Protein homeostasis is critical for cell health.

Protein Degradation in Practice

The ubiquitin-proteasome system (UPS) is one of 2 primary means of protein degradation in cells (the other is lysosomal proteolysis). The UPS tags intracellular proteins for degradation with a small protein called ubiquitin by the E3 ligase enzyme complex. Ubiquitination targets proteins for degradation by the 26S proteasome, a large complex of enzymes that initiate target protein degradation.

Two Approaches to Targeted Protein Degradation

Scientists are exploring 2 approaches to promote the degradation of target proteins that would not otherwise be degraded by using 2 different types of redirecting molecules: Molecular Glues and LDDs (ligand-directed degraders, also called heterobifunctional agents).

By redirecting the UPS within a cell through the introduction of protein degradation agents, scientists may be able to target thousands of previously “undruggable” proteins or proteins that are chemically intractable by direct pharmacology.

Targeting a cell’s protein degradation system

Many current approaches to treating cancer focus on inhibiting specific pathways or proteins.

Proteins are fundamental to cellular function. Protein homeostasis is critical for cell health. Protein degradation is part of a cell’s protein homeostasis regulatory network that ensures unnecessary proteins are removed from the cellular environment when they are no longer needed or are damaged or faulty in some way. By effectively leveraging the body’s natural system to target and remove the pathogenic proteins and maintain homeostasis, scientists are exploring 2 approaches to promote the degradation of target proteins that would not otherwise be degraded by using 2 different types of redirecting molecules: Molecular Glues and LDDs (ligand-directed degraders, also called heterobifunctional agents). These approaches bring the E3 ligase and the intended target protein into close proximity.

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When a cell is unable to degrade abnormal and/or unnecessary proteins, these proteins can accumulate within the cellular environment. The accumulation of proteins within a cell is implicated in the pathogenesis of many diseases, including several malignancies and neurodegenerative disorders.

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Redirecting the UPS through the introduction of protein degradation agents may lead to detrimental effects. Only up to 70% of all human proteins are traditionally considered targetable or “drugable” given their cellular location and/or structural limitations.

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