IARC 2015 Session 4 Lay Summary: Cellular and Systemic Pathways

Session 4 highlighted the use of cells and organisms such as worms, yeast and mice, to understand the pathology of ataxias, with special focus on Spinocerebellar ataxia 3 (SCA3) and Friedreich's ataxia (FA).

The first invited speaker, Prof Kamran Khodakhah (Albert Einstein College of Medicine, USA) discussed how dysfunction in the transmission of information signals between nerve cells in the cerebellum is associated with reduced motor coordination. The speaker also described mouse models used to examine how cerebellar cells process information signals in normal and disease conditions to subsequently uncover potential therapies for cerebellar ataxias.

The second invited speaker, Dr Henry Paulson (University of Michigan, USA), discussed the factors that contribute to the dysfunction of neuron cells and the loss of these cells in SCA3. A mouse model with SCA3 revealed that the ataxin-3 protein could form toxic aggregates in certain brain regions, but also that an alternative form of the protein could be found. Also in SCA3, Sofia Esteves (University of Minho, Portugal) described a drug screening using a worm containing the CAG triplet repeat expansion, a common mutation in SCA3, to reproduce the disease. This screening revealed that the drug Citalopram could improve the worm's motor coordination and resolve the toxic aggregation of the ataxin-3 protein. The speaker tested the drug in a SCA3 mouse model which showed a reduction of disease symptoms.

David Alsina (Universitat de Lleida, Spain) used a yeast model to analyze the function of the frataxin protein and the result of its deficiency in Friedreich's

ataxia. After switching off the frataxin (FXN) gene in yeast cells there was a loss of iron regulation, essential for the survival of cells, and an increase in oxidative stress, which damages cells. The speaker also talked about the importance of the interaction between frataxin and Yhb1, a protein relevant to iron regulation when frataxin protein is absent.

Dr Javier Diaz-Nido (Universidad Autonoma de Madrid, Spain) used neuron cells to study what happens when frataxin is removed. These cells were found to die prematurely and showed both increased oxidative stress and DNA damage. Moreover, neighboring cells that usually surround neurons also died and showed increased oxidative stress in the absence of the frataxin protein. Prof Joaquim Ros (Universitat de Lleida, Spain) also showed that removing frataxin from nerve cells leads to their premature death. Moreover, the speaker showed that treating these cells with cyclosporine A, which binds to surplus calcium inside these cells, would impede cell loss. Lastly, Angelical Martin (Duke University, USA) and Dr Amanda Stram (Indiana University, USA) both showed their work on a mouse model lacking frataxin only in the heart. When frataxin was absent, the energy production in heart cells was compromised and led to heart dysfunction. Treatment with nicotinamide was able to improve energy production in the heart cells of these mice.

Overall, all of these studies using various disease models proved to be invaluable to understanding the cause of these diseases and moving towards new potential therapies being uncovered.

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