Research Briefings

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Molecular mechanisms of neurodegeneration

MANY COMMON DISEASES OF THE NERVOUS SYSTEM RESULT FROM THE LOSS OF PARTICULAR CELL GROUPS OR TYPES. IN MOST CASES IT IS NOT KNOWN HOW OR WHY THESE CELLS DIE. BY STUDYING A PARTICULAR MUTATED GENE THAT CAUSES AN INHERITED FORM OF MOTOR NEURON DISEASE WE HOPE TO FIND CLUES ABOUT WHAT MOLECULAR PROCESSES CAUSES CELLS TO DEGENERATE AND ULTIMATELY DIE.

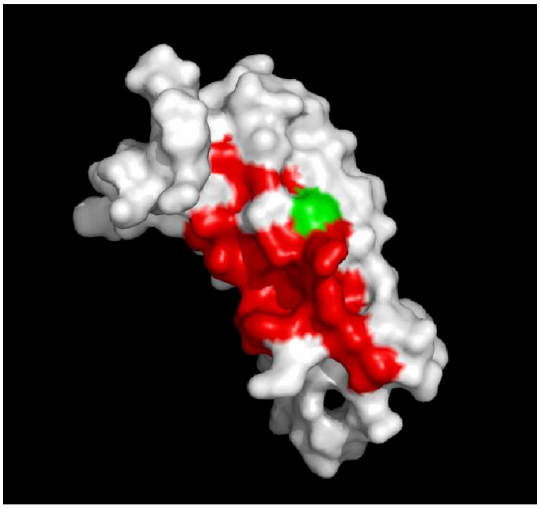
BACKGROUND.

Amyotrophic Lateral Sclerosis type 8 (ALS8) is a late on-set familial motor neuron disease (MND) that is inherited in an autosomal dominant fashion. Although inherited motor neuron diseases are much less common than sporadic, both share very similar pathologies. It is anticipated therefore, that the diseases share similar pathological mechanisms. ALS8 is caused by single a mis-sense nucleotide substitution in the human *vapB* gene that causes a proline residue to be replaced by a serine, $vapB^{P56S}$. One effect of this mutation is to cause the protein to aggregate. Protein aggregations are found as markers of pathology in many degenerative diseases. In most cases, however, the contribution of these aggregates to the pathological mechanisms of disease remains unclear. Similarly, the effects of intracellular protein aggregation induced by the ALS8 mutation are not known.

VAP PROTEINS.

VAMP/Synaptobrevin Associated Proteins A and B (VAPA and B) are a small family of highly conserved eukaryotic type II membrane proteins originally identified in the marine mollusc *Aplysia californica*. Both VAPA and VAPB are enriched on the surface of the endoplasmic reticulum, (ER). A number of functions related to membrane trafficking and metabolism have been ascribed to them, including association with the microtubule network, and interaction with soluble lipid transport proteins. VAP proteins may, therefore, be considered as docking points where cytosolic constituents interact with the surface of the ER.

The ER is the site of secreted and membrane protein synthesis and a store of readily releasable Ca^{2+} for intracellular signalling. Different cell types and physiological conditions



Picture 1.
The ALS8 mutation (shown in green) lies in the middle of a conserved region the protein predicted to participate in protein-protein interactions (shown in red).

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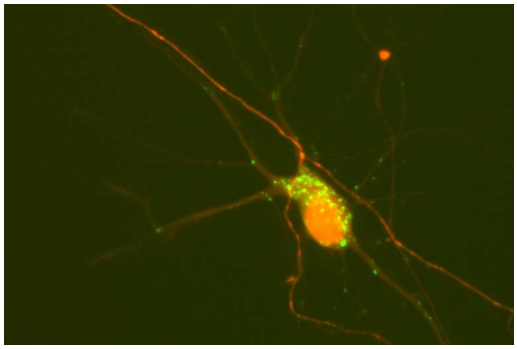
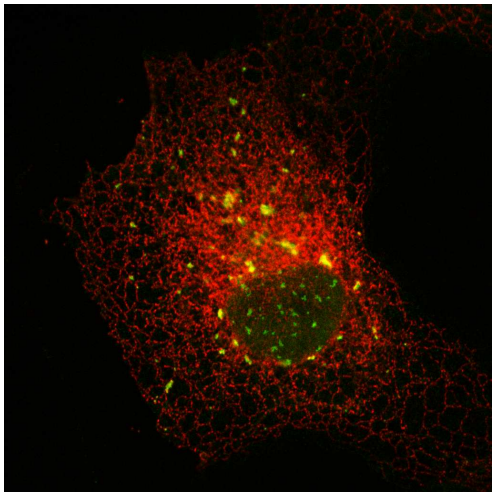
make specific demands on ER function. Stress response pathways controlling both transcription and translation act to adjust the capacity of the ER to particular cellular demands. One of these pathways is called the Unfolded Protein Response, or "UPR". In addition to their structural role, VAP proteins may also interact with these ER regulatory pathways.



Picture 2 &3 . Fluorescent fusion proteins of VAPB^{P56S} form intracellular aggregates when expressed in HEK293 cells or primary hippocampal neuron cultures.



The exact nature of this interaction remains controversial, but our work focuses on the effects of VAPB and VAPB^{P56S} on the transcription factors that mediate the UPR. By studying the physical and biochemical properties of VAP proteins and how these are affected by the ALS8 mutation we will learn about the cellular responses to VAP^{P56S} that ultimately lead to neurodegeneration.

In the future we hope to extend this work by generating genetically modified mice as models of ALS8. These may then be used to define genome wide effects of VAP^{P56S} expression and the pathophysiological effects of the mutation.

Selected references

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