ARC 2015 Session 5 Lay Summary: Drug discovery and emerging therapeutic strategies

This session on drug discovery and emerging therapeutic strategies addressed potential treatment modalities for Friedreich Ataxia (FA) and the spinocerebellar ataxias (SCA).

During this session several different molecular approaches were presented, all attempting to increase frataxin levels, the protein which is deficient in people with FA. Dr Elisabetta Soragni from the Scripps Research Institute in USA described how a loss of frataxin in FA is due to gene silencing, and that this silencing may be modifiable by targeting histone acetylation. Histone acetylation is a process which can turn gene expression on which results in the production of a protein, or off which results in the silencing of the gene - this is the case of the frataxin gene. Their group demonstrated that using a class of histone deacetylase (HDAC) inhibitors improves frataxin gene expression in patient cells by decreasing gene silencing. These increased levels were maintained for up to 12 hours after the treatment was stopped. The researchers are now selecting appropriate HDAC inhibitors as candidates for use in clinical trials as a future potential therapy.

Dr Hagar Greif from BioBlast Pharma (Israel) presented his research which involved testing protein replacement therapy for FA. Using this approach, they were able to transfer a new fusion protein which they've created, which includes the protein frataxin (usually deficient in people with FA), directly into the mitochondria of frataxin deficient cells. Patient cells treated this way showed increased levels of energy production and a better resistance to oxidative stress, both functions usually reduced in people with FA.

Then they tested this therapy on mice with FA, who were given injections of the fusion protein over a 21 day period. They found that the treated mice were able to take up and process frataxin in their mitochondria in multiple tissue types, including the kidney, heart and brain, as well as having an increased lifespan. The research group anticipates bringing this molecule to clinical trials in 18-24 months.

Additionally, Dr Fatih Ozsolak (RaNA Therapeutics, USA) presented a study using oligonucleotides, short sections of DNA or RNA strands, as agents to increase frataxin levels in cells and found positive results in a mouse model. Concurrently, Catherine Gérard from Laval University in Canada reported her research on the use of an un-harmful adeno-associated virus (AAV) as a vector to deliver frataxin into the cells. Their results demonstrated an increased expression of frataxin in mouse tissues, and this was associated with increased lifespan and improved heart function. The research discussed during this session displayed the wide variety of therapies that researchers are studying for people with FA.

There were also many talks on spinocerebellar ataxia research. For example, Dr Melvin Evers (Leiden University Medical Center, Netherlands) talked about his research using protein modification to lower the toxic effects of the protein ataxin-3, which usually only becomes toxic in people with SCA3. Despite its toxicity, it is still an important functioning protein in the human body, therefore by maintaining its function but decreasing its toxicity, the team hope to treat some of the symptoms of SCA3.

The research presented at the conference on drug discovery and emerging therapeutic strategies displayed the innovative and broad range of avenues that ataxia researchers are using to move ataxia research forward.

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