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The Advanced Photon Source

Shedding Light on an Anti-Cancer Drug

The copper sequestering drug tetrathiomolybdate (TM) has been shown in studies to be effective in the treatment of Wilson disease — a disease caused by an overload of copper — and on certain metastatic cancers. That much is known. Very little, however, is known about how the drug works at the molecular level.

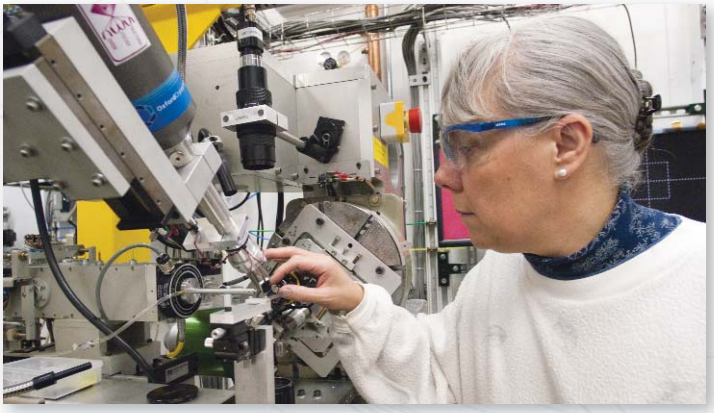
A new study by Northwestern University and University of Michigan researchers has provided an invaluable clue: The three-dimensional structure of TM bound to copper-loaded metallochaperones. The drug sequesters the chaperone and its bound copper, preventing both from carrying out their normal functions in the cell. For patients with Wilson disease and certain cancers whose initial growth is helped by copper-dependent angiogenesis, this very promising discovery opens the door to development of new classes of pharmaceutical agents based on metal trafficking pathways, as well as the further development of more efficient TM-based drugs.

The research team studied the copper chaperone protein Atx1, which provides a good model of copper metabolism in animal cells. They were curious about what effect the drug tetrathiomolybdate had on copper chaperones — proteins charged with safely ferrying copper within the cell. They found that the drug brings three copper chaperones into close quarters, weaving them together through an intricate metal-sulfur cluster in a manner that essentially shuts down the copper ferrying system. The nest-shaped structure of the metal-sulfur cluster discovered by the researchers was completely unanticipated.

When they mixed TM with copper chaperone proteins in a test tube, the color of the solution changed from light orange to deep purple, the sulfur atoms in the tetrathiomolybdate bound to the copper atoms to form an open cluster that bridged the chaperone proteins. In this manner, three copper proteins were jammed onto one thiomolybdate.

The three-dimensional crystal structure was solved using protein x-ray crystallography carried out at the Structural Biology Center Collaborative Access Team (SBC-CAT) and Industrial Macromolecular Crystallography Association (IMCA-CAT) beamlines at the U.S. Department of Energy's Advanced Photon Source at Argonne National Laboratory. This is the first example of a copper-sulfide-molybdenum metal cluster protein.

Based on the structure and additional experiments, the scientists propose that the drug inhibits the traffic of copper within the cell because of its ability to sequester copper chaperones and their cargo in clusters, rendering the copper inactive. They conclude that the biological activity of tetrathiomolybdate does not arise from a simple copper sequestering action, but through a disruption of key protein-protein interactions important in human copper metabolism. Inorganic elements, such as copper, zinc, and iron, are vital to the healthy functioning of all cells in living organisms. But they are high-maintenance nutrients, and too much can be toxic, as is the case in Wilson disease, a genetic disorder that prevents the body from getting rid of extra copper and leads to liver and neurological problems.



Norma Duke (Argonne National Laboratory), beamline scientist with the Structural Biology Center, in the SBC 19-BM beamline enclosure, one of two APS beamlines where this study was carried out.

Copper also is an important cofactor for tumor angiogenesis, the process of growing new blood vessels to feed the tumor. Researchers believe this is why tetrathiomolybdate has shown promise as an anti-cancer drug.

See: Hamsell M. Alvarez[1], Yi Xue[1], Chandler D. Robinson[1], Mónica A. Canalizo-Hernández[1], Rebecca G. Marvin[1], Rebekah A. Kelly[2], Alfonso Mondragón[1], James E. Penner-Hahn[2], and Thomas V. O'Halloran[1]*, "Tetrathiomolybdate Inhibits Copper Trafficking Proteins Through Metal Cluster Formation," Sciencexpress, published Online November 26, 2009, DOI: 10.1126/science.1179907.

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Note: This article is based upon a Northwestern University press release authored by Megan Fellman

Call for APS General-User Proposals

The Advanced Photon Source is open to experimenters who can benefit from the brightest hard x-ray beams in the Western Hemisphere.
General-user proposals for beam time during Run 2010-1 are due by Friday, March 5, 2010.
Information on access to beam time at the APS is at http://www.aps.anl.gov/Users/apply_for_beamtime.html or contact Dr. Dennis Mills, DMM@aps.anl.gov, 630/252-5680.

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