

Cell structures and transporters unit assessment



Parkinson's Disease (PD) is one of the most common neurodegenerative diseases that impacts the daily lives of those that are affected (Burbulla et al., 2017). There are a few different forms of PD that originate from specific mutations in a gene. Although the disease has many unknowns, these genes along with several different proteins play a role in PD. The specific proteins and genes that will be highlighted in this paper include α -synuclein protein, Parkin protein, PTEN-induced kinase 1 (PINK1) gene, leucine-rich repeat kinase 2 (LRRK2), vesicular monoamine transporter 2 (VMAT2), and the DJ-1 gene. These highly studied proteins and genes have normal roles and altered functions when associated with the predisposition of PD. Overall, the function of dopaminergic neurons and the production of dopamine has been essential to the progression and symptoms of PD (Burbulla et al., 2017).

First, α -synuclein functions are not perfectly clear, but they are involved in forming aggregates and inducing oxidative damage to dopaminergic neurons in the brain. It has been suggested that the α -synuclein protein is involved in vesicle trafficking and clustering (Grassi et al., 2018). The α -synuclein protein induces oxidative damage through point mutations that may potentially impact the ability of dopamine to become released which causes an imbalance of dopamine in the dopaminergic neurons (Gegg & Piston, 2018). Additionally, the α -synuclein protein can become phosphorylated which directly leads to aggregates forming. The aggregates that form from the α -synuclein protein phosphorylation induce a depolarization of the corresponding mitochondria. This mitochondrial dysfunction may lead to oxidative stress and further damage of dopaminergic neurons (Mortiboys et al., 2017). Furthermore, studies have shown that oxidative stress can also be

induced from oxidative phosphorylation and mitochondria DNA (mtDNA) become vulnerable to damage from the increased production of reactive oxygen species (ROS) (Mortiboys et al., 2017). The mitochondria dysfunction from α -synuclein contributes to potential dopaminergic neuron damage and the predisposition of PD.

Mitochondria are an essential organelle and are crucial to the function of the brain by generating Adenosine Triphosphate (ATP). With local mitochondria malfunctioning, an ATP output decrease may be a reason why it is increasingly difficult for dopamine to become metabolized. Studies have also shown that the α -synuclein protein undergoes a physical change from its natural form to an alpha-helix structure when bound to lipid membranes (Pirc & Ulrich, 2015). The alpha helix structure has a positively charged N-terminus that has the potential to react with negatively charged phospholipids (Pirc & Ulrich, 2015). These electrostatic interactions create a favorable environment, and this may be interpreted as a link between the α -synuclein protein and the pathogenesis of PD because the mutated α -synuclein protein will bind to the negatively charged phospholipids which may cause local mitochondria to malfunction, inducing cell death of dopaminergic neurons in the brain.

Lysosomal degradation is vital to cellular homeostasis by recycling proteins, enzymes, and organelles that may be dysfunctional. PINK1 and Parkin are involved in sequestering and digestion of abnormal mitochondria (Puspita, Chung & Shim, 2017). PINK1 is selective for mitochondria and is considered a kinase and one responsibility of PINK1 is the recruitment of Parkin to induce selective degradation in mitochondria through a process called autophagy, <https://assignbuster.com/cell-structures-and-transporters-unit-assessment/>

and another term for this process is called mitophagy. Additionally, Parkin works to ubiquitinate outer mitochondrial membrane (OMM) proteins which react with autophagy receptors to continue the process of mitophagy (Taanman & Protasoni, 2017). Studies have shown that fruit flies with a genetic mutation of PINK1 ultimately impacts the recruitment of Parkin, but it also leads to the dysfunction of dopaminergic receptors (Taanman & Protasoni, 2017). In a sense, PINK1 and Parkin work to signal for lysosomal degradation to occur which results in the elimination of malfunctioning mitochondria. PINK1 and Parkin have a positive relationship with lysosomal degradation to maintain consistent biomolecule recycling of the malfunctioning mitochondria. A genetic defect to either PINK1 or Parkin becomes detrimental because this creates an increase in reactive oxygen species (ROS) which contribute to oxidative damage to other local or adjacent mitochondria that are properly functioning (Puspita, Chung & Shim, 2017). Lysosomal degradation decreases, and cellular homeostasis is disrupted with a lack of either PINK1 or Parkin. Saturation of ROS develops as well as defective mitochondria which do not create enough ATP to meet the demands of dopaminergic neurons to have a steady release of dopamine. This leads to a possible link between genetic mutations of PINK1 or Parkin and a quicker progression of PD (Taanman & Protasoni, 2017).

Parkin has shown to have an impact on organelles such as the endoplasmic reticulum and mitochondria. In addition, Parkin plays a role in mitochondrial trafficking which is critical to the dopamine release and reuptake within dopaminergic neurons. Trafficking is required for organelles to move from one place to another. In the case of mitochondria, organelle trafficking is

especially important because our body depends on mitochondria to provide energy where there is a concentration of low energy. Studies have shown how Parkin is involved in the mitochondria vesicular trafficking pathway, and it was suggested that Parkin interacts with downstream trafficking and vesicle formation (Mclelland, Soubannier, Chen, McBride & Fon, 2014).

Parkin is involved in mitochondrial-derived vesicle (MDV) formation under oxidative stress, and that MDVs moderate the transportation of mitochondria and additional organelle targets. Once these vesicles are created, they have selectivity for lysosomes to initiate the degradation process (Mclelland, Soubannier, Chen, McBride & Fon, 2014). Although depolarization of defective mitochondria typically starts with PINK1, as previously mentioned, Parkin plays a vital role in the mitophagy of the mitochondria. Depolarization of mitochondria also allows for Parkin to be recruited which induces mitophagy. Additionally, recent studies observe that factors such as the abscission or removal of heart muscles that prevent depolarization prevents recruitment of Parkin leading to a prevention of mitophagy (Taanman & Protasoni, 2017). Proper mitochondrial function is just as important as mitochondrial trafficking because dysfunctional mitochondria lack the ability to produce an effective amount of ATP or energy of dopamine metabolism or the release and reuptake. Parkin works to immobilize these dysfunctional mitochondria to initiate mitophagy so effective mitochondria can be trafficked towards dopaminergic receptors to provide sufficient energy. Local mitochondria that function properly are more efficient at providing energy than damaged mitochondria.

Another factor that plays a role in predisposition of PD is VMAT2. It is located in neuronal cells, and VMAT2 is classified as an H⁺-ATPase antiporter that functions to package monoamines into vesicles to be released from neurons (Lohr & Miller, 2014). VMAT2 is critical to dopamine transportation from neurons, and an increase in VMAT2 function would protect dopaminergic neurons from cellular damage. Studies show that mice that had increased levels of VMAT2 had larger amounts of dopamine stored in their neurons. Ultimately, to prevent toxic interactions, an increase in VMAT2 activity protects dopamine from harmful interactions with oxidative damage created by the presence of ROS (Lohr & Miller, 2014). Production of VMAT2 prevents dopaminergic neuron degradation and ultimately cell death, resulting in the predisposition of PD.

Proteins such as LRRK2 and Rab are involved in maintenance of α -synuclein and reduction in misfolded α -synuclein aggregations. Studies have shown LRRK2 involved in signaling, vesicular trafficking, and autophagy (Stegar et al., 2016). Rab proteins are a type of GTPase, and are involved in vesicle trafficking including formation, mobility, and membrane fusion (Gao et al., 2018). Studies suggest that LRRK2 induces autophagy of α -synuclein and Rab proteins cooperate with LRRK2 to promote and direct vesicle trafficking to control α -synuclein's damaging effects on neurons (Steger, et al., 2016). Additionally, the DJ-1 gene activates astrocytes near neurons that have undergone cell death to promote repair of injured parts of the brain, and researchers call this process astrogliosis. Studies show that DJ-1 is a positive regulator of STAT3, which regulates further astrogliosis functionality (Choi, Kwon & Joe, 2018). Mutations to Rab, LRRK2, or the DJ-1 gene may

contribute to the pathogenesis of PD through an increase in α -synuclein misfolding and decrease in astrogliosis.

In conclusion, PD is one of the most common neurodegenerative diseases that have a severe impact on those that are affected. From primary literature, it is determined that although α -synuclein is not widely researched, it plays a role in damaging dopaminergic neurons through inducing oxidative damage and mitochondrial dysfunction leading to cell death and PD. There are also factors that help to reduce the degenerative impact of α -synuclein. These factors include Parkin, PINK1, LRRK2, VMAT2, and DJ-1 protein. These factors cooperate to prevent the predisposition of PD through methods of cellular homeostasis, mitophagy, organelle trafficking, and more. Mutations in any of the given factors may lead to dysfunctional methods of PD prevention mentioned above. A lack of ATP or dopamine production due to dysfunctional or damaged organelles may lead to an early onset of PD and predisposition of the disease.

References

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