Dynamics of chaperone protein critical in rescuing brains of Alzheimer's mice from neuron damage

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Jose Abisambra (left) was first author and Chad Dickey was principal investigator of the University of South Florida-led study investigating the dynamics of chaperone protein Hsp27 and turnover of tau. Credit: © University of South Florida

Dynamic regulation of the chaperone protein Hsp27 was required to get rid of abnormally accumulating tau in the brains of mice genetically modified to develop the memory-choking tau tangles associated with Alzheimer's disease, a University of South Florida-led study found.

Researchers at the USF Health Byrd Alzheimer's Institute demonstrated that the effective switching of Hsp27 between its active and deactivated states was critical on two fronts -- to promote the recycling of the tau protein in healthy nerve cells and to clear abnormal tau from the brain

before the protein could clump together into the sticky tau neurofibrillary tangles that kill brain cells involved in memory formation . Their findings were published online Nov.17, 2010 in the *Journal of Neuroscience*.

"Our study shows that Hsp 27 may be a double-edged sword depending upon the contextual environment of neurons in the brain," said the study's principal investigator Chad Dickey, PhD, associate professor of molecular medicine at USF Health. "By better defining the mechanisms linking chaperone proteins to both the tau aggregation and degradation pathways, we can move toward more individualized, effective therapies targeting Alzheimer's and other distinct neurological disorders."

Hsp27 is one of several "chaperone" proteins that supervises the activity of tau inside nerve cells, ensuring that the tau protein is properly folded into its complex form. If tau somehow becomes misfolded, the protein cannot accomplish its normal job of helping maintain the structure of nerve cells. The improperly folded (abnormal) tau starts stacking up into tangles inside cells involved in memory and destroying them.

The USF study was done using mice genetically engineered to develop tau protein tangles like those found in the brains of people with Alzheimer's disease. In one experiment, the researchers injected into the brains of 4-month-old Alzheimer's mice viral particles expressing either dynamic wild-type Hsp27 or genetically-altered Hsp27 that was continuously "on" or activated. By 4 months, the Alzheimer's mice have aged enough to have large amounts of tau accumulated but are still able to clear the protein before insoluble toxic tangles take over.

When they harvested the brain tissue of the mice two months later (at 6 months), the researchers discovered that both variants of Hsp27 interacted with tau. However, only the wild-type Hsp27 cleared tau from the brain, reducing neuronal tau levels. The genetically-altered Hsp27

was associated with increased tau levels.

In another experiment, the researchers examined the physiological effects of Hsp27 overexpression in the brain. Both variants of Hsp27 were administered to 2-month-old Alzheimer's mice. At 4 months, their brain tissue was examined to evaluate whether Hsp27 improved any neuron deficiencies brought on by the accumulation of abnormal tau over the previous 2-month period. The researchers found that overexpression of wild-type Hsp27 succeeded in rescuing the mice from neuron damage. The genetically altered (perpetually activated) Hsp27 did not.

The researchers concluded that Hsp27 must be able to fluctuate between activated and de-activated states to succeed at clearing abnormal tau, thus preventing the protein from sticking together and building up excessively in the brain. In addition, Hsp27 can only be effective in helping maintain healthy tau turnover if the chaperone protein interacts with tau while it's still soluble -- before tau has developed into solid nerve-killing tangles. The chaperone protein cannot disrupt already formed tau tangles.

"In some circumstances, the activated chaperone protein may help stabilize and recycle tau, restoring the protein so it can do its normal job of supporting nerve cell structure," Dr. Dickey said. "But when tau has become abnormally folded, activated Hsp27 may actually hold onto the bad tau without letting go, subverting tau's release or clearance from the brain. In that case, it would be better to inhibit or deactivate Hsp27 to get rid of the tau."

Provided by University of South Florida

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