CHEMICAL BIOLOGY

Extracellular protein degradation on demand

A protein degradation platform enables the targeted depletion of extracellular and membrane-bound proteins.

Controlling the abundance of a protein of interest can be crucial to discovering its function in a cell, modulating specific cellular pathways, and even treating disease. A number of approaches have been developed that can rapidly, efficiently and sometimes reversibly reduce the abundance of a protein using various strategies for sequestration, downregulation or degradation. The strategies that involve degradation, however, have largely been limited to cytoplasmic proteins.

Carolyn Bertozzi and her research group at Stanford University developed a strategy for specifically degrading extracellular and membrane-bound proteins of interest. Their approach fills a gap in the methodological toolbox for controlled protein degradation, as these proteins represent roughly 40% of protein-encoding genes.

Their method for targeting these types of proteins involves lysosome-targeting chimeras they have named LYTACs. LYTACs are made up of a protein-targeting moiety (small molecule or antibody) fused to glycopeptide ligands that bind and activate the cation-independent mannose-6-phosphate receptor (CI-M6PR), a membrane protein that transports certain glycosylated proteins to lysosomes. Thus, LYTACs bridge a target protein with CI-M6PR, ultimately resulting in degradation of the target protein in the lysosome.

In proof-of-principle experiments, the researchers showed that LYTACs could improve uptake of NeutrAvidin-647, a fluorescently labeled, degradation-resistant protein, 5- to 6-fold over controls. Microscopy revealed that the targeted proteins colocalized with labeled lysosomes, as expected for proteins internalized via CI-M6PR. The researchers further demonstrated general applicability on a range of proteins, including epidermal growth factor receptor, CD71, and programmed death ligand 1 (PD-L1). As an added demonstration of LYTACs, the team used their method in a CRISPR interference screen, which revealed that the exocyst complex is essential for CI-M6PR-mediated cargo internalization.

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Published online: 1 September 2020
https://doi.org/10.1038/s41592-020-0952-3

Research paper
Banik, S. M. Lysosome-targeting chimaeras for degradation of extracellular proteins. *Nature* https://doi.org/10.1038/s41586-020-2545-9 (2020).