Discovery offers hope of halting Amyotrophoic Lateral Sclerosis progression

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Scientists have discovered a causal link between the gene for a small protein involved in the formation of blood vessels and the development of some forms of Amyotrophoic Lateral Sclerosis (ALS).

Published in the journal *Human Molecular Genetics*, the findings could provide a basis for developing methods for halting the progression of some forms of the disease.

Their work builds on the discovery in 2006 by a research group from Ireland that some patients have a mutated form of the gene which produces angiogenin - a protein involved in blood vessel formation.

In a series of recent papers, including the latest one in HMG, Dr Vasanta Subramanian and colleagues from the University of Bath have shown that as well as playing a key role in the formation of blood vessels, angiogenin is also involved in maintaining motor neurones.

The researchers have also discovered that the mutant versions of the molecule are toxic to motor neurones and affect their ability to grow and extend.

The scientists behind the new research believe that the gradual build up of these faulty molecules may explain the late onset and gradual deterioration of function caused by the disease.

By targeting the altered form of angiogenin, it may be possible to better

maintain the neurones of people with the disease, in order to prevent them from degenerating and halt progression of the disease.

ALS, which is also known as Motor Neurone Disease, affects between one-five of every 100,000 people, and around 5,000 people at any one time in the UK.

Some ALS patients of Scottish and Irish descent as well some ALS patients in the USA have the mutated gene which produces faulty angiogenin.

“We know most about angiogenin from its role in helping blood vessels branch into the tree-like structures as they grow, particularly in tumour growth,” said Dr Vasanta Subramanian from the University of Bath’s Department of Biology & Biochemistry.

“Last year’s discovery that some patients with both familial and sporadic ALS have a mutated version of the human angiogenin gene was surprising because we didn’t know how angiogenin could be connected with the disease.

“Since then we have been busy trying to find out, and now we have shown that angiogenin also plays a key role in the maintenance and development of motor neurones.

“We have also found that mutated versions of this molecule are toxic to motor neurones and affect their ability to put out extensions called the axons.

“This clearer picture of how the altered angiogenin works at the cellular and molecular level enables us to think about ways of preventing the disease from progressing.

“The symptoms of ALS begin to appear as the neurones which control movement begin to degenerate.

“If we can block the function of the faulty angiogenin in patients in which it is present this may help to maintain healthy neurones and prevent further progression of the disease.”

Funded by the Wellcome Trust and the Medical Research Council, the researchers looked for where angiogenin is produced (expressed) in developing mouse embryos. They found that it was widely expressed in the nervous system both in the brain and in the spinal cord, mostly in the neurones.

As the mouse embryo developed, the amount of angiogenin gradually reduced but was still expressed in the brain and spinal cord of adult mice.

They then used a molecule to inhibit the activity of the angiogenin gene in neurones and discovered that the absence of angiogenin affected the neurone’s ability to extend nerve projections; a process known as neurite pathfinding.

They then examined the effect of a mutated angiogenin on motor neurones and found that the molecule effects motor neurone pathfinding. They also discovered that the mutated angiogenin is toxic to motor neurones when the nerve cells are subjected to oxidative stress.

This suggests that angiogenin acts as a neurotrophic and neuroprotective factor that helps neurones to survive.

“There is still much to be done in order to better understand the precise nature of the disease mechanism and the role played by the altered forms of Angiogenin,” said Dr Subramanian.

“When we figure out exactly what goes wrong, we can start to develop ways of preventing progression of this neurodegenerative disease.”

In ALS, the neurones responsible for transmitting the chemical messages that enable muscle movements become affected and subsequently die, causing muscle weakness and wasting leading to death by asphyxiation.

Famous people who have succumbed to the disease include actor David Niven and baseball player Lou Gehrig. Professor Stephen Hawking is exceptional; he has survived with the disease for more than 35 years.

Source: University of Bath