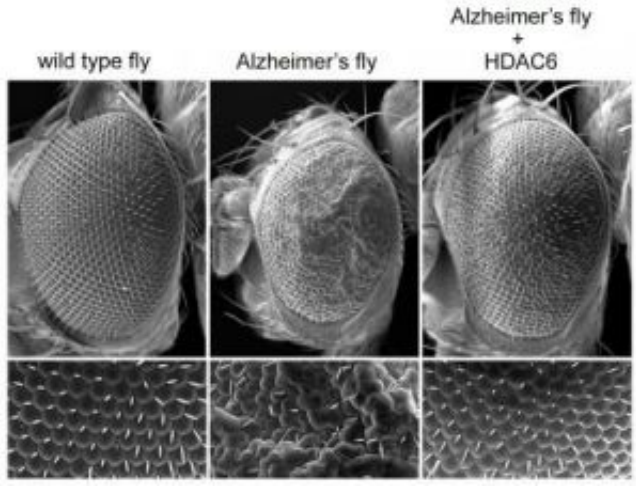
Penn researchers link cell's protein recycling systems

June 14 2007



Neurodegeneration in a fruit fly eye. Normal or wild type eye (left) appears uniformly structured. Eye in fruit fly model of Alzheimer's disease (middle) appears rough and deformed. Eye in fruit fly model of Alzheimer's disease in which extra HDAC6 protein is expressed (right) appears uniformly structured as in wild type. Credit: J. Paul Taylor, MD, PhD, University of Pennsylvania School of Medicine

Many age-related neurological diseases are associated with defective proteins accumulating in nerve cells, suggesting that the cell's normal disposal mechanisms are not operating correctly. Now, researchers at the University of Pennsylvania School of Medicine have discovered a molecular link between the cell's two major pathways for breaking down proteins and have succeeded in using this link to rescue

neurodegenerative diseases in a simple animal model. The study appears this week in Nature.

The cell has two internal pathways for breaking down proteins. The ubiquitin-proteasome pathway marks unwanted proteins with ubiquitin tags and shuttles them for rapid breakdown to a complicated structure called the proteasome. The second is the autophagy-lysosomal system, a more general process in which proteins are surrounded by membranes inside the cell for bulk digestion.

“The dogma has been that the autophagy-lysosomal and the proteasomal systems are trains that run on different tracks, with similar purposes, but no point of intersection,” explains senior author J. Paul Taylor, MD, PhD, Assistant Professor of Neurology. “The new finding directly challenges this thinking by showing that one system can be induced to compensate for the other. Cells are able to shift proteins between the systems. We think that this molecular link can be used to benefit a wide variety of neurodegenerative diseases because accumulation of toxic proteins is a common underlying feature of age-related neurodegeneration.”

Taylor and his group study fruit flies in which the proteasome is disabled by a genetic mutation, which results in neurodegeneration. They use the fly eye, a neuron-rich tissue, as a surrogate for the brain because it is easy to visualize. They discovered that making the lysosomal system more or less active dramatically influenced the severity of neurodegeneration.

“We found that whenever we knocked the lysosome system down, neurodegeneration always got worse,” says Taylor. “Then when we activated the autophagy system by feeding the flies a drug called rapamycin, neurodegeneration was prevented.” The accumulated misfolded proteins were cleared out by the lysosome system. “Then we

knew that this system can compensate for the impaired proteasome function, which in itself tells us that the two pathways intersect," says Taylor. "The question was, 'How is this working?'"

The Role of HDAC6

"That's where the power of fruit flies comes in," Taylor explains. "We can use fruit flies to rapidly screen through many genes to find the one we're interested in. In the process of screening, our attention was drawn to HDAC6 because we already knew that it could bind to ubiquitin-tagged proteins and transport them within the cell. So we wondered, could HDAC6 be the link"'"

Taylor's group showed that if the HDAC6 gene is knocked out, inducing autophagy no longer rescues the fly eyes from neurodegeneration. Therefore, autophagy requires HDAC6 to work. They also showed that by simply expressing extra HDAC6, neurodegeneration was prevented in flies with proteasome impairment. Taylor's group then moved on to fly models of human neurodegenerative disease and showed that they, too, are rescued by over-expression of HDAC6.

Therefore, the researchers suggest that the level of the HDAC6 in a cell regulates its sensitivity to accumulation of misfolded proteins, and that increasing the activity of HDAC6 can prevent the degeneration normally associated with accumulating old, damaged proteins. The researchers suggest further that when proteasomes are impaired or overwhelmed, which leads to accumulation of defective proteins, HDAC6 facilitates delivery to the autophagy-lysosomal system for degradation. "That's how we think HDAC6 links the two systems," says Taylor.

Dr Taylor and his team are now testing the ability of HDAC6 to prevent neurodegeneration in several mouse models, including motor neuron disease, Parkinson's disease, and Huntington's disease. They are also

attempting to identify pharmacologic approaches to augmenting HDAC6 activity.

Source: University of Pennsylvania School of Medicine