nature chemical biology

PRIMER

PUBLISHED ONLINE: 15 NOVEMBER 2010 | DOI: 10.1038/NCHEMBIO.490

Mass spectrometry for systems-level biological analysis

The ability of mass spectrometry (MS) to facilitate the investigation of exceptionally complex samples in a high-content, quantitative fashion has made this technique essential to the study of biomolecules. Advances in both instrumentation and analysis methods make possible the facile exploration of proteins, metabolites and their relationships within an organism. MS is critical to a variety of biological applications ranging from biomarker discovery to whole cell and tissue imaging. The technique's ability to facilitate investigation of whole biological systems instead of only single components will continue to make MS a fundamental bioanalytical tool. In this Primer, I illustrate the range of applications enabled by MS-based methods using three examples that also highlight the ability of MS to provide a comprehensive view of the interrogated system.

MS-based proteomics is essential for global protein analysis of an organism, for example, to characterize disease-associated biochemical pathways, map post-translational modifications or assemble multiprotein networks. Myriad proteomics methods exist, including quantitative approaches requiring incorporation of stable isotopes and chemical labeling strategies such as activity-based protein profiling (**top**).

Detection of proteins and small molecules also facilitates MS-based imaging by mapping the distribution of proteins, metabolites and drugs in cell and tissue samples (**bottom right**). Matrix-assisted laser desorption-ionization (MALDI) is a common tool for these studies, but many other sensitive techniques have also emerged. The final MS application highlighted here is the visualization of inter- and intra-protein interactions. Affinity purification can be combined with MS to examine protein complex composition. A number of tools to study native protein structures have also seen great utility (**bottom left**).

MS has facilitated the transition from single-target studies to systems-level exploration, dramatically increasing the rate of biomarker identification and validation of candidate targets. Moving forward, MS-based methods will remain critical to the development of a systems biology perspective of a disease state or organism, characterization of drug targets and pharmacological profiling. Additionally, the use of MS in clinical applications, such as diagnostics and imaging, will continually increase.

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COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

KEY RESOURCES

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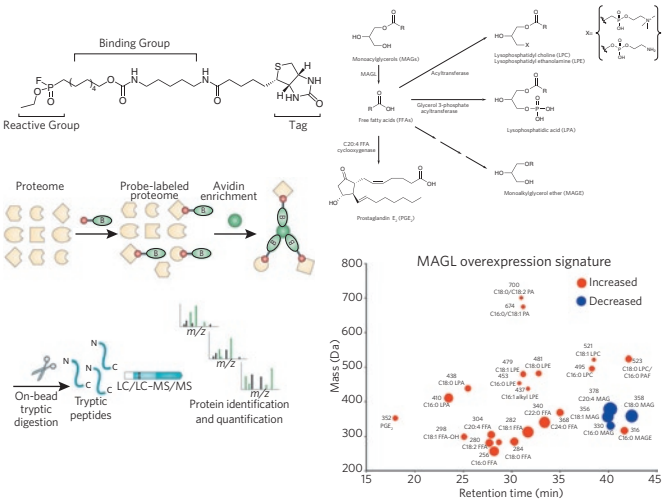
Biochemical network mapping of a cancer-associated enzyme



Combined application of proteomics and metabolomics facilitated the functional study of monoacylglycerol lipase (MAGL), an enzyme elevated in aggressive cancer cells and primary tumors. The role of this enzyme in cancer was identified using activity-based protein profiling (ABPP). ABPP labels specific enzyme classes in an activity-dependent manner to promote metabolic and signaling pathway assembly. The probe and strategy used for the profiling of serine hydrolases, including MAGL, are depicted (left). Following proteome labeling, biotin-tagged proteins are enriched and proteolyzed. The resulting peptides are analyzed with multidimensional protein identification technology (MudPIT), which incorporates multidimensional liquid chromatography (LC/LC) and tandem MS (MS/MS). Metabolomic profiling facilitated characterization of the metabolic network regulated by MAGL. Overexpression of this enzyme in several cancer cell lines resulted in heightened levels of free fatty acids and downstream metabolites and a decline in the substrates of MAGL, monoacylglycerols (metabolic network (top, right); lipidomic profile (bottom, right)). Parent masses (Da) of the metabolites are provided. Circle size indicates the relative magnitude of the metabolite change.
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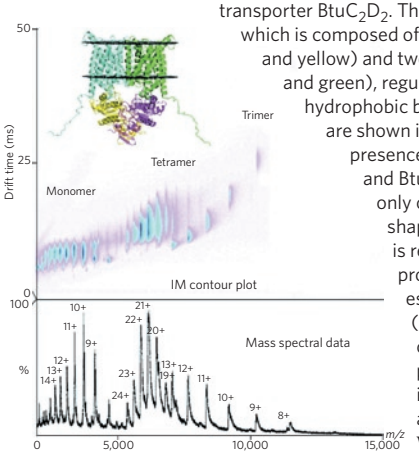
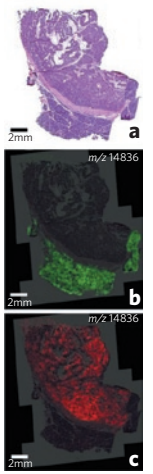
Visualization of a membrane-associated protein complex



Ion mobility (IM)–MS was used to examine the topology of the ATP-binding cassette (ABC) transporter $BtuC_2D_2$. This tetrameric membrane protein complex, which is composed of two ATP-binding cassettes ($BtuD_2$ in pink and yellow) and two transmembrane subunits ($BtuC_2$ in blue and green), regulates vitamin B12 uptake in bacteria. The hydrophobic boundaries of the transmembrane regions are shown in black. (bottom) Mass spectra show the presence of three states: tetramer, BtuC monomer and $BtuCD_2$ trimer. (top) IM separates ions not only on the basis of *m/z* but also based on their shape and size. An arrival time distribution is recorded, which can be compared to protein ions of known structure, facilitating establishment of the collision cross-section (CCS) of an unknown. Protein models can be generated from the stability, packing, subunit stoichiometry and CCS information gathered in experiments such as this one.
Wang, S.C., *et al. J. Am. Chem. Soc.*, doi:10.1021/ja104312e.

In situ analysis of pancreatic tissue



Matrix-assisted laser desorption-ionization imaging mass spectrometry (MALDI-IMS)–derived images for comparison of pancreatic tissue. (**a**) Histological staining of the tissue sample was performed with a hematoxylin-eosin staining technique, which is widely used in medical pathology. (**b**) Image derived from detection of a species (*m/z* 14,836) that correlated with the noncancerous tissue area. (**c**) Image derived from detection of a species (*m/z* 13,777) that correlated with the cancerous tissue area.
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