Mass Spectrometry for Single Cell Imaging

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Nowadays, it is essential in cellular analysis to visualize cellular populations and pharmaceuticals and disclose information about spatial distribution of biomolecules in a high-throughput mode. To serve this purpose, numerous techniques have been developed. One of them is mass spectrometry imaging (MSI). Its advantage over other technologies such as labeling with radionuclide or fluorescent tags is that it requires no information about biomolecules beforehand. Meanwhile, tons of biomolecules including unknown ones can be detected simultaneously from a single MSI experiment, which allows for direct sub-cellular mapping of biomolecules in a high resolution and high throughput way.

MSI can analyze a wide range of materials and molecules, for which identification, relative quantification, and even absolute quantification can be achieved [1-5]. Typically, there are two classes of mass spectrometry imaging: MALDI-MS (Matrix Assisted Laser Desorption and Ionization Mass Spectrometry) imaging and SIMS (Secondary Ion Mass Spectrometry) imaging. In MALDI-MS imaging, molecules within a matrix are desorbed from a surface as laser is scanned across the matrix [6] and then detected by a time-of-flight (TOF) mass spectrometer. In SIMS imaging, an accelerated primary ion beam bombards the surface and generates secondary ions [6], which are then analyzed by a time-of-flight (TOF) mass spectrometer in static SIMS imaging or by a magnetic/electrostatic sector mass spectrometer in dynamic SIMS imaging. SIMS imaging provides information about small fragments of a particular biomolecular species or class, e.g., phosphorous ions on the backbone of nucleic acids [7]. It offers the highest spatial resolution (<50nm) but is limited to a relatively narrow mass range. MALDI-MS imaging, on the contrary, is a soft ionization method and applies to a wide mass range. Hence, it is suitable for analysis of intact biomolecules such as proteins, lipids and DNA.

There are challenges faced by MSI analysis. For example, MALDI-MS imaging is restricted in terms of spatial resolution. SIMS imaging, on the other hand, can routinely reach spatial resolutions at the submicron level [8], but it is subject to narrow mass range [9]. There have also been progresses made to meet and tackle these challenges. For MALDI-MS imaging, one way of improving spatial resolution is through more advanced techniques of sample preparation. These techniques include MALDI matrix sublimation, which can help obtain more uniform microcrystals in matrix application and sample expansion by thaw-mounting the sample to be analyzed on a stretchable material prior to matrix application and sample expansion by thaw-mounting the sample to be analyzed on a stretchable material. This physically enlarges sample area prior to matrix application [10,11]. Spatial resolution of MALDI-MS imaging can also be improved by optimizing laser beam to either reduce the spot size or utilize overlapped laser spot [12,13]. For SIMS imaging, its mass range has been recently extended to around 2 kDa [14] by the use of cluster ion sources (e.g., C_{60} and Bi_3^+). Moreover, matrix enhancement has also been utilized to extend the mass range considerably [15].

Besides MALDI-MS and SIMS, other mass spectrometry methods can also serve as potential imaging techniques with high sensitivity and quantitative analysis platform. They include the inductively coupled plasma (ICP) MS [16], scanning near-field optical microscopy (SNOM) MS [17], and nanostructure-initiator mass spectrometry (NIMS) [18]. With all these powerful techniques, it is expected that mass spectrometry imaging will continue to play an essential role in single cell imaging and cellular analysis in general.

References


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