Mitochondrial Dysfunction in Parkinson’s Disease

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Parkinson’s disease (PD) is a common, progressive neurodegenerative disorder characterized by the selective death of dopaminergic neurons in a small region of the brain called the substantia nigra. The death of these cells results in a number of debilitating motor symptoms, including a distinctive tremor, bradykinesia, and joint rigidity. One of the enduring mysteries of PD is the cause of death of dopaminergic neurons. Many different mechanisms have been proposed, including oxidative stress, mitochondrial dysfunction, proteasome dysfunction, and inappropriate immune activation. However, the late diagnosis of PD makes it hard to separate cause from effect. This paper describes several mechanisms related to mitochondrial dynamics that have been suggested by neurobiology, metabolism, and immunology researchers. Following a brief introduction of the key players—the proteins α-synuclein, Pink1, and parkin—this paper explores the emerging relationships between PD and the mitochondrial autophagy and antigen presentation pathways.

In the brains of Parkinson’s disease (PD) patients, the protein α-synuclein forms neuronal aggregates, called “Lewy bodies,” that have been linked to disease pathogenesis [1]. Although α-synuclein is predominately cytosolic, the fraction that is associated with mitochondrial membranes is increased in PD [2]. Furthermore, there appears to be a bidirectional association between α-synuclein accumulation and the function of the mitochondrial electron transport chain. Chemical inhibition of mitochondrial Complex I results in α-synuclein accumulation and development of Parkinson’s-like symptoms in both mice and humans [3]. A profound example of the neurological effects of disrupting mitochondrial activity is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) a mitochondrial poison that is a contaminant of improperly produced synthetic heroin and produces permanent parkinsonism [4]. Conversely, α-synuclein accumulation has been shown to impair mitochondrial function by inhibiting TOM20, an essential subunit for the mitochondrial import of cytosolically-produced proteins [5]. Taken together, these mechanisms suggest that α-synuclein and mitochondrial dysfunction may be linked in Parkinson’s disease.

Several related mitochondrial pathways have also been implicated in the function of the proteins Pink1 and parkin, which are two proteins mutated in rare, hereditary forms of PD. Pink1 is a kinase targeted to the outer mitochondrial membrane (OMM), but it is usually rapidly removed by other proteins on the membrane. If Pink1 remains, it phosphorylates and activates the ubiquitin E3 ligase parkin, which marks the mitochondrion for lysosomal autophagy (“mitophagy”). Extreme mitochondrial stress may cause the collapse of the proton gradient (“mitochondrial depolarization”), inhibiting normal protein import from the cytosol. Pink1
is left on the OMM, allowing it to trigger mitophagy [6]. These later steps have not been well studied, but there is emerging evidence suggesting that autophagy may be dysregulated in PD. If key autophagy proteins are knocked out (such as Atg5 and Atg7), mice develop progressive motor and behavioral deficits and begin to accumulate unspecified protein inclusion bodies [7,8]. Of note, Pink1 and parkin are also involved in mitochondrial fission/fusion dynamics, which are believed to be important for mitochondrial repair [6,9]. This represents yet another way in which the mitochondrial stress response may be suppressed in PD.

These fascinating results are consistent with many potential models. One possibility is as follows:

1. α-synuclein dynamics are disrupted in the substantia nigra. Multiple cells may be affected, or the defect may be transferred between neurons by a prion-like mechanism.
2. α-synuclein misfolding inhibits Tom20, disrupting mitochondrial protein import.
3. Mitochondria start to break down internally, causing them to depolarize.
4. Pink1 accumulates on the OMM, activating parkin and leading to mitophagy.
5. If enough mitochondria are damaged, the neuron may die.
6. Ongoing neuronal death results in the progressive symptoms of PD.

Recent research on the immune response to mitochondrial antigens suggests an alternative to steps 4-6 outlined above. In 2012, Soubannier et al. reported a novel pathway by which small “mitochondria-derived vesicles” (MDVs) are produced and targeted to lysosomes via an autophagy-independent mechanism [10]. In a later paper, the authors showed that the MDV pathway is responsible for mitochondrial antigen presentation in primary biliary cirrhosis, a rare autoimmune disease in which the immune system becomes sensitized to the mitochondrial protein α-ketoglutarate dehydrogenase. Furthermore, this pathway is inhibited by both Pink1 and parkin [11]. This suggests that in the context of cellular stress, dysregulation of Pink1 and parkin might favor the production of MDV’s over mitophagy, increasing mitochondrial antigen presentation. Therefore, the mechanism of dopaminergic cell death may be immune attack, rather than direct mitochondrial damage. In this light, PD itself may be an autoimmune response to mitochondrial proteins. Although this is a bold idea, many recent papers have also suggested that inappropriate immune activation may be involved in PD pathogenesis [12].

The study by Matheoud et al. 2016 raises a basic question that remains unanswered [11]: why have humans evolved an elaborate mechanism to present mitochondrial proteins to the immune system? Three possibilities include the following:

(a) The pathway may have evolved to combat intracellular pathogens, but mitochondria still resemble their bacterial ancestors enough to be mistaken for a pathogen.
(b) The pathway may be important for self-tolerance.
(c) The immune system may help destroy cells that have a large number of slightly damaged mitochondria.

Current literature makes certain possibilities more or less likely. First, Pink1 and parkin are indeed associated with protection against intracellular pathogens. However, this process is dependent up-
on classical autophagy proteins like Atg5, rather than the mitochondria-derived vesicle pathway. This makes option (a) less likely [13]. Similarly, mitochondrial proteins are included in a self-tolerance pathway involving thymic medullary epithelial cells (TMECs) and the autoimmune regulator “Aire,” but this pathway is also dependent upon the autophagy pathway via Atg5 [14]. Option (b) could still be true if another mechanism of self-tolerance were involved, perhaps involving the peripheral immune system. Finally, the option of deliberate immune targeting could explain the observed immune response in PD, but this has not been directly studied on its own. If a study were to find that immune infiltration of tumors correlates with mitochondrial dysfunction, this would strengthen the likelihood of option (c).

Though the mechanisms of Parkinson’s disease remain uncertain, it seems very likely that mitochondria and mitochondrial proteins play an important role in disease pathogenesis. The research described here suggests the intriguing possibility that changes in the mitochondrial stress response may alter the balance between mitochondrial destruction and repair, potentially recruiting immune cells in a larger systemic response. Changes in α-synuclein, Pink1, parkin, Tom20, and mitochondria-derived vesicles may trigger this shift, or they may become dysregulated later in disease pathogenesis. Either way, this research brings to light a novel modality for targeting PD and invites important and collaborative projects between neurobiology, immunology, and metabolism researchers.

REFERENCES