

Alzheimer's Disease Research Review

Better Health Through Research

Winter 2011

Flushing Bad Proteins Away

Study finds new way of helping cells heal themselves

Scientists with Harvard Medical School have isolated a small molecule that helps cells dispose of the misfolded proteins that characterize Alzheimer's disease — a discovery that could open up new possibilities for drug therapies.

The breakthrough occurred when a research team led by Harvard Medical School researchers Daniel Finley, professor of cell biology, and Randall King, associate professor of cell biology, studied the breakdown of the body's protein destruction system under the influence of Alzheimer's disease and other neurodegenerative conditions.

In healthy cells, new proteins are created and damaged ones are destroyed at roughly the same rate. But in the brains of Alzheimer's disease patients, cells make new proteins faster than they rid themselves of old ones, leading to a toxic build-up of misfolded proteins.

The Harvard team found that a particular enzyme called Usp14, when activated, blocks the cell's protein waste-disposal system, the proteasome, from working properly. Researchers then screened 63,000 compounds and found one particular molecule that could inhibit Usp14, restoring the cell's ability to break down and discard bad proteins.

While previous research has focused on hindering proteasome activity, the Harvard findings suggest there may be more value in boosting proteasome activity. "If you take a typical cell growing in culture and kill its Usp14 activity, the cell will continue to thrive," says Finley. "If you kill its proteasome activity, it would immediately die."

King adds that the team's research could have implications not just for neurodegenerative diseases like Alzheimer's disease but any other illness linked to an accumulation of misfolded proteins.

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A Noted Researcher Reaps His Reward

A researcher previously funded by AHAF has just been awarded the country's highest honor for science and technology, the National Medal of Science.

Stanley B. Prusiner, M.D., of the University of California-San Francisco, was honored for his 1982 discovery of prions, infectious protein particles that play a major role in Alzheimer's disease and other neurodegenerative human diseases.

While non-infectious prion particles exist in all humans, they become lethal when they lose their normal corkscrew-shaped structure and flatten into "beta sheets." These sheets then latch onto neighboring proteins, twisting them into the same shape. The resulting domino effect triggers nerve-cell death throughout the brain.

In addition to changing the way scientists think about neurodegenerative disease processes, Dr. Prusiner's findings have earned him a Nobel Prize. In recent years, he has focused on developing preventions and cures for prion-related diseases and has become a particularly strong advocate for increased support of research into Alzheimer's disease.

Since 1985, Alzheimer's Disease Research has funded Dr. Prusiner with several grants aimed at understanding the structure of prion proteins and the best methods for blocking the conversion of "normal" proteins to misfolded, disease-causing versions. The American Health Assistance Foundation (AHAF) awarded more than \$1.2 million in research grants through its Alzheimer's Disease Research program to Dr. Prusiner to develop his prion theory as a model for Alzheimer's disease.

A New Angle on Alzheimer's Disease

Researchers ponder role of inflammatory enzyme

A team of researchers with the Jewish General Hospital has assembled evidence that Caspase-6, an enzyme that triggers cell inflammation, may play a larger-than-suspected role in the development of Alzheimer's disease.

"Our research has shown that neurons, the type of cells mainly affected in Alzheimer's disease brains, activate Caspase-6 when they are stressed," explains study leader Dr. Andréa LeBlanc. "We have also shown that otherwise healthy neurons degenerate when exposed to active Caspase-6."

The enzyme is found in high levels in the brains of people who died of Alzheimer's disease and is virtually absent in the brains of people who didn't have the disease or who were younger than 45. In addition, the researchers found elevated levels of Caspase-6 in the brains of older people who did not have Alzheimer's disease but who suffered from memory impairment.

"We determined that these normal people — who had active enzyme in the part of the brain that is



thought to be first affected by Alzheimer's disease — also had lower cognitive scores," LeBlanc said. "They had no clinical signs of Alzheimer's disease during their lifetimes but these results indicated that they may have developed Alzheimer's disease if they had lived longer. This makes a very strong link between Caspase-6 and Alzheimer's disease."

"Caspase-6 enzyme does not kill neurons," she adds, "but it causes neurodegeneration. The implication is that this process of neurodegeneration might be reversible. At the very least it might help us identify individuals early enough to try different therapies that could prevent the progression of the disease."

Research Roundup

Pass the red wine?

A molecular mechanism triggered by a compound found in red wine may actually boost memory and brain power, in addition to enhancing life spans, according to scientists with the Massachusetts Institute of Technology's (MIT) Picower Institute for Learning and Memory.

Previous studies have suggested that resveratrol, a compound found in the skin of red grapes, slows the aging process by activating a group of enzymes known as sirtuins. Now, in a study published in *Nature*, MIT scientists have found that Sirtuin1 — a protein encoded by the SIRT1 gene — also promotes memory and brain flexibility.

“In our cell and mouse models for Alzheimer’s disease, SIRT1 promoted neuronal survival, reduced neurodegeneration and prevented learning impairment,” said Li-Huei Tsai, director of the Picower Institute and lead author of the study. “This result demonstrates a multi-faceted role of SIRT1 in the brain, further highlighting its potential as a target for the treatment of neurodegeneration and conditions with impaired cognition, with implications for a wider range of central nervous system disorders.”

The diabetes-Alzheimer’s link

Elderly people with Type 2 diabetes are twice as likely to develop Alzheimer’s disease ... but why?



Scientists with the Mount Sinai School of Medicine think they may have the answer. According to a study published in *Aging Cell*, a gene associated with the onset of Type 2 diabetes is found at lower than normal levels in people with Alzheimer’s disease.

Lower levels of expression from the PGC-1 gene, may increase the process and generation of beta-amyloid protein. “Our research is the first to find that PGC-1 is a common denominator between Type 2 diabetes and Alzheimer’s disease,” says study leader Giulio Maria Pasinetti. We look forward to continuing to research this discovery and translate it into the development of novel approaches for disease prevention and treatment.”

Chairman’s Corner

Each year, some 500,000 people die with cancer. About the same number die with Alzheimer’s disease. Yet, as Dr. Stanley Prusiner has pointed out, Alzheimer’s research receives only \$450 million annually from the National Institutes of Health — about one-fifteenth the amount devoted to cancer research.

Clearly, if we are going to treat and ultimately cure this terrible disease, we need to find ways to close this funding gap.

Of course, Alzheimer’s Disease Research can’t

The funding gap

single-handedly make up that deficit. But with the help of our supporters, we can use the resources we have in the most efficient manner way — finding the most qualified researchers who are poised to take our understanding of Alzheimer’s disease further than ever before.

We won’t beat Alzheimer’s disease tomorrow. But with the help of our donors, we can make sure that every day takes us further toward our ultimate goal.

Brian K. Regan, Ph.D.

Become a Year-Round Force in Alzheimer's Disease Research

Monthly giving helps reduce overhead

Many of our donors find that the easiest and most efficient way to give to Alzheimer's Disease Research is to make monthly contributions of \$10, \$20, \$100 or more.

Automatic payments are particularly effective because they save us the cost of stamps and envelopes — reducing our overhead and allowing us to allocate more of every dollar to the fight against Alzheimer's disease.

Becoming a monthly donor is easy to do, and you can even choose to earmark your gifts strictly for research. For more information on this unique way of giving, please contact Cristel Siaobungco at 800-437-2423.



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