QnAs with Graham Cooks

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The first line of defense against brain cancers is often surgery. Surgeons strive to extract as much tumor as possible without removing healthy tissue important for brain function. Currently, tumor margins are delineated through MRI and visual examination. Mass spectrometry (MS) may change that approach, according to analytical chemist Graham Cooks, a recently elected member of the National Academy of Sciences. Cooks is testing the efficacy of portable, rapid MS for the analysis of small fragments of tissue in real time and for distinguishing between healthy and cancerous tissues (1). A professor of chemistry at Purdue University, Cooks has spent a career developing MS techniques and testing new uses for them. He recently spoke with PNAS about his efforts to use MS for cancer diagnosis.

PNAS: Your Inaugural Article (IA) (1) reports the use of MS to examine preserved tissue samples taken from people with brain tumors. Can you explain how this works and how it would benefit current methods of tumor resection?

Cooks: The IA uses a newer version of ionization called ambient ionization, where ionization is done on the intact sample without the typical kinds of sample work-up that would require extractions and separations. By avoiding that, we can get information more rapidly using simple low-resolution mass spectrometers. With tumors we're mostly looking at phospholipids and fatty acids and using the pattern of intensities of these ionized molecules to get information on the nature of a particular tissue section or a region of interest in a tissue. We create a library of representative spectra by looking at lots of tissue samples, which are read by pathology. This allows us to assign a particular type of MS as representing normal gray matter, white matter, high-grade glioma infiltrated into gray matter, or whatever the combination of characteristics. The MS reading represents a fingerprint. In two minutes we can take the sample, record the MS of the sample, and then, by comparison with the library, read out the disease or health state of the particular tissue.

Currently, during brain surgery no molecular information is obtained to guide the surgeon. Pathologic information could be acquired, but it would require placing the surgery on hold for 20 minutes, and this is not a good option. What we're providing in this experiment is rapid access to molecular information that is correlated with the type of tumor. The surgeon takes a tiny piece of tissue and smears it, then briefly interrogates it using DESI [desorption electrospray ionization] MS to create ions from that tissue. That information is immediately converted through the use of the library to a readout on disease state. So if a surgeon has reason to wonder whether diseased tissue has been resected, this additional piece of information can be brought to bear. Of course, the procedure is still in the experimental stage and not a standard method of practice.

Graham Cooks. Image courtesy of Xin Yan.

PNAS: You have used a similar technique with other cancers. How does this technique extend your approach?

Cooks: Yes, we've examined samples from renal cancer, also bladder, kidney, and several others. They are different in terms of some diagnostic compounds that are present. But the main features, the phospholipids and fatty acids, are similar. The relative amounts of these compounds are characteristically different, so on a tissue-by-tissue basis, one creates a library of MS and obtains the corresponding pathology data. The brain is by far the most important target because brain cancer is the hardest to treat, and the margins are very hard to assess. This is why recurrence of the disease is so common. The concentrations of phospholipids are very high, and this makes the experiment easy and the data highly reproducible.

PNAS: When talking about phospholipids, what is the difference between cancerous and noncancerous cells?

Cooks: We don't know anything on a cell-by-cell basis, but different lipid populations result from the biochemical processes involved in the growth of cancer cells. The relative amounts of phospholipids are different in different types of healthy tissues and even more different in cancer as opposed to healthy tissue. We acquire mass information and intensity information, giving a matrix of 100 by 100, which can be

populated in many ways. This gives a huge set of possible distinct "barcodes" by which to characterize tissue.

PNAS: At this point, what are the obstacles to moving this technology into the operating room?

Cooks: I don't think there is any limitation except the need to go through enough cases to acquire sufficient experimental data. We are actively working with a neurosurgeon, Aaron Cohen-Gadol at [the] Indiana University School of Medicine, and initial results are as good for intraoperative samples as they were when we were looking at banked tissue samples to create the library. We are not getting large numbers of patients, so the process of accumulating information is slow, but the quality of the information is really good.

PNAS: Your work with MS over the years has included invention, basic research, and applied research. Can you comment?

Cooks: I'd say that the invention side is the most basic side of the work. Instrumentation drives whole fields of science and the development of the new instrumentation is a major science driver; then the applications people come along and use the instrument to do "basic" research first and then applied research. In my career that's the way it has happened. In this laboratory we have invented new types of mass analyzers and ion sources, new configurations of MS, which led to the MS/MS concept of separating ions instead of the original neutral molecules present in complex mixtures. There are lots of examples like that.

1 Jarmusch AK, et al. (2016) Lipid and metabolite profiles of human brain tumors by desorption electrospray ionization-MS. *Proc Natl Acad Sci USA* 113(6):1486–1491.