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PHASE SEPARATION

Protein trafficking through TIGER domains

“ the TIGER domain facilitates 3' UTR-mediated protein–protein interactions that regulate protein trafficking at the ER ”

The 3' untranslated region (UTR) of mRNAs can serve as a platform for protein–protein interactions during mRNA translation at the endoplasmic reticulum (ER). For example, CD47 encoded by the long 3' UTR isoform of the CD47 mRNA (*CD47-LU*) but not that encoded by the short 3' UTR isoform (*CD47-SU*) interacts with the effector protein SET at the ER. This interaction requires the RNA-binding protein HuR and alters CD47 trafficking, resulting in higher plasma membrane CD47 levels. Now, Ma and Mayr show that a membraneless organelle at the ER establishes a permissive environment for 3' UTR-mediated protein–protein interactions.

As the SET–CD47 interaction occurs at the ER, the authors examined the subcellular localization of other RNA-binding proteins and found that TIS11B localizes to the perinuclear ER and forms an intertwining meshwork with a subdomain of the ER.

TIS11B is known to bind to AU-rich elements (AREs); the 3' UTR of *CD47-LU* contains 19 AREs, compared with 1 ARE in *CD47-SU* and importantly, *CD47-LU* but not *CD47-SU* significantly co-localizes with the TIS11B-labelled domain.

Furthermore, other ARE-containing mRNAs that encode membrane proteins also colocalize with TIS11B at the ER, as well as proteins such as HuR and the cytosolic chaperone HSC70, which may aid in the folding of membrane proteins translated in this region. Thus, TIS11B forms defined TIS granules that associate with an ER subdomain that the authors refer to as the TIS granule–ER (TIGER) domain.

Knockdown of *TIS11B* expression reduced the SET–CD47-LU interaction and CD47 plasma membrane levels (but not overall CD47 levels). Thus, TIS11B is necessary for the 3' UTR-mediated cell surface localization of CD47. Importantly, overexpression of TIS11B but not of SET increased plasma membrane CD47-LU protein levels, suggesting that TIS11B facilitates the transfer of SET from the *CD47* 3' UTR to CD47-LU protein to facilitate its plasma membrane localization. Additionally, SET transfer to other membrane proteins also occurs in TIS granules in a 3' UTR-dependent manner, as shown for *CD274* (which encodes PDL1).

Because TIS granules form a distinct compartment, the most likely mechanism for their formation involves biomolecular condensation through liquid–liquid phase separation. Indeed, fluorescence recovery after photobleaching (FRAP) analysis of TIS11B indicated that TIS granules are gel-like, whereas FRAP analysis of SET, HuR and HSC70 showed that the biophysical properties of TIS granules differ from those of the cytoplasm. Furthermore, the authors showed by mutational analysis that TIS11B is the scaffold for TIS granules and that the charge pattern in TIS11B (a highly negative N-terminal half and a positive C-terminal half) drives the formation of TIS granules.

In conclusion, the TIGER domain facilitates 3' UTR-mediated protein–protein interactions that regulate protein trafficking at the ER.

Grant Otto

ORIGINAL ARTICLE Ma, W. & Mayr, C. A membraneless organelle associated with the endoplasmic reticulum enables 3' UTR-mediated protein–protein interactions. *Cell* <https://doi.org/10.1016/j.cell.2018.10.007> (2018)

FURTHER READING Banani, S. F. et al. Biomolecular condensates: organizers of cellular biochemistry. *Nat. Rev. Mol. Cell Biol.* **18**, 285–298 (2017)