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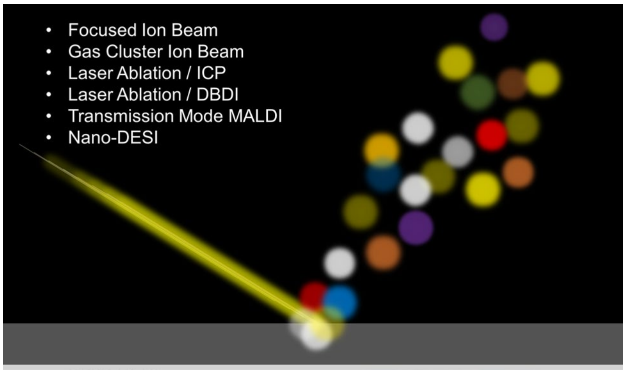
HIGHLIGHTS

Techniques for high spatial resolution in mass spectrometry

Eiji Sugiyama[1]



Mass spectrometry (MS) provides conclusive evidence regarding the chemical composition with high sensitivity. Typical recent example of the use can be found in the analysis of samples collected from the Ryugu (a primitive asteroid) [1], and the results provided numerous new insights on the relationships between the asteroids and meteorites. Although MS was only one of various analytical methods used in the project, the fact that various elements or molecules were directly detected from the samples as ions in a gas phase supported the methodological usefulness and left a strong impression on both specialists and people in other fields. Meanwhile, careful consideration of the data or analytical methods highlights the room for technical improvements. For instance, the spatial resolution of MS imaging for organic molecules requires significant improvement to visualize each localization, which would extend the understanding of their origin. Such technical improvement would also accelerate other research areas. In biology or pharmacology, subcellular or tissue distribution analysis for biomolecules or pharmaceuticals has long been desired to better understand their mechanisms of action. Therefore, as mentioned below, the researches for higher spatial resolution in MS or its application, related to new ionization techniques, attracts growing attention in broad research fields.

Morita et al. [2] analyzed matrix particles in a meteorite (the Allende meteorite) by focused ion beam time-of-flight secondary ion mass spectrometry (FIB-TOF–SIMS), which is capable of analyzing sample surface with a highest spatial resolution of 40 nm by using Ga$^+$ ion for the primary ion beam. By combining a cross-sectional polisher, which irradiates a beam of Ar$^+$ ions to process sample surfaces with a high depth resolution less than 30 nm, they visualized detailed distribution of multiple elements. The imaging with a resolution approximately 80 nm/pixel clarified that Al does not exist inside but adheres to the surface of the matrix particles. They suggested possible association between the production of Al-rich particles and the metamorphism of the matrix.

Gas-cluster ion beam (GCIB) extended the SIMS from fragment detection to molecular profiling. Recent advances significantly improved the spatial resolution of MS analysis using GCIB. Tian et al. [3] reported high-energy water GCIB and applied it to biological specimens. Their techniques were capable of imaging at a spatial resolution of 1 μm for intracellular cardiolipins and phosphatidylethanolamines, which could not be analyzed in conventional SIMS. They also provided important data regarding the sample preparation for cells, in which frozen hydration was clearly better than chemical fixation to maintain the distribution of the analytes.

Laser-associated technical developments also contribute to the improvement in the spatial resolution for MS analysis. Tanaka et al. [4] improved spatial resolution of elemental imaging with laser ablation (LA)/inductively coupled plasma (ICP) MS. Their improvement involves two technical aspects: one is the combination of newly designed small volume cell and in-torch gas mixing protocols to shorten washout times of the signals, and the other is the technique called shaving ablation, in which small laser pitch distance and preferential ablation of target area were applied. They selected the use of a laser beam diameter at 8 μm since the use of a small diameter of laser such as at 1–2 μm results

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✉ Eiji Sugiyama
esugiyama@u-shizuoka-ken.ac.jp

[1] School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-Ku, Shizuoka 422-8526, Japan

in shallower focusing tolerance. By setting the offset of the line-scanning (2 µm) smaller than the diameter of the laser beam (8 µm), they clearly visualized distributions of elements in the mouse bone. They also mentioned the importance of careful confirmation for complete ablation to minimize the influence of overlapping in this kind of analysis. Khoo et al. [5] combined LA with dielectric barrier discharge ionization (DBDI), which is a kind of plasma-based atmospheric pressure ionization method and produces a relatively stable plasma. While ICP is used for elemental imaging, DBDI can be used for the molecular imaging. In addition, the LA/DBDI does not require the use of solvents or matrices, required in matrix-assisted laser desorption/ionization (MALDI) or desorption electrospray ionization (DESI), and thus can be used in broader kinds of samples. By using the method, they showed the images of amino acids, sucrose, and vitamins in a tablet. The limitation of spatial resolution for LA/DBDI/MS seems to be similar to that for LA/ICP/MS.

MALDI in transmission-mode geometry (t-MALDI) [6], in which the laser beam irradiates the back side of the sample to obtain smaller laser spot size, has been proven to be a feasible choice for high spatial resolution analysis. The group of Dreisewerd and Soltwisch combined with MALDI-2 [7] and demonstrated superior spatial resolution (a pixel size of 600 nm) with a high sensitivity in the analysis of various lipids in cells and tissues [8]. The sensitivity can be expected to be further increased in the near future by using another post-ionization method developed by the same group [9].

Nanospray DESI (nano-DESI) is an ambient ionization technique with local liquid extraction of molecules from surfaces [10]. Nano-DESI can generate multiply charged ions with less fragmentation from broad kinds of biomolecules. The group of Laskin has recently optimized the design of the capillary-based probe and the thickness of tissue section, and they performed "proteoform" mapping at a spatial resolution down to 7 µm [11].

Application or further development of the techniques introduced here would accelerate a wide range of research conducted by the readers of Analytical Sciences.

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