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Researchers 'switch off' neurodegeneration in mice

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Researchers at the Medical Research Council (MRC) Toxicology Unit at the University of Leicester have identified a major pathway leading to brain cell death in mice with neurodegenerative disease. The team was able to block the pathway, preventing brain cell death and increasing survival in the mice.

In human neurodegenerative diseases, including Alzheimer's, Parkinson's and prion diseases, proteins "misfold" in a variety of different ways resulting in the build up of misshapen proteins. These form the plaques found in Alzheimer's and the Lewy bodies found in Parkinson's disease.

The researchers studied mice with neurodegeneration caused by prion disease, as these mouse models currently provide the best animal representation of human neurodegenerative disorders, where it is known that the build up of misshapen proteins is linked with brain cell death.

They found that the build up of misfolded proteins in the brains of these mice activates a natural defence mechanism in cells, which switches off the production of new proteins. This would normally switch back 'on' again, but in these mice the continued build-up of misshapen protein keeps the switch turned 'off'. This is the trigger point leading to brain cell death, as those key proteins essential for nerve cell survival are not made.

By injecting a protein that blocks the 'off' switch of the pathway, the scientists were able to restore protein production, independently of the

build up of misshapen proteins, and halt the neurodegeneration. The brain cells were protected, protein levels and synaptic transmission (the way in which brain cells signal to each other) were restored and the mice lived longer, even though only a very small part of their brain had been treated.

Misshapen proteins in human neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, also over-activate this fundamental pathway controlling protein synthesis in the brains of patients, which represents a common target underlying these different clinical conditions. The scientists' results suggest that treatments focused on this pathway could be protective in a range of neurodegenerative disease in which misshapen proteins are building up and causing neurons to die.

Professor Giovanna Mallucci, who led the team, said: "What's exciting is the emergence of a common mechanism of brain cell death across a range of different neurodegenerative disorders and activated by the different misfolded proteins in each disease. The fact that in mice with prion disease we were able to manipulate this mechanism and protect the brain cells means we may have a way forward in how we treat other disorders. Instead of targeting individual misfolded proteins in different neurodegenerative diseases, we may be able to target the shared pathways and rescue brain cell degeneration irrespective of the underlying disease."

Professor Hugh Perry, chair of the MRC's Neuroscience and Mental Health Board, said: "Neurodegenerative diseases such as Alzheimer's and Parkinson's are debilitating and largely untreatable conditions. Alzheimer's disease and related disorders affect over seven million people in Europe, and this figure is expected to double every 20 years as the population ages across Europe. The MRC believes that research such as this, which looks at the fundamental mechanisms of these devastating diseases, is absolutely vital. Understanding the mechanism that leads to

neuronal dysfunction prior to neuronal loss is a critical step in finding ways to arrest disease progression."

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