Biochemists develop new method for preventing oxidative damage to cells

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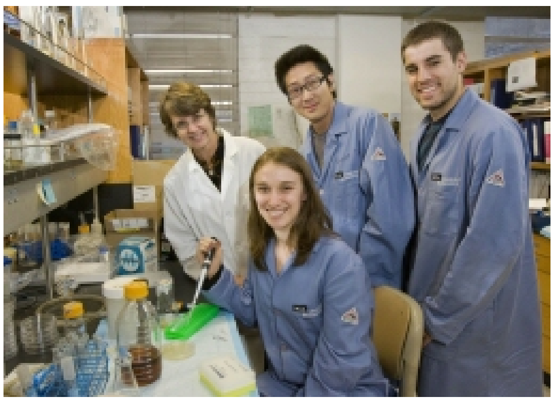

Catherine Clarke and UCLA researchers

(PhysOrg.com) -- The discovery by UCLA biochemists of a new method for preventing oxidation in the essential fatty acids of cell membranes could lead to a new class of more effective nutritional supplements and potentially help combat neurodegenerative disorders such as Parkinson's disease and perhaps Alzheimer's.

While polyunsaturated fatty acids are essential nutrients for everything from brain function to cell function, they are the most vulnerable components in human cells because of their high sensitivity to oxidative modifications caused by highly reactive oxygen molecules in the body.

The biochemists, led by UCLA chemistry and biochemistry professor

Catherine Clarke, have developed a new method for increasing the stability of polyunsaturated fatty acids. They have discovered a way to make these molecules harder to break apart so that oxidation is less likely to occur, rather than relying on antioxidants to repair damage after it occurs.

"These compounds (polyunsaturated fatty acids) are so important, yet so fragile," Clarke said. "In many diseases, cell membrane function deteriorates, and it's exciting to think an enhanced class of supplements may be able to correct neurodegenerative diseases, and perhaps even oxidative stress–related aging. It would be a new strategy to treat and reinforce the molecule at the place where it is most prone to damage, instead of taking more antioxidants. This could be a new approach to battling diseases resulting from oxidative stress.

"Our research highlights how vulnerable these essential polyunsaturated fatty acids are," she said. "They are so readily damaged. Many neurodegenerative diseases, such as Parkinson's disease and perhaps Alzheimer's disease, are tied to oxidative stress."

Polyunsaturated fatty acids are also used to produce a huge array of fatty acid–derived hormones that mediate pain, inflammation and blood clotting.

The research, federally funded by the National Institutes of Health, is published in the online edition of the journal *Free Radical Biology and Medicine*, a major source for research on oxidative stress, and is scheduled for publication in a 2011 print edition.

In the research, Clarke and her colleagues show that polyunsaturated fatty acids can be strengthened by replacing their most vulnerable hydrogen atoms, which are easily stripped away, with much more stable deuterium, an isotope of hydrogen with one extra neutron. The result is the creation of a fatty acid that serves the same function as its predecessor, but without the same susceptibility to oxidation.

The biochemists also describe applying this reinforcement process to two essential dietary fatty acids and show that yeast cells treated with the reinforced polyunsaturated fatty acids are much more resistant to oxidative stress than yeast treated with normal polyunsaturated fatty acids.

"You can think about polyunsaturated fatty acids like an oil-based paint," Clarke said. "When you spread the oil-based paint on the wall, it turns into a hard coat of enamel. That happens because of an oxidation reaction. A hard coat of enamel is great for a wall but lousy for a cell membrane. Cells have to deal with damage continually and have to be able to repair the damage that results from the oxidation."

Clarke's research team included four UCLA undergraduates: lead author Shauna Hill, who worked in Clarke's laboratory as many as 70 hours a week and earned a bachelor's degree in biochemistry in June; Bradley Kay; Vincent Tse; and Kathleen Hirano, who graduated from UCLA in 2009 with a bachelor's in biochemistry and is now a graduate student at UC Berkeley.

The researchers conducted experiments with a strain of yeast specially modified to lack antioxidants. They found that colonies treated with normal, naturally occurring polyunsaturated fatty acids died quickly, while those treated with the deuterium-reinforced fatty acids displayed resilience on par with wild, unmodified yeast. The replacement of a few hydrogen atoms with deuterium meant the difference between a rapid death and vigorous life for the yeast samples.

"Shauna, with Kathleen, Bradley and Vincent, tested fatty acids in yeast mutants that lacked the antioxidant coenzyme Q, where we know they are very sensitive to stress," Clarke said. "What they showed is that when the yeast were treated with the isotopically reinforced fatty acids, they were fine, but when the yeast were treated with standard polyunsaturated fatty acids, 99 percent of them died in just four hours."

"We tested the viability of yeast — with the hydrogen atoms — that lacked the antioxidant coenzyme Q, and our test showed that they were not able to survive," Hill said. "However, wild, normal yeast with coenzyme Q were able to grow, and survived."

The researchers then replaced four hydrogen atoms with four heavy deuterium hydrogen isotopes.

"The difference was enormous," Hill said. "We were really surprised that the heavy isotopes had such a drastic effect."

"Initially, I did not believe the results were correct," said Beth Marbois, a UCLA research chemist and co-author on the research. "But they were."

Yeast normally do not have these fats but will absorb both the normal and the isotope-reinforced fatty acids without preference when they are presented in solution, Hill and Marbois showed.

Other co-authors of the research included Mikhail Shchepinov, chief scientific officer of Retrotope Inc. in Los Altos Hills, Calif., and Dragoslav Vidovic from the department of chemistry at England's Oxford University.

The human body is unable to make polyunsaturated fatty acids such as omega-3 fatty acids and omega-6 fatty acids. Many people buy supplements such as fish oil, omega-3 fatty acids or flaxseed oil to get and preserve these nutrients. However, when a polyunsaturated fatty acid is oxidized, a hydrogen atom is stripped away from the molecule, causing it to form a new compound with the oxygen in the blood stream that impairs the function of the cell membrane.

Olive oil, walnut oil and flaxseed oil have some of the essential fats that we need for brain function, retina function and other critical body functions. Neurons in the brain and heart and in muscle cells have large amounts of these essential fats. Salmon has them because the fish eat microorganisms in the ocean that generate these fats.

Fish oil has 10 hydrogen atoms that are vulnerable and could be reinforced to be made less likely to degrade, Clarke noted.

Reinforced polyunsaturated fatty acids potentially could create membranes that are at least somewhat resilient to oxidative damage, Clarke said.

After one polyunsaturated fatty acid molecule is damaged, a chain reaction ensues as the adjacent fatty acids throughout the membrane become similarly degraded. What was once a semi-permeable barrier that regulated cell function becomes a rigid lattice of cross-linked fatty acids that prevents the cell from achieving its purpose — which could be anything from synthesizing a protein to sending a signal to the nervous system.

Antioxidants, found naturally in many types of berries and available in supplements such as vitamin E, target the gaps left in molecules when a hydrogen atom is removed through oxidation. The antioxidants quench the reactive oxidized lipids, forming a new compound that prevents the molecular degradation from spreading to its neighbors.

The start of the oxidation chain reaction in a cell membrane is like a house on fire, where the antioxidants are the firefighters that work to extinguish the blaze before it spreads to nearby homes. Because a deuterium atom has twice the mass of a hydrogen atom, the carbon-to-deuterium bond in the modified fatty acid is much stronger than the carbon-to-hydrogen bond in the naturally occurring version. Thus, a fatty acid reinforced with deuterium acts like a home with fire-retardant materials that make it difficult for the first spark to ignite. Ideally, no firefighters — or antioxidants — are needed.

Antioxidants are like a mop-up crew, Clarke said. After the hydrogen atoms are pulled off, antioxidants stop the harmful chain reaction. Using another analogy, Clarke said, "Instead of taking an antioxidant to jump in front of a bullet, you place bullet-proof vests on the hydrogen atoms."

While wild yeast are resistant to oxidation at room temperature, they do begin to experience stress as the temperature rises. At high temperatures, wild yeast colonies treated with deuterium-reinforced polyunsaturated fatty acids show much greater resilience than those treated with unmodified fatty acids — a result that indicates that even cells with integrated antioxidant mechanisms can benefit from the addition of deuterium-enhanced fatty acids, Clarke said.

Eat fish and stay physically active

UCLA's Marbois recommends eating fish frequently, especially fatty fish such as salmon, and staying physically active.

"Scientists who conduct aging research know that the one critical characteristic of people who live very long lives is not taking nutritional supplements but staying physically active," she said.

If you take fish oil, Marbois advises, keep the container in the refrigerator. "At room temperature, they will oxidize and degrade at a faster rate than in the refrigerator," she said.

Both Clarke and Marbois praised the student researchers.

"It's a real privilege to work with these students," Marbois said. "The undergraduates here constantly amaze me."

Clarke described working with the students as "fantastic, so much fun."

The students returned the praise of their mentors.

"Working in Professor Clarke's laboratory has been a life-changing experience for me," said Hill, who is applying to graduate schools in biochemistry and cellular and molecular biology. "If it weren't for this lab, I don't know if I would be applying for grad schools right now."

"Conducting research in Professor Clarke's laboratory is an amazing opportunity," Tse said. "Friends at other universities have a hard time working in laboratories, but at UCLA, the opportunities are here for us, and I feel privileged to be able to do this research."

"I wish I got involved in research earlier; it's so interesting and rewarding," Kay said.

Provided by University of California Los Angeles

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