IARC 2015 Session 3b: Cellular & Animal Models of other ataxias

The mechanisms leading to nerve cell damage in the brain of people with cerebellar ataxia are not yet fully understood. So far, no efficient treatment has been found to prevent, stop or reverse this neurodegenerative process occurring with ataxias. This emphasizes the need to create and use *in vivo* and *in vitro* models of cerebellar ataxias; in this session, investigators presented their work using animal and human cell-based models.

Using the worm *C. elegans*, Liliana Santos (The University of Minho, Portugal) investigated the causes behind neurodegeneration underlying spinocerebellar ataxia type 3/Machado Joseph Disease. She showed that some nerve cells are more affected by the production of the modified protein ataxin-3 than others. This could be due to the type of neurotransmitter the nerve cells are responding to (neurotransmitters are the chemicals responsible for transmitting signals from one nerve cell to another).

In both a fly and a mouse model, Dr Olga Baron (King's College London, UK) showed that the degeneration observed in Dentatorubral-pallidoluysian atrophy (DRPLA) may be due to the deregulation of the cellular process known as autophagy. This is when cellular proteins or components that are damaged or no longer needed by the cell are broken down or degraded, for example as a repair mechanism to remove damaged cellular proteins.

Moreover, Dr Natascia Ventura (Leibniz Institute for Environmental Medicine/Heinrich Heine University of Dusseldorf, Germany) showed that changes in the mitochondria (the energy production centre cells) were also associated with the onset of ataxia, and Dr Cecilia Mancini

(University of Torino, Italy) showed that this was particularly relevant to SCA28.

Several mouse models were used to decipher the development of SCA3 in Prof Olaf Riess' lab (University of Tubingen, Germany). The work presented reinforces the importance of the nuclear location of the modified protein in SCA3 and also how the protein is broken down in the body with regards to toxicity. Furthermore, Prof Riess also showed that turning off the production of the modified ataxin-3 protein in a mouse model of the disease reversed the phenotype in the early stages of SCA3.

Moreover, Isabel Onofre (Center for Neuroscience and Cell Biology, Portugal) presented a new human cell model of SCA3 that attempts to overcome the limitations of animal models, such as their ability to replicate how the human body behaves. Using fibroblasts, a type of connective tissue collected from patients through a skin biopsy, it was possible to induce their ability to become any type of cell, termed induced pluripotent stem cells (iPSCs). These can then be made into neurons, allowing further assessment of disease pathogenesis and drug screenings in a physiologically relevant context.

Despite the limitations of these animal and cell models, they are valuable tools for getting a better insight into the mechanisms of disease progression and to assess the potential therapeutic effects of new drugs.

By Ms Joana Duarte-Neves, the University of Coimbra, Portugal