Mass spectrometry imaging takes off

Recent advances in mass spectrometry imaging enable label-free molecular mapping in single cells and in 3D.

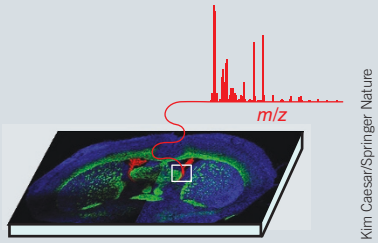
What if it were possible to image the locations of multitudes of molecules in a tissue or even a single cell and to determine their chemical identities without using any fluorescent labels or antibodies? It's not a fanciful idea—a technique called mass spectrometry imaging (MSI) has the potential to do just this.

Mass spectrometry was first used decades ago to image elemental distribution in tissues and cells. In 1997, the biomolecule-friendly technique of matrix-assisted laser desorption–ionization (MALDI) was applied for the first time to localize proteins and peptides in tissue samples. This breakthrough work by Richard Caprioli and coworkers launched a new field of label-free molecular imaging using mass spectrometry.

In a typical implementation of MSI, a laser scans a tissue surface to ionize molecules from defined spots; a mass spectrometer records a full mass spectrum for each spot. Images representing the distributions of mass signals of interest over the tissue section are then reconstructed using computer programs. Molecules can be identified by interpreting their mass spectra. As long as the signal is sufficient, the distribution of just about any molecule—such as peptides, metabolites, and lipids—can be mapped using MSI. Besides numerous applications in basic research, MSI also has great potential for following how a drug distributes in tissue or for disease diagnosis.

Recent advances in proteomics have benefitted other applications that depend on mass spectrometry, including MSI. New ion sources and high-resolution, high-accuracy mass analyzers have led to substantial improvements in mass spectrometry sensitivity. Such developments have also spurred numerous new approaches for data analysis.

In 2017, advances in MSI made it possible to resolve subcellular molecular distributions (e.g., *Nat. Methods* **14**, 90–69, 2017; *Nat. Methods* **14**, 1175–1183, 2017). Methods were also developed to improve the imaging of molecules in 3D samples



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Mass spectrometry imaging maps the molecular composition of tissues and cells. Reproduced in part from Kompauer, M. *et al. Nat. Methods* **14**, 1156–1158, 2017.

(*Nat. Methods* **14**, 1175–1183, 2017) and to capture corresponding information about sample topography (*Nat. Methods* **14**, 1156–1158, 2017). Statistical tools for assessing molecular identification by MSI also help advance research (e.g., *Nat. Methods* **14**, 57–60, 2017).

There is still much room for improving sensitivity to detect low-abundance molecules, quantification, and molecular identification—particularly of metabolites—from mass spectra. Will the developments of the last year and those yet to come open up MSI technology for broader application? It is an area worth watching. **Allison Doerr**

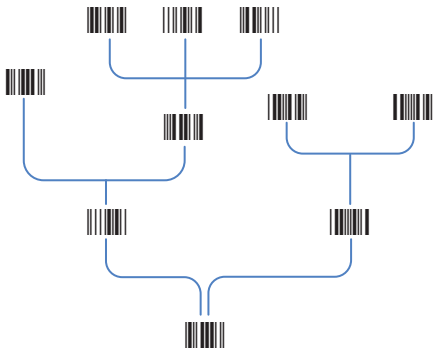
Tracing cellular descent

Sophisticated barcoding approaches are transforming cell lineaging.

The roundworm *Caenorhabditis elegans* may be best known for its cellular family tree, a series of cell divisions that produce the various cell types of the adult. The enormous effort it took in the mid-1970s to document this tree, consisting of countless hours of basic microscopy, is legendary. While methods to mark and track cells *in vivo* have improved over the decades, a recent set of approaches in particular has eased and extended the power of lineaging studies. They generate an extraordinary diversity of cell labels and read them out at high resolution.

Lineage information is important for understanding phenomena such as organogenesis, cell-fate choice, cell migration and tumor evolution. Many approaches have been developed to follow cells over time. Dyes or genetic markers can be introduced into a cell or cell population and then identified in descendants to determine lineage relationships. A second group of methods increases the number of progenitors that can be tracked; for example, sparse recombination can label cells with unique colors by producing different combinations of fluorescent reporters. Alternatively, libraries of viruses encoding a high diversity of DNA barcodes can be transfected into cells and read out in descendants by sequencing.

A new generation of tools uses the CRISPR system to evolve cellular barcodes



Evolving barcodes offer a powerful way to resolve cell lineages.

in vivo. The Cas9 nuclease is directed by a guide RNA to specific barcode regions, where it generates a cut that can produce a unique insertion or deletion during repair; these changes then accumulate over time. Different versions use integrated GFP reporters as targets for barcoding (*bioRxiv* http://dx.doi.org/10.1101/056499, 2017), synthetic multimerized target sites (*Science* **353**, aaf7907-1–aaf7907-10, 2016; *Nature* **541**, 107–111, 2017), or the guide RNA itself (*Science* **353**, aag0511-1–aag0511-10, 2016; *Nat. Methods* **14**, 195–200, 2017). Barcodes are read out by sequencing, or in one case, by sequential fluorescence *in situ* hybridization.

Variations are already being developed to provide high-resolution lineage and transcriptome readouts using single-cell RNA sequencing (*bioRxiv* http://dx.doi.org/10.1101/205534, 2017; *bioRxiv* http://dx.doi.org/10.1101/205971, 2017). We look forward to further improvements in barcode fidelity and interpretation, combination with epigenetic data, control of the timing and location of barcode generation, and to challenging applications such as whole-organism lineaging. **Tal Nawy**