Characterizing Modified Peptides by High-Resolution FAIMS Followed by Electron Transfer Dissociation

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Full characterization of proteins in living organisms, which is crucial to understanding biomedical processes, remains a stupendous analytical challenge. That especially holds for post-translational modifications, which influence the protein structure and thus function. The localization variants (isomers with identical PTMs on different residues) that commonly co-exist in vivo are particularly problematic. While electron transfer dissociation (ETD) has greatly advanced PTM analyses, only two variants in a mixture are detectable. Here we present a novel approach to resolve and identify variants: field asymmetric waveform ion mobility spectrometry (FAIMS) coupled to ETD. We implemented that on a Thermo LTQ XL ion trap mass spectrometer employing a custom high-definition FAIMS system using helium/nitrogen gas buffers. The resulting broad variant separations allow analyses of complex variant mixtures for small and medium-sized peptides. The method is demonstrated for the phosphopeptides from the tau-protein relevant to Alzheimer's and the D- and L- stereoisomers of neuropeptides.