Microreviews in Cell and Molecular Biology 2012

Interactions between PARK7, PINK1, and Parkin, and Their Function in the Pathophysiology of Parkinson's disease

Author: Jace Rickstrew
Major: Nutritional Sciences
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

Key Words:
Parkinson's disease, PARK7, PINK1, Parkin, physiology, interactions, neurodegenerative, dopamine, neurotransmitter, mutations, neurons, mitochondria.

Parkinson's disease is a slow onset, neurodegenerative disease that affects some 500,000 people in the United States alone. Mitochondrial dysfunctions, caused by mutations within dopamine generating cells, lead to the slow loss of functioning neurons. Three important genes have been identified in the causation and prevention of Parkinson's disease. PARK7, PINK1, and Parkin all work as cofactors within the mitochondria. PARK7 plays an important role in reducing free radicals (reactive oxygen species, ROS) in mitochondria. Likewise, PINK1 and Parkin are involved in mitochondrial morphology and function. Recent studies have indicated that PINK1 and Parkin work in series, which is parallel to the function of PARK7. These studies have brought insight into the interactions between the three complimentary genes, as little was known regarding their interaction previously. Additionally, studies of PARK7 have indicated two variants of the gene, which may determine the pathology of the disease. Wild type PARK7 encodes elongated mitochondria, which promotes normal function. In contrast, mutated PARK7 causes increased fragmentation of the mitochondria, thereby leading to a decrease in function. While a great deal of knowledge has been acquired about the pathophysiology of Parkinson's disease, more research is needed to determine exact mechanisms and potential treatments.

Introduction

Parkinson's disease (PD) is a degenerative neurological disorder that affects the central nervous system of those with the disease. The initial onset can be identified by troubled motor functions, caused by death of cells that produce dopamine in the brain. It is thought that progressive mitochondrial mutations and change in function within the dopamine generating cells are causes for the slow onset and progression of PD. Initial symptoms of PD include tremors, trouble walking, and other impaired motor functions. The gene PARK7 has an important role in the onset and progression of PD. While the exact role of PARK7 and other related genes, such as PINK1 and Parkin remain unclear, progress is being made towards tracking the entire mechanistic pathway. Previously, it was uncertain whether these work in series with each other, or remain as cofactors in separate pathways. What is clear, however, is that PARK7, PINK1, and Parkin all play important roles in regulating mitochondrial function within neuroblastoma cells, which are the neurological cells that are affected in PD.

PARK7 is a protein encoded by the PARK7 gene. Mutations in the gene have been linked with early-onset PD, an autosomal recessive disease caused by loss of protein function (Wang et al. 2012). As previously

mentioned, the exact mechanism for PARK7 is still unknown; however, it is evident that PARK7 plays an important role in relieving oxidative stress in the mitochondria.

There is very little outstanding evidence that solidifies an interaction of PINK1 (a protein kinase) and Parkin (a ligase) with PD and PARK7. All three are members of the same PD gene family (Wang et al. 2012).

Recent Progress

Recently, tremendous progress has been made in outlining the functions of PINK1 and Parkin. It is thought that PINK1 and Parkin play important roles in mitochondria function and regulation. Parkin expression has been indicated in clearing mutations within mitochondrial DNA, suggesting a quality control function. Deregulation is a potential cause of mitochondrial fragmentation, which has been indicated in the pathogenesis of PD. Mutations in PINK1 and Parkin cause a loss of function and account for about half of all autosomal recessive cases of PD (Cookson 2012).

In recent studies, two different variants of PARK7 appeared to have different functions. Wild type PARK7 appears to cause mitochondria elongation when overexpression occurs. In contrast, overexpression of the mutant PARK7 gene increased small particles, indicating mitochondrial fragmentation (Wang et al. 2012). This is representative of damaged mitochondria. Within cells containing a deficiency in normal PARK7 genes, higher levels of reactive oxygen species (ROS), which increases the mitochondria's susceptibility to stressors, is observed (McCoy et al. 2011). This suggests that PARK7 is important in the reduction of oxidative stress within a cell. Additionally, evidence suggests the change in morphology and autophagy observed is due to the enhanced oxidative stress. This indicates that the mutations caused by ROS lead to abnormal function, which is identified by decreased ATP and mitochondrial membrane potential. (McCoy et al. 2011, Wang et al. 2012).

Figure 1. (a.) A morphologically normal mitochondria. (b.) As a result of excessive ROS caused by a PARK7 deficiency, mitochondria become fragmented.

It is has been indicated in recent studies that a cell defective in a gene may be able to be "rescued" by a gene in the same family. For example, it has been shown that overexpression of Parkin can rescue a PINK1 deficiency. However, overexpression of PARK7 cannot compensate for the deficiency of PINK1 or Parkin. Overexpression of PINK1 or Parkin reverses the fragmentation caused by PARK7 deficiency (McCoy et al. 2011).

Discussion

The recent evidence suggests that mutations in PINK1 and Parkin are linked to mitochondrial dysfunction, providing insight into their mechanisms. It appears that Parkin is a nonspecific enzyme that may be involved in multiple mechanisms and functions. One function may be dependent on PINK1 for recruitment to the outer mitochondrial membrane. Mutations in PINK1 also do not allow Parkin to be recruited for its function. This suggests the recruitment process, dictated by PINK1, may be an important part of PD inheritance (Cookson 2012). Other functions may or may not be PINK1 dependent. This lack of specificity could indicate that PINK1 has evolved in a way that allows it to regulate several interconnected pathways (Cookson 2012). By identifying that PINK1 and Parkin are in the same biochemical pathway, progress can be made in determining their relationship with PARK7. While the general mechanisms are becoming more understood, the exact interactions remain abstract.

The discovery of two variants of PARK7 is a critical step in potential identification of its exact role in PD. By understanding its role, treatments may be developed in the future. Mutations in PARK7 lead to increased mitochondria fragmentation, decreased function, and decreased membrane potential (McCoy et al. 2011). This is also observed in cells with a deficiency in PINK1 and Parkin. While PARK7 is a vital component of preventing excessive ROS from affecting the mitochondria, it may not be the cells most efficient way of reducing these levels. This may indicate that PARK7 performs a very specific function as an antioxidant, such as preventing cytotoxin MPP^+. It could potentially indicate that another function has been evolutionarily conserved, such as a protease or chaperone (Cookson 2012). It is also possible that PARK7 plays a previously under recognized role in maintaining networks between neurons.

In addition to progression of PD, better understanding of mitochondrial mutations may have huge implications for the study of aging. It is widely known that ROS leads to mutations in DNA sequences. Abnormally high mutations in mitochondrial DNA lead to faster aging. By manipulating and preventing these mutations, perhaps aging can be slowed and medicine can progress to lengthening the human lifespan. How PARK7 relates to

the prevention of mutations may be an important mechanism to understand when dealing with aging.

Studies of the "rescue" effect between PINK1, PARK7, and Parkin have allowed an estimate of the pathways interconnecting the three, and their effect of mitochondrial regulation, to be derived. Overexpression of Parkin can partially rescue PINK1 deficiencies. However, the reverse situation does not hold true. This would suggest that PINK1 is upstream of Parkin in the mechanism pathway. Likewise, overexpression of PARK7 may compliment loss of PINK1, but not the function of Parkin. In recent observations, mitochondrial fragmentation caused by the absence of PINK1 or Parkin cannot be repaired by expression of PARK7 (McCoy et al. 2011). These findings suggest that PINK1 and Parkin work in a series parallel to PARK7 to limit and repair damage in the mitochondria caused by ROS.

Future work should be directed into developing a deeper understanding of the interactions between PARK7, PINK1, and Parkin. Additionally, studies should focus on their specific functions in the pathophysiology of PD. Performing various knockout studies, with different combinations of knockdown to see interactions and results, can complete these studies; however, these knockdown experiments do not always result in predicted outcomes. Fortunately, PARK7, PINK1, and Parkin are all highly conserved across species, allowing research to be conducted in animal models. Work should also focus on identifying and developing "rescue" molecules. If developed, these could shortcut the current progress and potentially be used as a therapy for PD. These studies can also be translated well into research dealing with aging. In addition, biomarkers in noninvasive procedures should be sought. A tool to screen and identify PD in early stages can delay the progression of the disease. Given our current understanding of the disease, this may be a more realistic option for the near future.

While all this information is great for science, very little of it translates into patient care for the time being. So much remains unanswered about the mechanisms and interactions of the pathogenesis of PD. Once this is better understood, progress can be made for an effective treatment for patients suffering from PD. Additionally, preventative treatments can potentially be developed. Currently, because of the lack of understanding, no treatments are available for PD. Management of symptoms is the primary goal of treatment until further therapies are developed.

References

Cookson, Mark. "Parkinsonism Due to Mutations in PINK1, Parkin, and DJ-1 and Oxidative Stress and Mitochondrial Pathways." *Cold Spring Harbor Perspectives in Medicine*. (2012).

McCoy, Melissa, and Mark Cookson. "DJ-1 regulation of mitochondrial function and autophagy through oxidative stress." *Autophagy*. 7. no. 5 (2011): 531-532.

Wang, Xinglong, Timothy Petrie, Yingchao Liu, Jun Liu, Hisashi Fujioka, and Xiongwei Zhu. "Parkinson's disease-associated DJ-1 mutations impair mitochondrial dynamics and cause mitochondrial dysfunction." *Journal of Neurochemistry*. no. 121 (2012): 830-839.

