Research project:

Investigating the role of bioactive sphingolipids in Friedreich's Ataxia

Principal researcher: Dr Sara Anjomani Virmouni, Brunel University, London (UK)

Scientific Summary

In recent years, there has been a growing interest in the use of metabolomics in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. However, insufficient resources have been dedicated to studying alterations in the levels of small molecules, metabolites, and lipids in Friedreich's ataxia (FA). The group recently applied mass spectrometric-based methods to identify, quantify and characterise differentially regulated molecules in FA human fibroblast cell lines. Their lipidomic profiling using Rapid Evaporative Ionisation Mass Spectrometry (REIMS) revealed potentially interesting sphingolipid species that were significantly different in FA cells.

Interestingly, among the altered sphingolipids, they identified two bioactive species, ceramide (C) and ceramide-1-phosphate (C1P), which together with sphingosine-1-phosphate (S1P), are part of the "sphingolipid rheostat". These interconvertible molecules have opposing effects in signalling pathways that are major determinants of cell fate. Therefore, alteration in the expression or the activity of the enzymes regulating the balance of these sphingolipids can trigger pathways that contribute to neurodegenerative processes. These findings suggest that modulating the sphingolipid rheostat could serve as therapeutic target for FA.

During this project, the group aims to assess the efficacy of targeting relevant metabolic enzymes involved in the altered sphingolipid pathways with implications for future FA therapy.

Lay Summary

Friedreich's ataxia (FA) is caused by the reduction of a specific protein found in cells, called frataxin. Although this has been known for many years, the knock-on effects that the loss of frataxin has on other processes in cells are constantly being discovered. This project aims to study one of these processes in more detail, which could lead to alternate options for treatments.

Lipids are important components of all living cells. A specific group of lipids, called sphingolipids, are particularly important for brain function. Sphingolipids are known to have a role in a number of other neurodegenerative conditions, such as Parkinson's disease. These researchers previously measured the levels of sphingolipids in cells from people with FA. They found that the levels were different when compared to cells taken from people that did not have FA. This suggests that sphingolipids could also play a role in the neurodegeneration that occurs in FA.

Sphingolipids can determine the fate of a cell. A specific sphingolipid, called Cer, can trigger a cellular pathway, which ends in the death of the cell. If the level of Cer gets too high in brain cells it would contribute to neurodegeneration. Another sphingolipid, called CerP, promotes

survival of cells, which would protect against neurodegeneration. Therefore, the different levels of these sphingolipids is very important for maintaining cells in the brain and preventing neurodegeneration. During this project, the researchers will study the respective levels of these different types of sphingolipids to determine the role they might play in FA.

Finally, Dr Anjomani Virmouni and her team will use drugs to increase or decrease the levels of these sphingolipids in cell models of FA. This will tell them whether this could be a way to treat the condition in people.

Dr Anjomani Virmouni said: “The aim of this project is to have a clear picture of the sphingolipid changes in FA, and to identify potential targets for the development of treatments. The results from this study will provide valuable information to allow us to test this theory in animal models of FA, and eventually, if successful, to bring this approach to clinical trials.”

For more support or information please contact: Ataxia UK, 12 Broadbent Close, London, N6 5JW
Website: www.ataxia.org.uk.
Helpline: 0800 995 6037 Tel: +44 (0)20 7582 1444
Email: helpline@ataxia.org.uk.