UTR chaperone mechanism described by Luo et al., these examples reveal an emerging principle: RNAs and proteins collaborate and safeguard each other to enable cellular function in ways we are only beginning to appreciate.

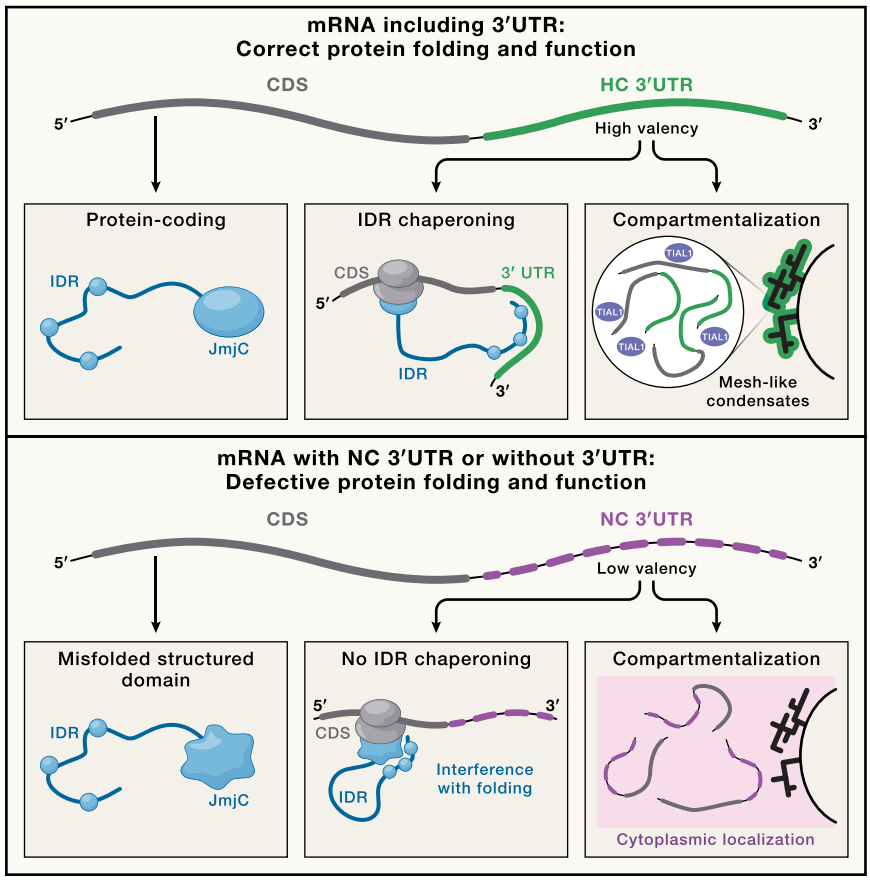

Figure 1. mRNA 3′ UTRs can act as co-translational chaperones for proteins with long IDRs

Top: mRNAs that contain a protein-coding sequence (CDS) and a highly conserved (HC), high-valency AU-rich 3′ UTR are enriched in mesh-like cytoplasmic condensates containing RNA-binding proteins such as TIAL1 (purple ovals). During translation in this environment, the 3′ UTR loops back to engage hydrophobic clusters (HPCs, blue dots) in the JMJD3 IDR, blocking aberrant contacts with the nascent JmjC domain and yielding a properly folded, fully active demethylase. Although illustrated as interaction between the nascent protein and the 3′ UTR of the same mRNA being translated, interaction with the 3′ UTR of a neighboring mRNA within the condensate cannot be excluded.

Bottom: mRNAs with a CDS and a non-conserved (NC), low-valency 3′ UTR or those lacking a 3′ UTR remain in the open cytosol. In this context, HPCs in the IDR inappropriately interact with the folding JmjC domain, producing a misfolded JMJD3 with reduced H3K27me3 demethylase activity.

This work also establishes a compelling conceptual parallel with strategies to mitigate aberrant aggregation of RNA-binding proteins with IDRs in neurodegenerative disease. Short RNA chaperones (25–34 nucleotides) derived from human 3′ UTRs dissolve aberrant cytoplasmic aggregates of TDP-43 and FUS, restore nuclear localization, and mitigate neurodegeneration in model systems.[9,10] These therapeutic RNAs act post-translationally, engaging structured RNA-recognition motifs to exert allosteric effects on appended IDRs, whereas the 3′ UTR chaperones described by Luo et al. operate co-translationally to prevent misfolding during biogenesis. Intriguingly, one short RNA chaperone against TDP-43, Clip34, is derived from the 3′ UTR of the *TARDBP* transcript,[9,10] raising the possibility that in the endogenous 3′ UTR context, Clip34 may chaperone nascent TDP-43 upon emergence from the ribosome. We suggest that RNA-based modulation of IDR conformation is a broad biological principle that is operative during normal protein biogenesis and amenable to therapeutic exploitation to reverse disease-associated aggregation.

Many questions lie ahead. Why have cells evolved an RNA-based co-translational mechanism for HPC-containing IDRs rather than delegating this task to canonical molecular chaperones? The dynamic, malleable nature of RNA and IDRs may allow more versatile engagement of labile folding intermediates than protein chaperones permit. Whether mutations in HC 3′ UTRs, increasingly cataloged in cancer genomes, compromise RNA chaperone activity and contribute to pathological protein dysfunction is entirely unexplored. Finally, a practical implication should not be overlooked. Expression constructs to study IDR-containing transcription factors and chromatin regulators should include their native 3′ UTRs to produce fully active protein, a caveat that may alter interpretations across decades of experimental work.

Luo et al. show that mRNA is more than a messenger. Crick's central dogma described a clean unidirectional flow of information from DNA to RNA to protein, with each step discrete and separable.

What this study makes clear is that the RNA-to-protein transition is far more entangled than that elegant framework anticipated. The very RNA carrying the blueprint for a protein also directly chaperones the protein into the functional form. As more such RNA-protein collaborations emerge, the final step of the central dogma may need to be reframed not as a relay race where the baton is passed and forgotten but rather as an ongoing conversation between RNA and protein.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Englander, S.W., Mayne, L., Kan, Z.Y., and Hu, W. (2016). Protein Folding-How and Why: By Hydrogen Exchange, Fragment Separation, and Mass Spectrometry. Annu. Rev. Biophys. *45*, 135–152. https://doi.org/10.1146/annurev-biophys-062215-011121.

2. Balchin, D., Hayer-Hartl, M., and Hartl, F.U. (2020). Recent advances in understanding catalysis of protein folding by molecular chaperones. FEBS Lett. *594*, 2770–2781. https://doi.org/10.1002/1873-3468.13844.

3. Holehouse, A.S., and Kragelund, B.B. (2024). The molecular basis for cellular function of intrinsically disordered protein regions. Nat. Rev. Mol. Cell Biol. *25*, 187–211. https://doi.org/10.1038/s41580-023-00673-0.

4. Luo, Y., Zhong, Y., Basu, S., Wu, M.C., and Mayr, C. (2026). mRNA 3' UTRs chaperone intrinsically disordered regions to control protein activity. Cell *189*, 4619–4636.e16. https://doi.org/10.1016/j.cell.2026.05.017.

5. Ma, W., and Mayr, C. (2018). A Membraneless Organelle Associated with the Endoplasmic Reticulum Enables 3'UTR-Mediated Protein-Protein Interactions. Cell *175*, 1492–1506.e19. https://doi.org/10.1016/j.cell.2018.10.007.

6. Ma, W., Zhen, G., Xie, W., and Mayr, C. (2021). In vivo reconstitution finds multivalent RNA-RNA interactions as drivers of mesh-like condensates. eLife *10*, e64252. https://doi.org/10.7554/eLife.64252.

7. Huang, Z., Ghosh, K., Stull, F., and Horowitz, S. (2025). G-quadruplexes catalyze protein folding by reshaping the energetic landscape. Proc. Natl. Acad. Sci. USA *122*, e2414045122. https://doi.org/10.1073/pnas.2414045122.

8. Song, Y.J., Shinn, M.K., Bangru, S., Wang, Y., Sun, Q., Hao, Q., Chaturvedi, P., Freier, S.M., Perez-Pinera, P., Nelson, E.R., et al. (2026). LncRNA-splicing factor condensates regulate hypoxia-responsive pre-mRNA processing near nuclear speckles. Mol. Cell *86*, 1061–1080.e10. https://doi.org/10.1016/j.molcel.2026.02.014.

9. Copley, K.E., Mauna, J.C., Danielson, H.L., Chen, Q., Ozguney, B., Ngo, M., Xie, L., Smirnov, A., Davis, M., Mayne, L., et al. (2026). Short RNA chaperones promote aggregation-resistant TDP-43 conformers to mitigate neurodegeneration. Science *392*, eadv3301. https://doi.org/10.1126/science.adv3301.

10. Guo, L., Mann, J.R., Mauna, J.C., Copley, K.E., Wang, H., Rubien, J.D., Bergmann, C.A., Carey, J.L., Merjane, J., Ngo, M., et al. (2026). Defining RNA oligonucleotides that reverse deleterious phase transitions of RNA-binding proteins with prion-like domains. Mol. Cell *86*, 114–134.e10. https://doi.org/10.1016/j.molcel.2025.12.009.