Chemists Clarify Protein-Receptor Complex's Role in Iron Uptake to Cells

April 20 2010

(PhysOrg.com) -- In recent years cancer researchers, particularly brain tumor specialists, have pinned some hope for delivering anti-tumor drugs on transferrin, a protein that carries the essential element iron into cells. This is because unlike most other proteins, transferrin can cross the blood-brain barrier. But a new study of transferrin and its receptor by chemists at the University of Massachusetts Amherst reveals that transferrin isn't as open to drug loading as hoped, so creating a good delivery system may be more challenging than previously thought.

Nevertheless, work led by UMass Amherst researcher Igor Kaltashov and doctoral student Rachel Leverence, now at the University of Wisconsin-Madison, with Anne Mason of the University of Vermont College of Medicine, highlights for the first time the great potential of the mass spectrometry method they used in this study, for providing precise details of complex protein-receptor interactions under conditions that closely mimic those inside the body. Their findings appear in the current online edition of Proceedings of the National Academy of Sciences.

As Kaltashov explains, "Our research looked at how the transferrin protein interacts with its receptor and how this has relevance for anti-cancer therapy." One reason medical researchers have been so hopeful about transferrin and its drug-delivery potential is that cancer cells demand huge amounts of iron to thrive. Scientists long believed that after the transferrin protein delivered its iron load into a cell, it would emerge again not bound to the receptor, leaving a space for drug uptake

and delivery into the tumor cell, thus providing a way to introduce toxins to kill the cancer.

“But we found that life is much more complicated,” says Kaltashov. “One of our important conclusions is that transferrin would probably interfere with the binding between the receptor and any anti-cancer drug one might try to attach.” Despite this, his findings do not represent a dead end, the analytical chemist adds. The mass spectrometry technique was extremely effective in allowing the researchers to observe and examine the transferrin receptor complex and its behavior in detail. The method is generalizable and can be applied to any system, including potential new anti-cancer drugs, Kaltashov adds.

Specifically, he and colleagues used an ion cyclotron resonance mass spectrometer, a cross-over between more familiar medical magnetic imaging devices such as MRI and classical mass spectrometers. It is powerful enough to analyze proteins, DNA and other biological molecules. First the ions, the electrically charged forms of molecules, are extracted from a fine aerosol produced by spraying solutions containing biomolecules. These ions are then guided to a magnet through a system of ion optics under ultra-high vacuum conditions.

Once inside the magnet, the ions move along circular orbits; the frequency of this movement provides very precise information on molecular masses. This new type of instrument is so powerful it can measure the mass of nano-objects ranging from single atoms to giant biomolecules with precision better than 0.0001 percent, the chemist says.

Further, the Kaltashov laboratory recently purchased a powerful new mass spectrometer with an $800,000 Major Research Instrumentation grant from the National Science Foundation to aid research in life sciences, where knowledge of molecular structure is critical for understanding processes as diverse as drug delivery and protein folding.

Thus the UMass Amherst campus now has one of the best equipped mass spectrometry laboratories in the nation.

As Kaltashov explains, the usefulness of such mass spectrometers to life sciences research extends far beyond simply measuring atomic and molecular masses. For example, one can break a large molecule apart inside the instrument and measure masses of the resulting fragments. “Figuring how these fragments may fit together in pretty much the same way a puzzle is pieced together provides a way to determine the structure of proteins, DNA and other biomolecules,” he says.

Now his group is developing new methods to probe other traits of proteins and their brethren in the biological world, such as three-dimensional organization and interactions with physiological partners. This technology will be critical for advancing knowledge in areas ranging from fundamental problems in biophysics and structural biology to design and testing of new biopharmaceutical products.

Provided by University of Massachusetts Amherst