Module 7 - Case Study: Aging by Arghya Sharma **10/16/2021**

Background: By the process of mitophagy, dysfunctional mitochondria is removed which further reduces the mitochondrial mass. As we age mitochondrial biogenesis declines, this leads to accumulation of mutations which decrease the mitochondrial DNA volume, functionality and its integrity [1]. Mitophagy is a kind of macro-autophagy in which mitochondria are specifically targeted for autophagic degradation. Defects in mitophagy are thought to be also the cause of oxidative damage induced by reactive oxygen species (ROS) [3]. These factors could further accelerate the process of aging.

Aim: Increase in ROS production and decrease in mitochondrial function is predicted to promote aging. Since mitophagy is the process that controls both mitochondrial functioning and ROS production through this case study I aim to build a model to understand how defects in mitophagy's impact on cellular senescence.

Research plan: Monitoring of accumulation of ROS, and the presence of dysfunctional mitochondria will be used to understand how defects in mitophagy will affect the life span of living organisms. Cells execute mitophagy through several non-redundant mechanisms, one of the best understood pathways for mitophagy are PINK1/Parkin induced mitophagy [3].

For this study, I will have two groups of mice (same aged mice in both groups). Group 1 will be healthy mice that carry mitophagy normally. Group 2 will be mutated mice. I will introduce mutations in the PINK1 gene in group 2 mice, by using a gene editing tool based on a bacterial toxin that can help in editing mitochondrial DNA by changing one letter into another [2]. This gene editing tool has the same approach as the CRISPR/Cas9 system, but we use this new tool for the case study instead of CRISPR/Cas9 system because CRISPR/Cas9 system relies on a small piece of “guide” RNA, and how to transport guide RNA into mitochondria is still unknown [2]. Once the mutated group of mice is ready, we can start the monitoring of ROS production and presence of dysfunction mitochondria (in both group 1 and group 2).

We will use fluorescent probes for ROS (ROS assay kit can help in detecting ROS in live cells) and to test for mitochondrial dysfunction we will perform a brain and spine MRI of the mice. These two techniques can help us visualize and help us understand how disruption in the process of mitophagy affects ROS production and mitochondrial functioning. Last step of the study would be to observe which group of mice are living longer (given that both groups of mice will be kept on the same diet, lifestyle and environment).Through this study we will be able to find the role defects in mitophagy play not only in shortening a life span but also on factors like ROS and mitochondria, that are seen as major contributors of aging. If we get definitive answers through this study, researchers can come up with therapies that can focus on improving the process of mitophagy (as it slows down due to age or illness), which can directly affect ROS production and mitochondrial functioning, and enable an individual to live a longer life.

References:

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