Research Project:

Towards a pharmacological model of Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

Principal researcher: Dr. Federico Herrera, University of Lisboa (Portugal)

Scientific summary

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is a rare ataxia caused by loss-of-function mutations in the sacsin chaperone protein. Researchers led by Dr. Federico Herrera at the University of Lisboa, Portugal, as well as others, have shown that alterations in the intermediate filament (IF) of the cytoskeleton and mitochondrial networks are likely the most common hallmark in current cell culture and in vivo models of ARSACS.

A naturally occurring compound called Withaferin A (WFA) inhibits the organisation of fibres of type III IFs. In this project, the researchers now propose that WFA could mimic ARSACS features caused by sacsin deletion, at least those dependent on IF organisation. The team recently developed and characterised two glial cell models of ARSACS in C6 rat glioblastoma and HMC3 human microglial cell lines, with preliminary results showing anomalous distribution of glial IFs and associated proteins, mitochondria and Golgi apparatus. In HMC3 sacsin knockouts and C6 rat glioblastoma, treatment with WFA produced IF and mitochondrial phenotypes similar to genetic models of ARSACS.

Therefore, the researchers propose a pharmacological model of ARSACS which would differentiate between IF-dependent and independent alterations in ARSACS. They plan to analyse the proteome of C6, HMC3 and primary mouse astroglia with and without WFA, characterise the effects of WFA incubation on several aspects of C6, HMC3 and primary mouse astroglia, and analyse the effect of WFA and sacsin deletion on glial intermediate filaments networks.

The alterations observed in this pharmacological model of ARSACS will be compared with the alterations found in genetic models of the disease recently developed in their laboratory. The researchers hope their results will lay the groundwork for the use of WFA as a pharmacological model of ARSACS and advance knowledge of the disease.

Lay summary

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Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is a rare form of ataxia caused by the loss of function of a protein called sacsin, which is thought to be due to the inactivation of the sacsin gene that codes for the sacsin protein. Sacsin proteins are needed to organise filament structures that make up part of the scaffolding of cells called the cytoskeleton. These filaments, known as intermediate filaments, help nerve cells to communicate with each other, and with muscle cells, needed for movement. Researchers led by Dr. Federico Herrera at the University of Lisboa, Portugal, have previously shown using animal and human cell models that changes in intermediate filaments, as well as in the energy centres of cells called mitochondria, are key features of ARSACS.

A drug called Withaferin A (WFA) could mimic the cellular effects caused by inactivation of the sacsin gene in ARSACS. In this project, the researchers now plan to treat animal and human cells with WFA to observe its effects on the cell cytoskeleton and the mitochondria. The team will compare results from their WFA model of ARSACS to results from their genetic models of ARSACS.

The researchers believe that this could be a new, easy to use, model to study ARSACS and can be used to test therapies for the condition.

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