Nature Reviews Molecular Cell Biology | AOP, published online 19 June 2013; doi:10.1038/nrmIB1

IN BRIEF

RNA DECAY

NMD broadens its reach

mRNAs carrying premature termination codons are targeted for degradation by the nonsense-mediated decay (NMD) pathway. Previous work had suggested that in mammals NMD is restricted to the pioneer round of translation and thus to transcripts bound to the cap-binding complex (CBC). This would suggest that mRNAs associated with the eukaryotic translation initiation complex eIF4F (which replaces the CBC after export of mature transcripts to the cytoplasm) are immune to this pathway. Two studies have used various approaches to test this theory in human cells. Both groups observed that transcripts associated with eIF4E (the cap-binding component of eIF4F) were susceptible to NMD, and that their degradation kinetics were comparable to that observed with CBC-bound mRNAs. So, it seems that NMD can target mRNAs that are actively being translated in human cells, which is consistent with previous observations in yeast.

ORIGINAL RESEARCH PAPERS Durand, S. & Lykke-Andersen, J. Nonsense-mediated mRNA decay occurs during eIF4F-dependent translation in human cells. *Nature Struct. Mol. Biol.* **12**, 551–564 (2013) | Rufener, S. & Mühlemann, O. eIF4E-bound mRNPs are substrates for nonsense-mediated mRNA decay in mammalian cells. *Nature Struct. Mol. Biol.* **20**, 710–717 (2013)

POST-TRANSLATIONAL MODIFICATION

Setting limits on protein folding

Proper protein folding in the endoplasmic reticulum (ER) is mediated by chaperones. This can take multiple folding attempts, and Xu *et al.* now show that an *O*-mannosylation pathway is in place that tags proteins for degradation if they fail to fold within a certain time frame. They characterized this pathway by comparing the regulation of two GFP variants, one that folds slowly (ER-GFP) and one that is fast-folding. Misfolded proteins are known to be modified by *O*-mannosylation by the PMT1–PMT2 complex. This pathway also mediated the modification of ER-GFP specifically, and in *pmt1* or *pmt2* mutants ER-GFP folding was increased. Moreover, *O*-mannosylation impaired ER-GFP protein refolding *in vitro* and prevented association with the chaperone KAR2. This mechanism may therefore restrict how many rounds of protein folding can be attempted before a protein is instead targeted for degradation.

ORIGINAL RESEARCH PAPER Xu, C. *et al.* Futile protein folding cycles in the ER are terminated by the unfolded protein *O*-mannosylation pathway. *Science* **340**, 978–981 (2013)

PROTEIN METABOLISM

pH power over the proteasome

Proteasome activity can be regulated through its accumulation in cytoplasmic proteasome storage granules (PSGs). In yeast, PSGs assemble when glucose or other carbon sources are low, and this is thought to protect the proteasome during stress conditions. Peters *et al.* show that a functional vacuolar ATPase (v-ATPase) proton pump is necessary for normal kinetics of PSG formation and disassembly. Lower cytosolic pH due to impaired v-ATPase function resulted in faster-forming granules and slow release of the proteasome from the granules. Interestingly, low pH also promoted the formation of actin bodies, another type of yeast cytoplasmic granule that assembles during starvation. Thus, the authors propose that intracellular pH functions as a cellular signal for glucose sensing and granule formation.

ORIGINAL RESEARCH PAPER Peters, L. Z. *et al.* Formation and dissociation of proteasome storage granules are regulated by cytosolic pH. *J. Cell Biol.* **201**, 663–671 (2013)