SPECTROSCOPY

The secret of NIMS

A new mass spectrometry surface-based ionization method offers up advantages in sensitivity and the ability to directly analyze biological samples, especially for metabolomics studies.

Mass spectrometry instrument manufacturers are continually pushing the envelope to develop faster, more powerful and more sensitive detectors. But sometimes rethinking the fundamentals can also lead to important advances. Gary Siuzdak of the Scripps Research Institute and his colleagues have done just that—with their development of a new ionization method they call nanostructure-initiator mass spectrometry, or NIMS for short.

Ionization, or getting molecules to 'fly' in the gas phase, is the first step in mass spectrometry. Efficient ionization is thus critical for efficient detection. Though several different ionization methods have been developed, the best known and most important methods used to ionize biomolecules are the surface-based matrix-assisted laser desorption/ionization (MALDI) and the liquid-based electrospray ionization (ESI).

Like MALDI, NIMS is a surface-based method, but the physical processes of ionization are very different. In MALDI, the analyte is mixed with a matrix solution to form co-crystals that are irradiated by a laser, which as they heat up and expand leads to ionization and subsequent transfer of the analyte to the gas phase. Conversely, NIMS is akin to "pulling the rug out from under a molecule; … if you're trying to get a big molecule off of a surface, the best way would be if somehow you could remove the surface, then it would automatically be in the gas phase," says Trent Northen, co-lead author of the study with Oscar Yanes. Basically, the analyte is placed on top of a nanostructured surface containing pores that have trapped an 'initiator' material, in this case a perfluorinated siloxane compound that does not solubilize the analyte. When the surface is heated with a laser, the initiator violently erupts from the pore, triggering the desorption-ionization of the analyte or, in cruder terms, blasting it into the gas phase (**Fig. 1**).

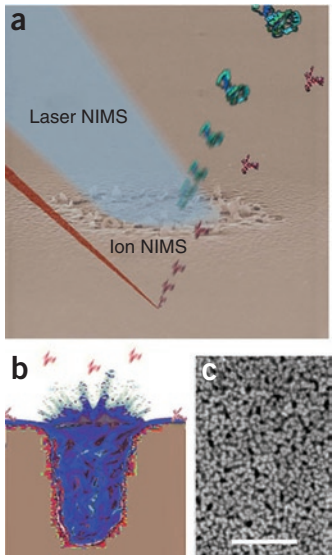

Figure 1 | The NIMS concept. (**a**) SEM image of a NIMS surface after laser irradiation, showing surface distortion and destruction. (**b**) The proposed SIMS mechanism: irradiation of the initiator trapped in a surface pore triggers its vaporization and subsequent analyte desorption-ionization. (**c**) The NIMS surface consists of 10-nm pores. Scale bar, 100 nm. Reprinted from *Nature*.

Though MALDI is better for analyzing large molecules like intact proteins, the researchers discovered that NIMS has particularly good sensitivity for looking at smaller molecules like peptides and metabolites. "For metabolites, MALDI is not very effective because of the matrix suppression effects in the low mass region," explains Siuzdak. NIMS also offers advantages over ESI for metabolomics, for which "you have to clean up the sample, or it's impossible to do electrospray directly," says Yanes. Notably, NIMS allowed the researchers to directly analyze biofluids without any prior sample preparation. It was a somewhat painful discovery, however, as Siuzdak recounts: "I came into the lab and saw Oscar sticking himself with a needle; … he wanted to see if he could look at pure blood samples!" Fortuitously, this impromptu experiment turned out pretty nicely.

The researchers also showed that NIMS was quite suitable for analyzing the phospholipid component of a single breast cancer cell, for directly characterizing peptides on a microarray and for imaging metabolites in a tissue slice from a mouse embryo.

The lack of requirements for sample preparation makes NIMS potentially attractive for clinical applications, in which simplicity, high sensitivity and low costs are necessary for routine implementation. "Tandem mass spectrometry has turned out to be, in metabolomics, a very valuable tool for diagnosing disease, and what we're trying to do here is ultimately make the approach simpler and more sensitive," says Siuzdak. "I don't know if this will ultimately end up being a diagnostic technique, but we're just trying to push the frontiers of mass spectrometry a little further."

For the moment, however, intrepid scientists will have to look at the detailed supplementary material for this work and visit Siuzdak's website (http://masspec.scripps.edu/research/nims/create.php) to learn how to make NIMS chips themselves.

The researchers also acknowledge that there is still a lot of room for improvement of the NIMS technique. "Unfortunately, we're not a materials lab or a synthetic organic chemistry lab, so we have really limited ability to make these surfaces and different initiators," says Northen. "So we really do hope that other people will have answers and expertise and develop things that hopefully broaden the application [of NIMS] in terms of sensitivity for looking at different molecules, possibly expanding the range."

Allison Doerr

RESEARCH PAPERS

Northen, T.R. *et al.* Clathrate nanostructures for mass spectrometry. *Nature* **449**, 1033–1036 (2007).