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Proteome-wide Analysis of Protein Carboxy Termini: C-Terminomics

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The sequence and nature of the amino (N) and carboxy (C)-termini of proteins provides important functional annotation of proteomes since their modification or truncation affects all proteins, often influencing protein fate and function. Although characterization of the N-terminus is relatively well studied, relatively little is known of such modifications of the C-terminus. Proteome-wide analysis of protein N-termini has recently become the focus of intense research effort providing information on protein isoforms, acetylation, the functional state of the protein, and can be used to identify protease cleavage sites. However, this development has not been complemented by similar progress towards the proteome-wide analysis of protein C-termini by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Present approaches employ anhydrotrypsin, a combination of LysC protease and amine-capture, carboxypeptidase ladder sequencing or diagonal electrophoresis. Generally, these techniques are not used for complex proteome samples and their application is restricted to samples consisting of only few proteins. We present a polymer-based approach for the enrichment of carboxy-terminal peptides from complex proteomes and their identification by liquid chromatography-tandem mass spectrometry. The workflow optionally incorporates isotopic labeling to distinguish and quantitatively compare carboxy-termini from different samples, thus enabling applications in protease substrate profiling.