Protein Protects Neurons in Brain from Damage due to Inflammation

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Could provide target for therapy to treat Parkinson's disease; other neuro-degenerative diseases

A research team from the University of California, San Diego School of Medicine and the Salk Institute for Biological Studies in La Jolla has identified a protein in the brain of mice that protects neurons from excessive inflammation, which can lead to neurodegenerative disorders such as Parkinson's disease. Their study, which identifies the protective function of a protein called Nurr1 and defines the pathway by which it works, will be published in the April 3 edition of the journal *Cell*.

Nurr1 is a transcription factor that has been known for some time to play an essential role in the generation and maintenance of dopaminergic neurons in the brain. Rare mutations in Nurr1 are associated with familial Parkinson's disease, and the loss of dopaminergic neurons – which are the main source of dopamine in the central nervous system – is associated with the disease. Dopamine helps control multiple brain functions such as movement, attention, pleasure, emotion and motivation. The new findings have uncovered a second and previously unexpected role of the Nurr1 protein in two other cell types in the brain – microglia and astrocytes. The brain's microglia are macrophage-like cells that are active components of the immune defense in the central nervous system, while astrocytes are large star-shaped cells that normally play important support functions in the brain.

Working in mice, researchers in the Laboratory of Genetics headed by Fred H. Gage, PhD, professor at the Salk Institute, reduced the expression of Nurr1 in the brain to see how it affected the inflammatory stimulus when the brain was infused with either bacterial lipolysaccharide (LPS) – a potent activator of microglia – or with a mutant form of alpha synuclein that is associated with an early form of familial Parkinson's disease. They found that, in the absence of Nurr1, inflammation was increased in the region where dopaminergic neurons are found, resulting in a toxic effect on those neurons.

fred Gage, PhD

"LPS won't normally kill neurons, but the neurons died when Nurr1 was removed, so we realized that another cell type in the brain must be responding to LPS to cause this toxic effect," Gage said.

Working with isolated cells, researchers in the laboratory of Christopher Glass, MD, PhD, professor of Cellular and Molecular Medicine at UC San Diego School of Medicine and principal investigator of the study, found that microglia were the initial sensors of inflammation. "We found that if we get rid of Nurr1 in microglia, they become very sensitive to inflammatory stimulation and they over-respond, leading to the production of toxic factors." The researchers then found that factors produced by activated microglia are sensed by astrocytes. This cross-talk between the microglia and astrocytes created further inflammatory mediators that were toxic to neurons.

The second part of the study explains the molecular mechanisms that enable Nurr1 to protect the neurons by shutting off inflammatory responses in microglia and astrocytes. The researchers describe a very complex pathway made up of more than a dozen key proteins. Ultimately, the function of this pathway is to shut off expression of genes that produce inflammatory and neurotoxic mediators.

These findings are consistent with a growing appreciation of the potential roles of inflammatory responses in the central nervous system as inducers or amplifiers of a spectrum of neurodegenerative diseases that include Parkinson's disease.

"Although no prospective clinical trials have yet been performed in humans that show a benefit of inhibiting inflammation in any neurodegenerative disease, the presence of signs of inflammation in Parkinson's disease patients suggest that this could be a valuable strategy", said Glass. "The value of the present studies is that they bring to light a cell communication pathway that serves to protect the cells that make dopamine from exaggerated inflammatory responses."

christopher Glass, MD, PhD

Glass added that defects in any one of the proteins involved could thus increase susceptibility to neurodegenerative disease, and that understanding this communication pathway in the brain could provide potential new therapeutic targets to inhibit the production of factors that promote neuronal death.

Additional contributors to the paper include Kaoru Saijo and Jana G. Collier, UCSD Department of Cellular and Molecular Medicine; Beate Winner and Christian T. Carson, Laboratory of Genetics, Salk Institute; Leah Boyer, UCSD Biomedical Science Graduate Program and the Salk Institute; Michael G. Rosenfeld UCSD Department of Medicine and the Howard Hughes Medical Institute.

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