The Regulation of Mitochondrial Quality Control Via Autophagy and the Scope for Pharmaceutical and Nutraceutical Approaches

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Abstract
The homeostasis of eukaryotic cells relies on efficient mitochondrial function. The control of mitochondrial quality depends on the combination of distinct but interdependent mechanisms spanning biogenesis, regulation of a dynamic network, and finely tuned degradation through targeted autophagy. There is continuous evolution on the pathways orchestrating the mitochondrial response to stress signals and the organelle adaptation to quality control during acute and subtle dysfunctions. Degradation of defective mitochondria via mitophagy influences tissue homeostasis, but it remains uncharted as to how we can pharmacologically and metabolically control this mechanism. Common efforts are therefore indispensable to conceive novel approaches to design pharmaceutical and nutraceutical strategies for treating conditions associated with defective mitochondria both in human and veterinary medicine.

Glossary of Abbreviations
ATP: Adenosine Triphosphate
Drp1: Dynamin-Related Protein 1
OMM: Outer Mitochondrial Membrane
PET: Positive Emission Tomography
PMBR: Peripheral Mitochondrial Benzodiazepines Receptor
TSPO: Translocator Protein

Key Words
Mitochondria Pharmaceuticals
Autophagy Nutraceuticals

Mitochondria and Mitophagy
In mammals, mitochondria play many important roles. They produce the majority of cellular energy by coupling with unique efficiency oxygen into molecules of adenosine triphosphate (ATP). They can nonetheless act as major consumers of this key source of intracellular energy when respiratory balance in the surrounding environment does not support its coupling, such as during an absence of oxygen leading to ischemia.[1] Mitochondria also play a prominent role in controlling programmed ways of cell death by releasing death-triggering molecules from their intermembrane space or by generating toxic-free species of oxygen in consequence of the impaired respiration.[2] All of this requires constant and careful control of their function. And the catabolic process of targeted autophagy is pivotal to this controlling function.[3] Autophagy is an intracellular degradation system that delivers cytoplasmic constituents to the lysosomes.[4]

Recent progress has demonstrated that autophagy plays a wide variety of physiological and pathophysiological roles. Even though autophagy has long been considered to be a nonselective mechanism of degradation that indiscriminately eliminates cellular components, it is now clear that autophagy can instead be highly selective against subcellular organelles[5] as mitophagy, which does so against mitrochondria.[6] This organelle-specific type of autophagy was first defined by Lemasters and collaborators,[7] though as early as 1962, it was seen that lysosomes in the liver contained mitochondrial fragments.[8] In 1977, two independent research studies, one on metamorphosis in silkworms[9] and the other on the photoreceptor cells of the ground squirrel during hibernation,[10] concluded that autophagy could be selective toward mitochondria rather than other intracellular components and that once mitochondria develop functional alterations, autophagy would be activated to engulf them.

Since then pioneering studies have described the mechanisms through which the disposal of mitochondria via autophagy takes place. These have detailed genes and signaling pathways through which the selectivity of the process is exerted and preserved. Currently, mitophagy mechanisms are classified in two major types of processes: (i) Parkin-dependent and (ii) Parkin-independent.

Parkin is an E3 ubiquitin ligase identified as one of the most important players in recruiting autophagosomes to damaged

mitochondria.[11] Parkin promotes the ubiquitin-proteasome system of mitochondrial proteins degradation leading to fulfillment of the pathway, removal of the defective organelles, and quality control of the network. Loss-of-function mutations in Parkin are known to cause heritable forms of Parkinson's disease, as well as other neurodegenerative conditions such as Alzheimer's disease, amyotrophic lateral sclerosis and Huntington's disease. On the other hand, Parkin overexpression has been found in long-lived flies, suggesting a link between aging processes and life span.[12]

The Regulation of Mitophagy

The variety of recent studies on mitophagy mechanisms during aging in invertebrate and rodent models highlighted mitochondrial quality control as an attractive target in slowing down aging processes by preventing and tackling related diseases. It has therefore become of paramount importance to regulate the process via pharmacological approaches.

We described a negative regulator of the Parkin-dependent process of mitophagy: the mitochondrial 18-kDa translocator protein (TSPO).[13] TSPO, which was first discovered as a peripheral mitochondrial benzodiazepines receptor (PBR), is situated on the outer mitochondrial membrane (OMM) of mammalian cells where it lies in strict interaction with the organelle's channels. The core biochemical function of TSPO resides in the translocation of cholesterol in the mitochondria for metabolism and steroids synthesis. In the brain, TSPO is expressed in low levels at physiological conditions, but these markedly increase at sites of brain injury and inflammation as well as during aging.[15] In fact, TSPO is used as a biomarker/molecular sensor of active brain disease in both experimental animals and human studies. For over two decades TSPO ligands have been therefore used to profile expression of the protein in the brain via means of positive emission tomography (PET) to help diagnose patients affected by brain conditions.

In light of a significant clinical potential of TSPO, these ligands have been prompted for their biological efficacy in experimental models and human patients. Among these, one potent cholesterol-like TSPO ligand has been described as a neuroprotective compound.[16] Limitation of cell mitophagy by TSPO leads to incremental redox stress in cells underlying long-term damage that act therefore as a propathological factor. The dependency of TSPO activity by cholesterol pools has pointed the attention on mitophagy efficiency and regulation via dietary regimen and quality of the food. Thus it is general knowledge that activation of nonselective (macroautophagy) and selective (mitophagy) are strictly dependent on nutrient supply.

Interestingly, mitophagy could be induced under nutrient-rich conditions that end up removing redundant or dysfunctional mitochondria when general-bulk autophagy is not even activated.[11] When autophagy is induced, mitochondrial degradation does not necessarily follow. Mitophagy is the attempt to leave as much energy as possible, leaving the mitochondria therein inhibited during starvation in order to provide cells with as much energy as possible. Confirmation of this arrived when mitochondrial elongation was observed during starvation-induced autophagy in various cell models via inactivation of the dynamin-related protein 1 (Drp1), which helps with the segregation of large mitochondria into smaller ones to facilitate their removal by autophagy.[18] For the same reason we are inclined to speculate that when cholesterol metabolism is increased, such as following TSPO downregulation,[13] the consequent metabolic alterations lead to mitophagy inactivation to retain the maximal organelle capacity to deal with trafficking of the lipid.

Conclusions and Prospective

The acknowledged importance of the process in various pathological conditions calls for timely investments to unveil the interplay between diet and mitochondrial quality. This could in turn lead to the development of products to cure or prevent conditions caused by deregulated mitochondrial function. In both human and animal medicine, an increasing number of dietary supplements have become available for the prevention and treatment of diseases.

Thankfully, compounds targeting authophagy[19,20] to counteract oxidative stress[21] have emerged over the past decade. Of these, supplements of resveratrol and omega-3 fatty acids have become a paradigm example,[22] which further stimulated attention toward novel approaches, based on the utilization of naturally derived products[23,24] to regulate both general and targeted autophagy (mitophagy). Endeavors on this account must nonetheless progress in order to achieve tangible impact on both human and veterinary medicine.

Conflict of Interest

The authors declare no conflict of interest.

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