Randy Maysaud – EN.585.685.81 – Module 2 Case Study – Models in Neurobiology

Question/Biological Problem (10 points)

Friedreich ataxia (FA) is a disease that produces nervous damage and movement problems. FA degenerates the peripheral nerves and the nerve fibers in the spinal cord.[1] This disease ultimately affects the whole-body causing scoliosis, foot deformities, heart problems, hearing and vision impairment, and slurred speech.[2] FA is caused by a mutation in the gene FXN which holds the genetic code for the frataxin protein. The defect creates a frataxin deficiency which results in the damage of iron-sulfur cluster synthesis causing abnormalities in ATP production.[3] The disease is spread by autosomal recessive inheritance, meaning both parents must pass down the faulty FXN gene for the individual to inherit the disease. There is currently no cure for FA and is still being researched for further understanding.

AIM: To build a model that examines the effect of genetically correcting Friedreich ataxia cells and introducing it as cell replacement therapy.

Research Model and Plan (10 points)

- To genetically correct and reintroduce cells from Friedreich ataxia, I need to build a model using induced pluripotent stem cells (IPSCs). This model will incorporate pluripotency genes (KLF4, SOX2, c-Myc, and Oct-3/4) to fibroblast cells to create induced pluripotent stem cells. The IPSCs will be used to genetically correct the FXN gene creating healthy cells, allowing for cell replacement therapy.
- To genetically correct the FXN gene, I will need to perform a gene replacement. I need to replace the defect FXN gene with a healthy FXN gene. To perform this action, I will need to use CRISPR since it has the adaptability to perform a gene knockout and knock in. CRISPER works by using sgRNA which forms a ribonucleoprotein that works with the CAS9 which guides the protein to the targeted FXN. It then will create a double stranded break knocking out the faulty gene and knocking in the healthy FXN gene.
- With the cells now fixed and healthy we can introduce it back to the body with the process of cell replacement therapy.
- I believe this model to be most effective, because IPSCs are efficient in creating accurate environments for human diseases and the versatility of CRISPR will allow for gene replacement (gene knockout and knock in). What I hope to accomplish with this model and aim is to examine cell therapy as a possible treatment for FA. This model can determine the effectiveness of cell replacement therapy for FA, which can help further research for an FA treatment.

References:

[1] U.S. Department of Health and Human Services. (n.d.). *Friedreich ataxia fact sheet*. National Institute of Neurological Disorders and Stroke. Retrieved September 10, 2021, from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Friedreichs-Ataxia-Fact-Sheet.

[2] *Friedreich's ataxia*. Johns Hopkins Medicine. (n.d.). Retrieved September 10, 2021, from https://www.hopkinsmedicine.org/health/conditions-and-diseases/friedreich-ataxia.

[3] Clark E;Johnson J;Dong YN;Mercado-Ayon E;Warren N;Zhai M;McMillan E;Salovin A;Lin H;Lynch DR; (n.d.). *Role of frataxin protein deficiency and metabolic dysfunction In Friedreich ataxia, an autosomal RECESSIVE mitochondrial disease*. Neuronal signaling. Retrieved September 10, 2021, from https://pubmed.ncbi.nlm.nih.gov/32714592/.