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**PROGRESS IN UNDERSTANDING THE ROLE OF
MITOCHONDRIA IN PARKINSON'S DISEASE.**

The rapidity with which new discoveries are exploited to provide mechanisms for key cellular events is remarkable. A good example is provided in the area of our understanding of Parkinson's disease. The new developments described here began with genetic studies of PD patients that identified genes for parkin, pink 1 and Drp1, as important for this condition. We now know how these gene products function together in the cell and can hypothesize plausible mechanisms for what goes wrong in PD.

In a recent review Narendra and Youle put the current information together to describe how parkin and pink1 act in quality control of mitochondria by identifying damaged organelles and "trimming" them from the mitochondrial network for mitophagy (NARENDA DP & YOULE RJ. 2011. Targeting mitochondrial dysfunction: role for pink1 and parkin in mitochondrial quality control. *ANTIOXID. REDOX SIGNAL* 14:1929-38).

Optimal utilization of ATP in nerve cells depends on the mobility of mitochondria that have been primed for ATP synthesis to allow concentration of the organelle at the synapse. Not surprisingly then alterations in mitochondrial movement can be a cause as well as a consequence of changes induced in PD, then parkin and pink1 are in fact involved in regulating mitochondrial movement. In a recent report, Wang et al. show that pink1 phosphorylates Miro, a component of the primary motor/adaptor complex that anchors kinesin to the mitochondrial surface. The phosphorylation of Miro activates proteasomal degradation in a Parkin-dependent manner. Removal of Miro from mitochondria also detaches kinesin from the mitochondrial surface (WANG X. et al. 2011. Pink1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial mobility. CELL. 147:893-906).

Parkin controls the functioning of pink1 by moving between the cytosol and mitochondria. Involved in this process is a newly identified protein on mitochondria named klokin 1 (KURODA Y. et al. 2011. Parkin interacts with Klokin 1 for mitochondrial import and maintenance of membrane potential. HUM.MOL.GENET. NOV 14 ahead of print).

Another protein important for mitochondrial dynamics is Drp1. A recent study shows that parkin interacts with and subsequently ubiquitinates Drp1 (WANG H. et al. Parkin ubiquitinates Drp1 for proteasome-dependent degradation: implication of dysregulated mitochondrial dynamics for Parkinsons disease. 2011. J.BIOL.CHEM. 286:11649-58).

Other proteins are a substrate for the pink1-parkin machinery. Taanman et al showed that parkin ubiquitinates mitofusin1 and mitofusin 2 (GREGG ME. et al. 2010. Mitofusins 1 and 2 are ubiquitinated in a pink1/parkin dependent manner upon

induction of mitophagy. HUMAN MOL. GENET. 19:4861-70).

See also; RAKOVIC A. et al. 2011. Mutations in pink1 and parkin impair ubiquitination of mitofusins in human fibroblasts PLOS ONE. 6 e.16746).

MITOCHONDRIAL DYNAMICS IN OTHER NEURODEGENERATIVE DISORDERS

There is now considerable evidence that beta-amyloid interacts with mitochondria and inhibits key enzymes of the respiratory chain. According to Westermann and others, nitric oxide produced by disruption of OXPHOS by beta-amyloid causes S-nitrosylation of Drp-1 leading to excessive mitochondrial fission, synaptic loss and neuronal damage. This idea is supported by the observation that brains of patients with Alzheimers contain large amounts of S-nitrosylated Drp1 (WESTERMANN B. 2009. Nitric oxide links mitochondrial fission to Alzheimer's disease. SCI. SIGNAL. 2 pe29; CHO DH et al. 2009. S-nitrosylation of Drp 1 mediates beta-ameyloid related mitochondrial fission and neuronal injury. SCIENCE 324:102-5).

Recent studies by Reddy and colleagues have established a role of Drp1 in Huntington's disease as well. Using both post mortem HD brains as well as primary neurons from transgenic mice, these workers identified interaction of mutant Huntingtin with Drp1, and observed altered axonal transport, defective anterograde mitochondrial movement, and synaptic deficiencies (SHIRENDEB UP.et al. 2011. HUMAN MOL.GENET. OCT13 ahead of print).

NEW METHODS OF MONITORING MITOCHONDRIAL STRUCTURE AND FUNCTION.

MONITORING ATP AND Ca TOGETHER.

Noji and colleagues have developed a fluorescent probe for imaging ATP in single living cells, which they call GO-ATeam. They use this along with an intracellular Ca⁺⁺ in FRET studies to measure ATP and Ca⁺⁺ levels simultaneously in histamine stimulated HeLa cells (NAKANO M. IMAMURA H. NAGAI T & NOJI H. 2011. Ca regulation of mitochondrial ATP synthesis visualized at the single cell level. ACS CHEM BIOL 6:709-15).

A NEW DYE FOR TWO PHOTON MEASUREMENTS

In this study Tani et al. describe a new fluorine based dye for two photon analysis of mitochondrial structure (TANI S et al. 2011. Fluorescence Imaging of mitochondria in living cells using a novel fluorine derivative. CURR. PHARM BIOTECHNOL. OCT 31 Epub ahead of print).

A NOVEL DYE FOR RATIOMETRIC pH MEASUREMENT.

Ramshesh and Lemasters describe a ratiometric pH-indicating fluorescent probe called SNARF1 for monitoring mitochondria in living cells by laser confocal microscopy and the method for its use. They measure pH changes in cytosol and mitochondria in myocytes during hypoxia (RAMSHESH VK & LEMASTERS JJ.

2012. Imaging of mitochondrial pH using SNARF1. METHODS MOL.BIOL 810:243-8).

PIONEERS OF MITOCHONDRIAL RESEARCH REMEMBERED. 4) ALBERT LEHNINGER.

It was my first Gordon Conference in New Hampshire. Things were not going well. It was hot and very humid, there were mosquitoes everywhere and my room smelled strongly of dirty feet, as did most in the boarding school that was to be my home for 5 days. My bed was 6 inches shorter than me, and its regular occupant had stuck fluorescent stars on the ceiling above the bed to mock me through the long sleepless nights. My talk, the first of the morning, had gone badly: half of my slides had gotten stuck in the carousel (remember slides?) making for a choppy presentation, and now the speaker after me was trying to convince the audience that the proton to electron ratio in OXPHOS was more than 2. I went out for fresh air. Within 5 minutes a helicopter came over and then landed quite close to where I was sitting, a military- looking man got out, walked toward me and the auditorium, stuck out his hand and said "Hi I'm Al Lehninger, has Dr B..... started to speak yet?" I responded that it was some fellow droning on about proton to electron ratios. His face reddened and he rushed in to listen. How was I supposed to know Dr B. was Al's colleague?

Albert Lehninger is remembered by most for his books, including Principals of Biochemistry, which even now is regularly used and is still a very authoritative source after recent updates. However, he also made many seminal contributions to our understanding of mitochondria. Specifically, it was he along with Eugene Kennedy in 1948, who first showed that mitochondria were the site of oxidative

phosphorylation and of fatty acid oxidation, thereby ushering in the modern study of energy transduction. The website <http://www.tc.umn.edu/%7Eallch001/papers/lehninger.pdf> provides an excellent review of the man and his work.

Pete Pedersen remembers his time as a student with Lehninger as follows:

I first met Albert Lehninger in the Spring of 1964 at which time he was Professor and Chair of the Department of Physiological Chemistry (now Biological Chemistry) at Johns Hopkins University, School of Medicine, Baltimore, MD. This was shortly before I received my Ph.D at the University of Arkansas working with the late Professor Jacob Sacks. Sacks encouraged me to start seeking Postdoctoral positions. After searching for some time, I decided that Dr. David Green at the Enzyme Institute at the University of Wisconsin would be my best choice. I was very impressed with Dr. Green's work on mitochondria perhaps because of his Scientific American article (1964. Vol 210, pages 67-74) near that time. My mentor Dr. Sacks at the University of Arkansas was not happy about my decision and encouraged me to consider Albert Lehninger at Johns Hopkins in Baltimore. Dr. Sacks set the trip up for me and informed Lehninger that I was coming.

The trip from Fayetteville, Arkansas to Baltimore Maryland in 1964 was my first plane ride and although an enjoyable experience, my first impression of Baltimore was not. It was at the time, in contrast to today, a depressing city and the Johns Hopkins Medical School where I would meet Lehninger was in the most depressing area. Upon entering Lehninger's Department of Physiological Chemistry (now Biological Chemistry) at Johns Hopkins and being greeted by his secretary, I was told I would not be able to see him until late in the day as his schedule was so busy. So, I was shunted to other

faculty throughout the day until late in the afternoon my moment came.

I found Lehninger to be a very low key and nice person, a true "gentleman and scholar". Although the interview seemed to be going well, I was not sure that Lehninger was too impressed with me, and the thought occurred that I had better do something soon to hit a "home run" or I would be out the door and on my way back to Arkansas. Then, Lehninger ask me if I had read his new book on Bioenergetics. I was happy to say that I had, at which time he said that if I found any typos or other mistakes to please let him know. When I pulled out a piece of paper listing several typos and mistakes, Lehninger was a little embarrassed but knew that I had read his book. My foot was now in the door but it could slam at any minute.

The subject with Lehninger then turned to whether I was considering other biochemists with whom to do a Postdoc. I said only one, David Green at the University of Wisconsin. I could see Lehninger's expression changing, his face becoming a little red at which time he said something to the effect "so why are you coming here to interview and not Wisconsin". I said "because Dr. Sacks, my Ph.D. mentor at Arkansas said that Dr. Green is (words not said here)." Lehninger almost fell over laughing. A few days after returning to the University of Arkansas, I received a nice letter from Lehninger accepting me as a Postdoctoral Fellow. I came to Johns Hopkins in 1964 to work with Lehninger, after which in 1967 he invited me to join the faculty of his Department. To this day, I do not know whether I landed the Postdoc with Lehninger because I had read his book, because of my comments about his rival David Green, or both.