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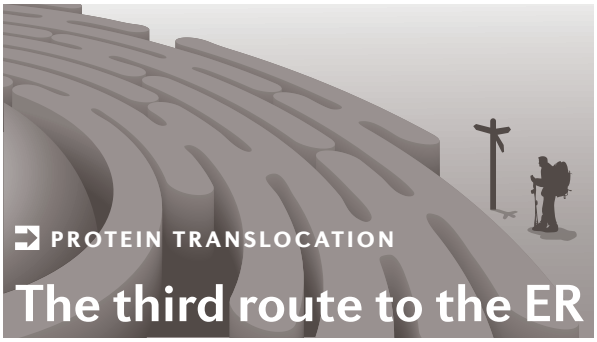

Targeting of proteins to the endoplasmic reticulum (ER) occurs co-translationally, through the signal recognition particle (SRP) pathway, or post-translationally, through the guided entry of tail-anchored proteins (GET) pathway in yeast and the homologous transmembrane recognition complex of 40 kDa (TRC40) pathway in mammals. Aviram *et al*. now identify a novel ER targeting pathway that functions in parallel with the SRP and GET pathways.

To identify novel factors involved in ER targeting, the authors analysed the subcellular localization of fluorescently tagged Gas1 (a protein that is targeted to the ER independently of SRP and only partially dependently on the GET pathway) in *Saccharomyces cerevisiae* mutants, searching for strains in which Gas1 was mislocalized. Gas1 accumulated in the cytosol instead of being localized to the cell wall and vacuoles in three previously uncharacterized mutants. As substrates that depend on the SRP pathway for translocation were unaffected in these mutants, they named the respective proteins Snd1–3 (for SRP-independent targeting). Further analysis indicated that Snd proteins function in a single targeting pathway (SND pathway), as they interacted with each other and with the ER translocation machinery.

Using proximity-specific ribosome profiling, the authors found that in *snd* mutants, some transcripts were depleted from the ER membrane, suggesting that the SND pathway has the potential to function co-translationally. Transcripts that encode proteins with an amino-terminal transmembrane domain (TMD), which are preferential SRP substrates, were not affected, whereas transcripts encoding proteins with more downstream TMDs were depleted. This indicates that the position of the first TMD influences the involvement of the SND pathway in ER targeting. Indeed, targeting of proteins with downstream TMDs was impaired in *snd* mutants.

Furthermore, Snd proteins were necessary for the viability of yeast with reduced SRP function, and their overexpression rescued the viability of yeast with complete SRP loss. Similarly, concomitant loss of SND and GET components was lethal in yeast; it also impaired translocation of proteins that are delivered to the ER post-translationally. Thus, the SND pathway collaborates with both SRP and GET pathways and can function as their backup.

Together, this study identified the SND pathway as a new component of the ER targeting system, and showed that the SND, SRP and GET pathways work in parallel to ensure efficient ER targeting of a wide range of proteins.

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ORIGINAL ARTICLE Aviram, N. *et al.* The SND proteins constitute an alternative targeting route to the endoplasmic reticulum. *Nature* **540**, 134–138 (2016)