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In Situ Peptide Identification by Parallel-Accumulation-Serial Fragmentation Supported MALDI MS/MS imaging: A Tool for Spatial Proteomics in Complex Disease Tissues

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Spatial proteomics by matrix-assisted laser desorption/ionization (MALDI) imaging enables rapid, label-free peptide analysis directly from tissue sections. However, in situ peptide identification remains a major challenge, limiting the broader utility of this technique. In this study, we present a novel workflow that integrates Trapped Ion Mobility Spectrometry-based Parallel Accumulation–Serial Fragmentation into MALDI imaging to enable multiplexed MS/MS imaging and MASCOT peptide-to-spectrum matching for spatial peptide identification. We demonstrate the feasibility of this pipeline across three distinct samples: a tumor xenograft model, mouse kidney tissue, and an amyloidosis tissue microarray (TMA) comprising different subtypes. In each case, iprm-PASEF enabled the identification of multiple tryptic peptides in a single imaging experiment, with spatially resolved fragment ion maps and identifications corroborated by LC-MS/MS and fragment colocalization. In the TMA, we successfully identified seven amyloidosis-associated peptides, including markers from vitronectin, apolipoprotein E, and transthyretin receptor, with clear spatial correlation to Congo red-positive deposits. These three tissue types, xenograft, kidney, and amyloidosis TMA, collectively illustrate the method's applicability to resolve peptide distributions and molecular characterization from complex physiological and pathological heterogeneous tissues. These findings underscore the promise of tryptic peptide MS/MS MALDI imaging for advancing spatial proteomics in oncology and pathology research, with potential applications in tumor characterization, microenvironment profiling, and treatment response studies, particularly when integrated with complementary omics and histological approaches, though further validation across different tissue samples is needed.

Preferred type of presentation

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