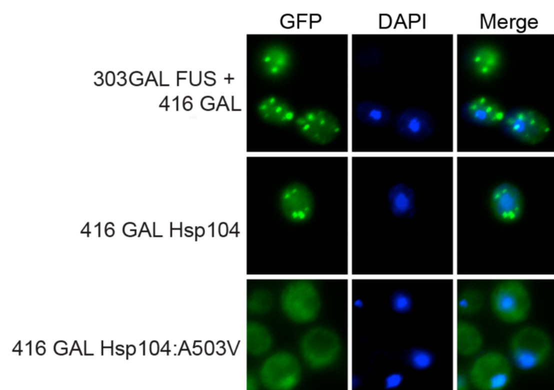
lipids and lipid families likely play important structural and signaling roles in the cell division process, and indicate that the cell has regulatory processes directing lipid biosynthesis and localization as it moves through its life cycle.

Eva J. Gordon, Ph.D.

DISAGGREGASES TARGET AGGREGATION DISORDERS



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Several neurodegenerative disorders, including Parkinson's disease and amyotrophic lateral sclerosis, are caused by protein misfolding. For certain proteins, misfolding can lead to the formation of neurotoxic protein aggregates; development of therapeutic strategies to target this destructive process has been a formidable challenge. Hsp104 is a protein chaperone that facilitates refolding of aggregated proteins in bacteria and yeast. Though the protein does not exist in higher animals, this "disaggregase" has been shown to synergize with other chaperones to solubilize misfolded proteins involved in human disease, albeit with limited efficacy. Now, Jackrel *et al.* (*Cell*, 2014, *156*, 170–182) report the reprogramming Hsp104 as a novel approach for targeting protein misfolding.

By mutating residues in either the small domain of nucleotide binding domain 1 or the helices of the middle domain of Hsp104, the authors identified several variants with enhanced disaggregase activity in yeast. Specifically, the mutants were capable of rescuing the toxicity caused by TDP-43, α-syn, or FUS, all proteins that are toxic when aggregated. In addition, the enhanced Hsp104 variants could untangle the protein aggregates and restore proper localization of the proteins in the cell. Moreover, when tested in a *Caenorhabditis elegans* model of Parkinson's disease, the variants conferred protection against α-syn toxicity in neurons. This study offers proof-of-principle that protein aggregates may be tractable therapeutic targets for protein misfolding disorders. In addition, it provides rationale for the development of engineered chaperones with enhanced disaggregase activity as potential new treatments for these devastating diseases.

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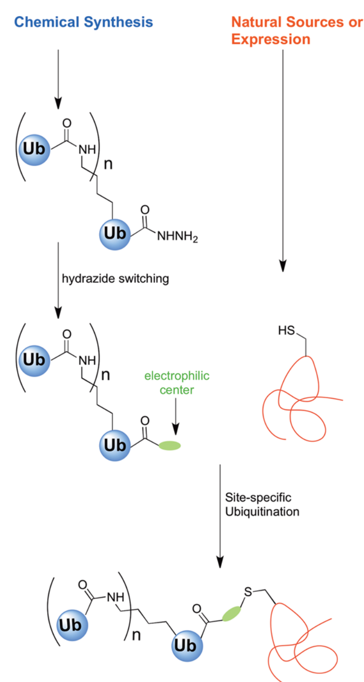
SYNTHETIC TOOLS FOR STUDYING UBIQUITINATION



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Eukaryotic cells modify proteins with a single or multiple copies of ubiquitin, providing molecular signals that regulate a variety of events such as protein degradation and localization and protein–protein interactions. But researchers have not had good ways to synthesize a range of ubiquitinated proteins and study their biological effects. Now Hemantha *et al.* report a non-enzymatic method to chemically modify expressed proteins with multiple copies of ubiquitin linked to each other (*J. Am. Chem. Soc.*, published online January 17, 2014; DOI: 10.1021/ja412594d).

In cells, ubiquitin forms an amide bond between its C-terminal glycine residue and the side chain nitrogen of a lysine residue on the modified protein, and polyubiquitination links C-terminal glycines of each ubiquitin with one of several lysines within the next ubiquitin molecule. Instead Hemantha *et al.* added an electrophilic center (generated from an acyl hydrazide) to the C-terminal glycine of ubiquitin produced using solid phase synthesis to site specifically label cysteine residues on expressed proteins. They also synthesized other modified ubiquitin molecules that they could mix and match to produce chains containing up to 4 ubiquitin moieties.

To demonstrate their tagging technique, the researchers chose α-globulin, which causes β-thalassemia when it accumulates in hemoglobin, and used the native cysteine residue in α-globulin for chemical conjugation. They successfully tagged α-globulin with ubiquitin moieties via disulfide and thioether bonds. The formation of thioethers using a maleimide was a faster and higher yielding reaction, and the researchers used that reaction to attach mono- and diubiquitin to α-globulin. (The larger ubiquitin chains reacted too slowly.)

Hemantha *et al.* then investigated how the di- and mono-ubiquitinated α-globulin behaved in a protein degradation study. Proteins that were dilabeled underwent degradation, while those with a single ubiquitin did not. Further optimization should

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