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Short Communication

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Pancreas: Do All Roads Lead to Mitochondria?

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Over several millions of years of evolution, mitochondria have transformed into specialized organelles. Today, they cannot live outside the cell nor can the host cell live without them, resulting in a symbiotic relationship. Richard Altmann, in 1894, documented them as cell organelles and called them "bioblasts". Later, the term "mitochondria" itself was coined by Carl Benda in 1898. Ever since these findings, we in the field of medicine have learned a lot about this tiny organelle, but numerous aspects continue to be discovered. In this article, we will review the significance of this organelle in terms of pancreatic dysfunctions.

Mitochondria are a double membrane organelle and are often considered to be "the powerhouse of the cell." This organelle is extremely important to the maintenance of vital biological processes such as the Krebs cycle, Tricarboxylic acid (TCA) cycle, the generation of Adenosine Triphosphate (ATP) (the body's main energy source), signal transduction, cell growth, cell death and much more. Due to the many roles that the mitochondrion plays in these biological processes, it is evident that any type of mitochondrial dysfunction would result in a myriad of diseases. Over the past decade, we have become aware of several clinical syndromes that might be associated with mitochondrial DNA (mt-DNA) mutations. The increasing recognition of mt-DNA involvement in disease is partially due to the relative ease of sequencing the mitochondrial genome.[1] Mitochondrial DNA (mt-DNA) carries only 37 genes that encode 13 polypeptides, 22 transfer RNAs (tRNAs) and 2 ribosomal RNAs (rRNAs).[2] A number of the common diseases that have shown to have possible mt-DNA variations are Alzheimer's disease, Parkinson's disease and diabetes. The associations of these diseases with mt-DNA mutations have encouraged a large number of studies.[1] The mitochondrial electron transport chain is an important site of Reactive Oxygen Species (ROS) production within the cell. Despite intracellular protective mechanisms, including superoxide dismutase, catalase and reduced glutathione, excess ROS is detrimental to cellular physiology.[3] Aging, defined as an irreversible decline in physiologic function overtime, is also characterized by mitochondrial dysfunctions. Neurons are also known to be vulnerable to mitochondrial dysfunction, synaptic regions of axons are known to contain abundant mitochondria, thus suggesting that mitochondrial dysfunction may play a key role in many neurological diseases such as Parkinson's and Alzheimer's disease.[4] Current research is starting to highlight the relationship of mitochondrial dysfunction with a multitude of diseases. The pancreas is one such organ where more research is necessary to identify possible treatments for mitochondrial related ailments. Already, pancreatitis, diabetes, and pancreatic cancer have shown a connection with mitochondrial dysfunction to certain subgroups of these diseases.

Diabetes may be one of the most studied diseases when it comes to mitochondrial dysfunction related to pancreatic issues. Diabetes includes a wide group of conditions that overall cause hyperglycemia.[5] Recent research has shown mutations in mt-DNA can be related to diabetes. Wang, et al. suggested that the mitochondrial gene $tRNA^{(Leu\ (UUR))}$ 3243 A to G mutation is a potential risk factor in developing diabetes.[6] Along with mitochondrial dysfunction leading to diabetes, problems in the mitochondria have also been shown to lead to pathologic changes caused by diabetes. For example, diabetic retinopathy is one of the hallmarks of progressive diabetes. It is known that apoptosis of capillary cells precedes the development of retinopathy.

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Mitochondrial ROS is increased in the retina, which impairs mt-DNA.[7] Also, Transcription Factor A Mitochondrial (TFAM) is a key regulator of the transcription of mt-DNA.[7] Santos, et al. have shown that ubiquitination of TFAM in diabetes prevents its transport to the mitochondria, which disrupts mitochondrial homeostasis indicating the strong relation with diabetes and mitochondrial dysfunction.[7]

Kearns-Sayre Syndrome (KSS) is a rare cause of diabetes in children. KSS has a group of diseases, known as the classic triad, which includes retinitis pigmentosa, progressive external ophthalmoplegia, and cardiac conduction problems.[8] Mitochondria Deoxyribonucleic acid (DNA) deletions have been shown to be abnormal in pancreatic islet cells in patients with KSS. Surprisingly, insulin receptor abnormalities do not appear to contribute to the development of diabetes in KSS, further highlighting the role of mitochondrial dysfunction.[8] Another rare mitochondria disorder that can cause diabetes is Pearson Marrow Pancreas Syndrome (PMPS). This disorder is caused by impaired mitochondrial respiratory chain complexes, although the specific mutations may differ among individuals with PMPS.[9]

Unfortunately, compared to diabetes, research on mitochondria related dysfunction to pancreatitis has been thus far extremely limited. However, from what has been published, it has been demonstrated that mitochondrial irregularities can be linked to pancreatitis. Pancreatitis is often described as an inflammation of the pancreas and can represent as an acute or chronic form.[10] Recent studies have shown mitochondrial damage leading to ATP depletion as a common factor related to acute pancreatitis. Also, the generation of ROS is another major cause of acute pancreatitis.[11]

Similar to pancreatitis, there has not been enough research on the relation between mitochondrial dysfunction and pancreatic cancer. However, there has been an increase in understanding the possible involvements of mitochondria in pancreatic cancers.[12] It has been shown that pancreatic cancer cells have a greater density of mitochondria, which could be used as a potential diagnostic marker.[13] Mathematic modeling has shown that perhaps a random mutation in the mt-DNA can cause homoplasmy among mitochondria in pancreatic cancer cells, which in turn can lead to an increase in dysfunctional mitochondria in the cancer cells.[13]

In conclusion, this review supports that many human ailments including diabetes, pancreatitis and pancreatic cancers are in part, due to faulty mitochondrial function. Hence, it is necessary to understand the nature of mitochondrial involvement in pancreatic dysfunction for proper treatment regimens. It has been over 100 years since Richard Altmann's discovery of mitochondria and we continue to learn new things today. With this, we wish the *Pancreas - Open Journal* all the success in their endeavor; and we hope that future researches related to mitochondrial dysfunction and pancreatic ailments will be discussed in this Journal dedicated to the pancreas.

CONFLICTS OF INTEREST

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