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Ageing caused by CISD2 (Wolfram Syndrome 2)**Neda Niazi****Introduction:**

Wolfram Syndrome is a rare, inherited neurodegenerative disorder. There are two types Wolfram Syndrome 1(WFS1) and Wolfram Syndrome 2 (WFS2). They are both inherited in an autosomal recessive pattern, which means both copies of the gene carry mutations. Wolfram Syndrome 1, aka DIDMOAD syndrome, is characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness¹¹. The causative gene for WFS1 is wolframin, which functions in maintaining the homeostasis of the endoplasmic reticulum in pancreatic β cells. Basically when a WFS1 gene mutation produces the wolframin protein, calcium levels are not balanced and the ER doesn't function properly. Studies have shown that cells from affected individuals with Wolfram syndrome 2 did not show differences in resting intracellular calcium concentrations when compared to controls but when stimulated, affected cells had significantly higher calcium influx than control cells. Thus, cellular and endoplasmic reticulum calcium concentrations may also be important in Wolfram Syndrome 2¹. Calcium concentrations can increase and decrease ER stress. ER stress can lead to the unfolded protein response (UPR), which is involved in the cell's fate of life or death. In a resolvable ER stress condition, the UPR promotes β -cell survival; however in an unresolvable ER stress condition, the UPR activates death, leading to β -cell apoptosis¹. This is a problem in the cells of pancreas, particularly in the pancreatic beta cells, which make insulin, die. Therefore, diabetes is developed because levels of glucose cannot be regulated.

Recently CISD2, the causative gene for WFS2 has been identified. WFS2 results in diabetes mellitus, optic atrophy, and shorten lifespan (premature aging); however, there is no diabetes insipidus. CISD2 gene provides instructions for making the CSID2 protein, which is located in the outer membrane of mitochondria and endoplasmic reticulum⁸. Mitochondria produces ATP; therefore, they are energy producing organelles in all cells that have a mitochondrion. The function of CISD2 is unknown; however it may help mitochondria function normally. The mutated CISD2 protein is a small nonfunctional protein; therefore, mitochondria cannot be sustained. Basically the loss in mitochondria means that there is not enough energy provided for the cells. Cells that do not have enough energy will eventually die¹¹. Chen et al concludes that CISD2 is involved in mammalian lifespan control. The experiment, which compared Mice with CISD2 with a control and the results revealed that premature age was characterized by prominent eyes, protruding ears, corneal opacities and degeneration, thinner bones and hair, and decreased muscle mass, all of which were consistent with premature aging. Also tissue from mutant mice showed progressive mitochondrial breakdown and dysfunction, accompanied by autophagic cell death, which precede nerve and muscle degeneration¹¹. Basically CISD2 affects a protein that is part of the mitochondrial membrane and if this organelle is no longer able to carry out its energy production function, then this will damage those cells that require a large supply of energy such as muscle and nerve cells because energy is always required by these cells to carry out their normal functions.

Experiment:

The purpose of this experiment is to identify aging due to a mutation in the CISD2 gene. There will be two groups. Group #1 will be the knockout mice (containing mutated CISD2 gene). Group #2 will be 10 wildtype mice. The physical activity performance as both groups of mice

age will be measured. Also the glucose blood levels and death rates in both groups will be measured.

Physical Activity:

Both groups of mice will have to go through an obstacle course and the amount of time it takes them to finish the course will be recorded. This will be done six times (2 times each month) over the course of 3 months.

Glucose/insulin Blood levels:

A 7 mm cut will be applied to the tail. Next blood samples will be collected from tail tips. The blood glucose levels will be measured using glucose test strips (LifeScan; Johnson & Johnson) and Sure Step Brand Meter³.

Death Rate:

How long it takes mice from both groups stay alive. Death rates may take a long time, about two months, but it's a good thing to measure because it reveals that we need cells that work properly and have enough energy! Without energy, our cells cannot function properly and eventually will lead to apoptosis, which will affect many parts of the body.

Discussion:

If all goes well the Knockout mice with WFS2 will show decreased physical abilities, low glucose levels and an increase in death rate. These results will establish WFS2 as a mitochondrial-mediated disorder; therefore the dysfunction in these cellular energy regions (mitochondria) underlies muscle and neural cell degeneration, and accelerated aging. I believe glucose is going to be low in the blood since ER stress causes pancreatic Beta cells to die and insulin doesn't reach the cell. Basically when we eat, glucose levels rise, and insulin is released into the bloodstream. The insulin acts like a key, opening up cells so they can take in the sugar and use it as an energy source. However, since insulin won't be produced cells won't have energy to function. A shortage of ads to progressive loss of [beta] cells and impaired glucose tolerance, which is presumably caused by increased stress and apoptosis in [beta] cells⁸. An increase in running time in the obstacle course or jumping time will reveal a muscle and nerve cell degeneration. This will show age progression because there will be a loss of function in many parts of the body. Also death should be increased in the mice with WFS2 since aging leads to death and degeneration of cells and muscles.

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