IARC 2015 Lay Summary Session 2: Genetic and Molecular Mechanisms of ataxias

The second session of the conference proved to be very informative with regards to our understanding of genetic processes occurring with ataxia. In particular, some researchers shed light on the molecular underpinnings of gene silencing in the frataxin gene (FXN), which is responsible for causing Friedreich's ataxia (FA). Additionally, the identification, characterization and mechanisms of several spinocerebellar ataxias (SCA) were also the major focal points of this session.

Dr Evans-Galea (Murdoch Childrens Research Institute, Australia) showed how different types of mutations in FXN gene can affect the level of the protein frataxin in the cell. This is shown to correlate with different secondary disorders (an additional disorder that co-occurs with ataxia). In particular, individuals with FA that inherit GAA repeat expansions from both parents seem to have a greater likelihood of developing heart disease. Genetic expansions are mutations whereby a trinucleotide, in this case GAA, is repeated by accident in the DNA code, causing the production of a modified protein. Alternatively, those with mutations that produce a protein with no function (instead of frataxin) are more likely to have diabetes mellitus.

The importance of the length of GAA repeats in the expression of frataxin was also discussed. It was shown that the greater the length of repeats, the lower the level of frataxin protein there will be. For example, Prof Bidichandani (University of Oklahoma, USA) described his research involving a specific histone deacetylase (HDAC) inhibitor. HDAC is important for the expression of proteins such as frataxin as it is responsible for changing the structure of DNA

which leads to the gene being switched off. This is because the structural change prevents transcription from DNA to RNA (the first step of protein production) from occurring. Thus by inhibiting HDAC, it allows for transcription

to take place and frataxin to be produced. Prof Bidichandani found that treatment with a specific HDAC inhibitor increased the amount of new RNA being produced which encoded for the protein frataxin. This was found to be dependent on the lengths of the repeats found in the FXN gene.

Another very exciting talk from this session was given by Prof Steve Jackson (University of Cambridge, UK), who used genetic principles as a guiding tool for drug discovery. Currently, Prof Jackson is using the principle of synthetic lethality to guide his search for drugs to treat ataxia telangiectasia mutated (ATM). Synthetic lethality is when a mutation in one out of two genes doesn't cause a problem as they can compensate for one another, however a mutation in both causes cell death. The genetic principle of synthetic lethality can be applied to drug design to prevent DNA damage and neurodegeneration in ATM. This has proven to be very useful in other areas of biomedical research, such as cancer therapy and drug development.

Progress in our understanding of the molecular mechanisms behind SCAs was also made. Dr Thorsten Schmidt (University of Tuebingen, Germany) presented his research on finding treatments for spinocerebellar ataxia type 3 (SCA3), which is characterised by an abnormal ataxin-3 protein due to a mutation in the gene ATXN3 which encoded for this protein. Dr Schmidt and his colleagues had demonstrated previously that the abnormal ataxin-3 forms clusters (also called "aggregates") inside the nucleus of cells which damage the cell. If however the abnormal protein stays outside of the nucleus of the cell, it does not do the same damage. They looked for possible drugs that would stop the abnormal protein from going into the nucleus, and have found a promising candidate.

Conclusively, great progress was made in our understanding of what goes on inside the cells of people with all different forms of ataxias, which is crucial information for furthering new developments in treatments.

By Ms Angelical Martin (Duke University, USA), Dr Simona Donatello (Université libre de Bruxelles, Belgium) & Dr Rebekah Jobling (The Hospital for Sick Children, Toronto, Canada)