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Signal Amplification-Enabled Ion Mobility-Mass Spectrometry (SAIMS): A General Strategy for the Discovery of Mass-Remaining Protein Modifications

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Commentary

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DESCRIPTION

The mission of protein Post-Translational Modification (PTM) identification and quantification has driven enormous, community-wide efforts towards technological advancements in Mass Spectrometry (MS)-centered techniques and strategies. To be noted, traditional PTMs generally decorate proteins with certain chemical groups which results in known mass shift. However, it is equally or even more challenging to dissect mass-remaining PTMs as the established workflows for traditional PTMs cannot be directly adopted, which is limited by nature of MS for mass differentiation. Protein "StereoChemical" Modification (SCM) is a unique type of low-abundance mass-remaining PTMs associated with many human diseases, which frequently results in the conformational transition of backbone amino acid from the L- to D-form. Ion Mobility-Mass Spectrometry (IM-MS) provides the capability of ion size, shape and conformation-based separation dimension, and embraces the potential in fast identification and rapid separation of protein SCMs analysis. Yet, it is still not well demonstrated for its application in SCM identification at large scale, primarily due to the limitations in structural resolution of current commercially available IM-MS instrumentations and in the lack of compatible data searching algorithm specifically designed for isomeric ion species.

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In order to resolve minor structural differences induced by SCM at few sites, we previously proposed a Signal Amplification-enabled IM-MS (SAIMS) strategy based on metal-enhanced chiral amplification: (Nat. Commun. 2019, 5038). The key to effective differentiation of SCM relies on the specific, structure-reflective metal-target peptide/protein binding, which frequently requires the use of copper and other biologically meaningful metals. In this regard we can resolve most SCMs at small peptides, e.g. traditional neuropeptides of ~ 10 residues with single D-residue at the N terminus. To extend the capacity of chiral recognition, we recently introduced a multi-dimensional signal amplification strategy: (Anal. Chem. 2023, 2221) modifying from the one-dimension version (metal-based amplification). The updated workflow was tentatively named as, multi-component-enabled multidimensional ion mobility-mass spectrometry (3M-SAIMS), aiming to facilitate the accurate quantification or unambiguous identification of peptide stereoisomers. The 3M-SAIMS strategy comprises the powerful mathematical tools of Continuous Wavelet Transform (CWT) and Gaussian fitting-enabled peak splitting. 3M means 1) multi-metal specific complexation, 2) multi-processing algorithm and 3) multi-IM instruments (TWIMS, DTIMS, TIMS etc.) With a bunch of examples, we observed effectively improved resolution and sensitivity for the detection and quantification of SCMs by over five folds, including those present at low levels. In a most recent study: (Chem. Sci. 2023, 5936) we further testified the possibility of the multi-dimensional signal amplification strategy in resolving a relatively more complicated SCM system, D-isomerization of Asp- and Ser-residues at intact amyloid peptide (Aβ42). In this case, a novel structural dissection regime for SCM was constructed based on IM-MS-guided replica exchange molecular dynamic simulation. Resultantly, tentative gas-phase structural models were established for a series of multi-conformer species with only less than 0.5% difference in Collisional Cross-Section (CCS) of a 42-residue protein, which represents the highest structural resolution as far as we know for protein SCM to date.

Along with the efforts from Sweedler group (UIUC), Raskatov group (UC Santa Cruz), Julia group (UC Riverside), Li group (UW-Madison), LimsLab (Nankai University) and some others, we believe that although the discovery of mass-remaining PTMs like SCM is still in its infancy from the proteome-wide perspective, we are more than anxious to see its continuous breakthrough in the next five to ten years with the international support across multi-funding agencies. To continue with the SAIMS-based study on SCMs, we envision that further methodological development and innovative applications are still urgently needed to achieve more general results across the whole human proteome atlas. Facing this direction, one of the hurdles we have to solve is how to extend the above-mentioned SAIMS workflow to an untargeted mode that is applicable to profiling large-scale peptide and protein species. In a recent experiment,

we found that the established SAIMS workflow not only can be applied to resolve CCS signal, but also can be directly used to deconvolute chromatograph signal for SCM separations in a relatively complex case. The LC trace from five groups of SCM peptides (WT/dS- α Syn81-93, WT/dS- α Syn123-135, WT/dS, WT/dS-SST and WT/dS/dD/dDdS-p53) comprising binary and quaternary stereoisomers, has been significantly polished by utilizing CWT and GA algorithms, resulting in the greatly improved resolution by ~ 5 times to an extent of baseline separation for all SCMs. This series of preliminary experiment represent the most recent effort on the untargeted signal amplification mode for SAIMS. Looking into the future, advanced algorithm and further instrumental upgrade are two effective directions this community should pursue to finally achieve the goal of SCM discovery at the whole human proteome scale.

In summary, the SAIMS strategy of a novel, instrument modification-free analytical framework, incorporating CWT and Gaussian fitting, represents a valuable analytical tool for the identification, quantification, and characterization of stereoisomers in peptides and proteins, and has the potential to greatly enhance our understanding of the roles and functions of peptide and protein SCMs in health and disease, and may lead to the development of new therapeutics for a variety of human disorders.

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