

Hunting neuron killers in Alzheimer's and traumatic brain injury

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Levels of the protein appoptosin in the brain skyrocket in Alzheimer's disease and traumatic brain injury. Appoptosin is known for helping the body make heme, the molecule that carries iron in the blood. In a study published Oct. 31 in the Journal of Neuroscience, Huaxi Xu, Ph.D. and his group at Sanford-Burnham Medical Research Institute discovered that excess heme leads to the overproduction of reactive oxygen species and triggers apoptosis, causing neurons to die.

Dying neurons lead to cognitive impairment and memory loss in patients with neurodegenerative disorders—conditions like Alzheimer's disease and [traumatic brain injury](#). To better diagnose and treat these neurological conditions, scientists first need to better understand the underlying causes of [neuronal death](#).

Enter Huaxi Xu, Ph.D., professor in Sanford-Burnham's Del E. Webb Neuroscience, Aging, and [Stem Cell Research](#) Center. He and his team have been studying the protein appoptosin and its role in neurodegenerative disorders for the past several years. Appoptosin levels in the brain skyrocket in conditions like Alzheimer's and stroke, and especially following traumatic brain injury.

Appoptosin is known for its role in helping the body make heme, the molecule that carries iron in our blood (think "hemoglobin," which makes blood red). But what does heme have to do with dying [brain cells](#)? As Xu and his group explain in a paper they published October 31 in the [Journal of Neuroscience](#), excess heme leads to the overproduction of

[reactive oxygen species](#), which include cell-damaging [free radicals](#) and peroxides, and triggers apoptosis, the carefully regulated process of [cellular suicide](#). This means that more appoptosin and more heme cause neurons to die.

Not only did Xu and his team unravel this whole appoptosin-heme-neurodegeneration mechanism, but when they inhibited appoptosin in laboratory [cell cultures](#), they noticed that the cells didn't die. This finding suggests that appoptosin might make an interesting new therapeutic target for neurodegenerative disorders.

What's next? Xu and colleagues are now probing appoptosin's function in mouse models. They're also looking for new therapies that target the protein.

"Since the upregulation of appoptosin is important for cell death in diseases such as Alzheimer's, we're now searching for small molecules that modulate appoptosin expression or activity. We'll then determine whether these compounds may be potential drugs for Alzheimer's or other neurodegenerative diseases," Xu explains.

Putting a stop to runaway appoptosin won't be easy, though. That's because we still need the heme-building protein to operate at normal levels for our blood to carry iron. In a previous study, researchers found that a mutation in the gene that encodes appoptosin causes anemia. "Too much of anything is bad, but so is too little," Xu says.

New therapies that target neurodegenerative disorders and traumatic brain injury are sorely needed. According to the CDC, approximately 1.7 million people sustain a traumatic brain injury each year. It's an acute injury, but one that can also lead to long-term problems, causing epilepsy and increasing a person's risk for Alzheimer's and Parkinson's diseases. Not only has traumatic brain injury become a worrisome

problem in youth and professional sports in recent years, the Department of Defense calls traumatic brain injury "one of the signature injuries of troops wounded in Afghanistan and Iraq."

More information: Zhang H, Zhang YW, Chen Y, Huang X, Zhou F, Wang W, Xian B, Zhang X, Masliah E, Chen Q, Han JD, Bu G, Reed JC, Liao FF, Chen YG, & Xu H (2012). Appoptosin is a Novel Pro-Apoptotic Protein and Mediates Cell Death in Neurodegeneration. *The Journal of Neuroscience* : the official journal of the Society for Neuroscience, 32 (44), 15565-15576 PMID: 23115192

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