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Cooperative Roles of PINK1 and PARKIN in Mitochondrial Cell Function

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The mitochondria are one of the most important organelles that are responsible for energy production in the cell. Unfortunately with age, the mitochondria accumulated damage when energy is converted and could lead to mitochondrial dysfunction. One of the most common diseases caused by the dysfunction of the mitochondria is Parkinson's disease, which is one of the most common neurodegenerative movement disorders. The cell undergoes Quality Control processes in order to slow down the accumulation of damage, depending on whether the damage is moderate to severe. In a severe case, where the mitochondria are unusable then the PINK1 and Parkin pathway is used to undergo autophagy on the damaged mitochondria and is replaced with a more bio energetic mitochondria.

Introduction

The mitochondrion itself is one of the most important organelles, which is considered the primary producer of energy in the cell that promotes cell activity and function (Winklhofer et al 2009). Unfortunately, while the mitochondrion converts energy for the cell, the organelle accumulates damage with age that can cause mitochondrial dysfunction. In the article, Targeting Mitochondrial Dysfunction, in order to slow or sustain the mitochondrial damage derived from aging, the cell has two mechanisms called Quality Control (QC) processes. In the first process, if the accumulated damage is not severe to loss of function, functional complementation occurs where the mitochondria harboring oxidatively damage mtDNA can fuse with another more bio energetically active mitochondria to borrow missing components of their electron transport chain. If the damage to the mitochondrion are severe and cannot maintain a membrane potential, then the mitochondria is targeted to lysosomes and degraded in a process called quality control Autophagy, and after autophagy, the damaged mitochondria is replace with bio energetically active mitochondria (Narendara et al 2011).

The dysfunction that contributes to diseases of aging leads to various disorders such as amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease, which are prevalent with age of the mitochondria. Parkinson's disease one of the most common neurodegenerative movement disorders that are most frequently caused by PINK1 and Parkin mutations. The results of the damage to the mitochondria are development of the degenerative diseases and aging, which has two key factors, that regulates the existence of healthy or damaged mitochondria are PINK1 and Parkin.

PTEN-induced kinase 1 (PINK1) as explained in, "PINK1 as a Molecular Checkpoint in the maintenance of Mitochondrial Function and Integrity" is a cytosolic kinase found in the mitochondria and plays a role in protection of mitochondria and neurons. Parkin as an E3 ubiquitin ligase; confer specificity to ubiquitination by recognizing target substrates; is one of the most commonly mutated PD- associated gene (Koh et al 2012).

Pink1 was studied by extending the function of the PINK1-Parkin pathway by mitochondrial fission/fusion, and it showed PINK1 involvement as a second Parkinson's disease-associated gene in mitophagy, autophagy selective for degradation of mitochondria. Therefore, the translocation of PINK1 recruiting Parkin to damage mitochondria requires PINK1 kinase activity and mitochondrial targeting. Parkin's investigation of involvement of its ubiquitin ligase activity was viewed when they stained the endogenous ubiquitin with an antibody specific for poly- but not mono-ubiquitin species. In result, the presence of functional Parkin, they found poly-ubiquitin chains that are formed at clustering mitochondria; as well they revealed the formation of different poly-ubiquitin chains, which was classified as K27 and K63 of ubiquitin. It was also shown that both linkage types are correlated with lysosomal localization and/or autophagic degradation of proteins (Geisler et al 2010).

Discussion:

In their discussion, they revealed that mitochondrial dysfunction and failure of selective protein degradation can result in the pathogenesis of Parkinson's disease, but the mechanisms are still unclear. In PINK1/Parkin-mediated mitophagy, they dissected the mechanisms of parkin-directed mitophagy and discovered missing links between mitochondrial damage, ubiquitylation and selective clearance. The first step in mitophagy implicitly requires PINK1 and Parkin to damage mitochondria, as mitochondria are depolarized PINK1 and Parkin will bind to each other and Parkin is phosphorylated, activating its E3 ligase activity to degrade the mitochondria.

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