Preface

Our first close-up views of mitochondria, achieved using transmission electron microscopy, revealed their intracellular distribution and organized double-membrane structure. We know now that fixation techniques used to capture these snapshots deceived us into thinking that these "powerhouses of the cell" existed as a static collection of kidney bean-shaped organelles. Modern technology has revealed that, in fact, mitochondria comprise a highly dynamic network in which sections can break off, move rapidly throughout the cell to deliver energy and calcium-buffering capabilities, and then rejoin the network or be digested in lysosomes. We have learned that mitochondria may have evolved from invasive bacteria to become the most important sensors of cell stress and the gatekeepers of apoptosis. Because most cells rely so heavily on mitochondrial ATP production, and because mitochondrial stress can initiate apoptosis, many deadly diseases are known or thought to be caused by aberrant mitochondrial function. Parkinsonism, which is characterized by the presence of particular motor symptoms caused by degeneration of a subset of dopaminergic neurons in the midbrain, can be induced in animals and humans when they are exposed to mitochondrial toxins. Additionally, common Parkinson's disease (PD)-causing mutations implicate poor mitochondrial function in PD pathology. Indeed, aberrations in mitochondrial function and turnover are evident in genetic models and even in patients who inherit these mutations.

Time and time again, hypergeneration of mitochondrial reactive oxygen species (ROS) has been shown to contribute to cellular aging, decreased ATP production, various diseases pathologies, and necrotic and programmed cell death—probably as a result of macromolecule oxidation. Idiopathic PD models are generated by inducing excessive ROS levels either by administration of a reactive dopamine analogue or mitochondrial toxins, and increased ROS levels have been detected in most models of familial PD. Whether ROS are the direct cause of neurodegeneration in PD is unclear, as is whether the culpable source of mitochondrial ROS is dopamine metabolism, effects of mutated mitochondrial DNA, oxidative phosphorylation, or a combination of these. Further, excessive ROS production could be induced by non-mitochondrial sources like inflammation. While there is no treatment that can halt or delay degeneration for PD patients, strides have been and are being made in

the advancement of our understanding of PD pathology. We have learned that manipulation mitochondrial fusion and fission events can improve or even rescue model phenotypes. We also know that PD is less prevalent in the tobacco cigarette-smoking population and that nicotine exposure can prevent cell death in PD animal models. Modulation of peroxisome proliferator-activated receptor (PPAR) family of transcription factors has been shown to improve mitochondrial function in some PD models as well. Still, when we finally understand how altering mitochondrial dynamics, nicotine exposure, or PPAR activity protects cells, delivery of therapeutic molecules to affected mitochondria may be our most daunting obstacle. Yet, with each passing year, nanobiotechnologists create more promising delivery systems.

Here we discuss the products of tireless efforts put forth by many researchers around the world who are optimistic about the idea that PD and other neurodegenerative disorders will one day be treatable. Due to advances in imaging technology and our ability to understand and manipulate gene expression, our understanding of disease mechanisms has expanded exponentially, paving the way for potential therapeutic strategies and delivery methods to be discovered.

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