

New method revolutionizes study of metalcontaining proteins

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This photo illustration shows cells from the heat-loving organism *Pyrococcus furiosus* entering the 8,000 degree Celsius plasma in a mass spectrometer. The instrument tells scientists which metals are present in the organism. Credit: Michael W. Adams/University of Georgia

Metals and proteins are crucial partners in keeping organisms healthy and stable. And yet the extent to which this molecular metalloprotein team works at the cellular level is not known because the numbers, amounts and types of metal-containing proteins in any organism have remained something of a mystery.

Now, in a study led by a researcher at the University of Georgia and just published in the the advance online edition of *Nature*, a team of scientists has shown through an entirely new method that these so-called metalloproteins are much more diverse and extensive than previously recognized and that it is now possible to determine all the metals in an organism in one fell swoop through a reliable, genome-wide approach.



"Metalloproteins play key roles in most biological processes, including respiration, photosynthesis and drug metabolism," said Michael W. Adams, Distinguished Research Professor in the department of biochemistry and molecular biology at UGA and lead author on the new research. "But predicting from a <u>genome sequence</u> the numbers and types of metals an organism assimilates from its environment or needs to function has been impossible for a number of reasons."

The new method, which combines liquid chromatography, highthroughput tandem mass spectometry and inductively coupled plasma mass spectometry, reveals all the metalloproteins in an organism—and what the team found has been very surprising, since metals now seem to be much more important for proteins than ever before suspected. Knowledge about how metals work in proteins has given insights into such things as how proteins repair DNA damaged by cancer-causing processes, how organisms get energy for growth and how some biofuels are produced. The importance of the work may therefore go in many diverse directions and promises to lead to important discoveries and applications in many biological fields, Adams said.

Other authors on the paper include Aleksandar Cvetkovic, Angeli Menon, Michael Thorgersen, Joseph Scott, Farris Poole, Francis Jenney, Andrew Lancaster, Jeremy Praissman, Saratchandra Shanmukh and Brian Vaccaro of the University of Georgia; Sunia Trauger, Ewa Kalisiak, Junefredo Apon and Gary Siuzdak of the Scripps Center for Mass Spectometry and the departments of molecular biology and chemistry at the Scripps Research Institute; and Steven Yanonne and John Tainer of the Life Sciences Division of the Lawrence Berkeley National Laboratory

One of the major surprises of the study is the sheer number of proteins in microbial metalloproteomes that remain uncharacterized. (A metalloproteome is the complete number of metal-containing proteins in



any individual organism.) This means that the role of metals in proteins, already known to be important, extends considerably beyond what science currently knows.

Since the team is now involved in automating and miniaturizing the steps in the method, it is entirely possible that dramatic and as yet unknown roles for metals in organisms may soon be discovered. And that could lead to such things as new drugs that might correct the misincorporation of metals into cells that potentially can lead to diseases or disorders as well as new diagnostic methods for detecting diseases and in determining the toxic effects of heavy metals.

What researchers have learned about metals and proteins has, in years past, typically been a byproduct of other aims and goals. Identifying metals in host proteins has been slow and tedious, which has meant that obtaining an overall picture of the number of metals present in a cell and their roles in how organisms use them has been an unsolved problem for scientists. Now, with the new method, a rapid understanding of the total metals in all proteins within a cell and insights into how they work could revolutionize metallobiology and lead to a more complete understanding of cell biology in general, the authors imply.

The team's test subject in designing the new approach was Pyrococcus furiosus, an extreme-heat-loving microorganism that in nature lives around undersea thermal vents and thrives at temperatures near the boiling point of water. Using the new method, the team found that Pyrococcus cells contain a suite of metals no one had ever suspected, including, surprisingly, lead and uranium.

"In order to see if these results were typical of any type of cell, we also analyzed, using the same approach, two additional microbes, Escherichia coli and Sulfolobus solfataricus," said Adams. "Each revealed a number of metals, including tin and antimony, we had no idea they had



assimilated. Once revealed, a metal cofactor adds new dimensions to understanding protein structure and function. And yet the presence of the <u>metal</u> is often unsuspected until the protein is analyzed."

One reason the new method may be important in lab-based studies is that it does not require the use of radioactive-labeling materials that require safety measures and special handling. Moreover, the new method can detect more than 50 metals at once, in contrast to the one-metal-a-time radiolabel approach.

The new method also promises to make culturing microbes in the lab for study much easier, Adams said, since knowing what metals cells need to function properly will allow scientists to create media better suited to their rapid and efficient growth in a laboratory environment.

It was previously thought that at least a third of all proteins in organisms had metals as essential cofactors. The new approach shows that this is a significant underestimate, said Adams, with implications for a more complete understanding of protein structure and function and of the roles of metals in all cellular processes.

More information: The paper describing this work, titled, "Microbial metalloproteomes are largely uncharacterized" appears in the July 18, 2010 advance online publication of the journal Nature. <u>www.nature.com/nature/journal/ ... ull/nature09265.html</u>

Provided by University of Georgia

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