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A. Varshavsky, A. Bachmair and D. Finley

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The N-end rule of selective protein turnover and its implications [abstract only]

By A. Varshavsky, A. Bachmair and D. Finley
Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts, U.S.A.

When a chimeric gene encoding a ubiquitin:β-galactosidase fusion protein is expressed in the yeast *Saccharomyces cerevisiae*, ubiquitin is efficiently cleaved off the nascent fusion protein, yielding a deubiquitinated β-galactosidase (βgal). With one exception, this cleavage takes place irrespective of the nature of the amino acid residue of βgal at the ubiquitin–βgal junction. This result, in effect, allows one to expose different residues at the N-termini of the otherwise identical βgal proteins produced *in vivo*. The βgal proteins thus designed exhibit a striking diversity of *in vivo* half-lives, from more than 10h to less than 3 min, depending on the nature of the amino acid exposed at the N-terminus of βgal. The N-terminal location of an amino acid is essential for its effect on βgal half-life. The set of individual amino acids can thus be ordered with respect to the half-lives that they confer on βgal when present at its N-terminus (the 'N-end rule'). The known N-terminal residues in long-lived intracellular proteins from both prokaryotes and eukaryotes are exclusively of the stabilizing class as predicted by the N-end rule. In contrast, a majority of the N-terminal residues in compartmentalized (e.g. secreted) proteins are of the destabilizing class. The N-end rule may thus underlie both the diversity of protein half-lives *in vivo* and the selective destruction of otherwise normal but mis-compartmentalized proteins. The N-end may also account for the function of the previously described post-translational addition of single amino acids to protein N-termini. Thus the recognition of an N-terminal residue in a protein may mediate both the metabolic stability of the protein and the potential for regulation of its stability.