Protein Recycling, TPD, and Neurodegenerative Disease

Cells have two main strategies for degrading and recycling proteins:

1) The ubiquitin (Ub) proteosome system (UPS)
2) Autophagy.

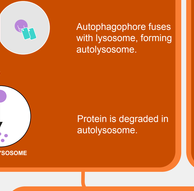
However, faults in proteins or these degradation systems can lead to neurodegenerative diseases, such as Parkinson's, Alzheimer's, and Huntington's disease.

Targeted protein degradation (TPD) is a therapeutic strategy that hijacks protein degradation pathways, which could potentially treat neurodegenerative diseases.

Protein Recycling Centre

Sorting Station: Ubiquitination of Proteins

Ubiquitination of proteins, where proteins are modified with ubiquitin (Ub), is a process that relies on a series of enzymes: E1, E2, and E3 (such as MDM2). Multiple Ub molecules can be added to proteins, creating diverse ubiquitin 'tags' that determine the fate of proteins.



Waste Processing Station: Protein degradation

Autophagy

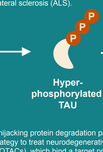
1) ULK1/Atg1 complex, PI3KC3 complex I — Autophagy is initiated.
2) Adapter (e.g. p62), LC3-I — Phagophore forms.
3) PE, LC3-II, p62 — AUTOPHAGOSOME — Phagophore elongated and matures, forming autophagosome.
4) Acid hydrolases — LYSOSOME — Autophagophore fuses with lysosome, forming autolysosome.
5) AUTOLYSOSOME — Protein is degraded in autolysosome.

UPS

1) PROTEASOME — Protein binds to proteasome.
2) Ubiquitin removed.
3) Protein is unfolded and degraded.

Interconnecting Pathways

Faulty proteins in the ER can activate UPS and autophagy.

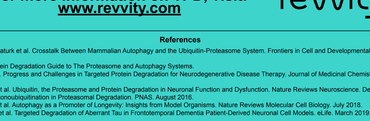


UPS and autophagy can be regulated by each other through protein degradation.

Waste Collection: Broken down protein products ready to be reused by cells

Neurodegenerative disease and TPD

Misfolded proteins–such as Tau and TDP-43–can clump together, forming aggregates that are toxic to cells. If found in neurons, these aggregates can lead to neurodegenerative diseases such as Alzheimer's Disease and amyotrophic lateral sclerosis (ALS).



TPD involves hijacking protein degradation pathways to clear pathological proteins—which may provide a therapeutic strategy to treat neurodegenerative diseases. For example, TPD can use PROteolysis TArgeting Chimeras (PROTACs), which bind a target protein and E3 ligase. The target protein is ubiquitinated and degraded.

For more information on TPD, visit: www.revvity.com

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