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Targeted degradation of NTAQ1 using a cereblon molecular glue to study the N-degron pathway

Abstract:

The N-degron, or N-end rule, pathway facilitates selective proteolysis determined by N-terminal residues, known as degrons. As a critical part of the ubiquitin-proteasome system, this pathway affects numerous cellular processes including protein quality control, regulation of gene expression and DNA repair, and response to environmental stress. Its ability to regulate these processes makes it an attractive target for anti-tumor therapies.

N-terminal glutamine amidase 1 (NTAQ1) is a key component of the N-degron pathway. It hydrolyzes Nterminal glutamine to glutamate, enabling subsequent arginylation by ATE1. This modification results in recognition by E3 ligases, leading to ubiquitination and proteasomal degradation. Although previously deemed undruggable, we identified a selective cereblon (CRBN) based molecular glue degrader of NTAQ1, called EM12-FS. In this study, we explore the effects of NTAQ1 degradation by EM12-FS on cellular viability and function.

Using cell-based assays, proteomics, and genomic approaches, we demonstrate that EM12-FS-mediated degradation of NTAQ1 leads to increased levels of RAD21 and p21. Furthermore, combining EM12-FS with certain targeted cancer therapies, including Palbociclib and Olaparib, enhances cellular response to these treatments. Targeted degradation of NTAQ1 by EM12-FS serves as a useful strategy for chemically probing the N-degron pathway. Advancing our understanding of this pathway may present new therapeutic opportunities.

Biography

Catherine Ingram is a fourth year student at Northeastern University (Boston, MA), where she majors in Cell & Molecular Biology and is a coxswain on the Women's Rowing Team. She completed her first coop at Takeda Pharmaceuticals in the fall of 2023 and is currently working at Center for Protein Degradation at Dana Farber Cancer Institute. As the Biology Co-op, she studies therapeutically relavent degrader and non-degrader molecular glues.