MOLECULAR ORCHESTRATION OF MITOCHONDRIAL FITNESS VIA REPLACEMENT OR REPAIR

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MOLECULAR ORCHESTRATION OF MITOCHONDRIAL FITNESS VIA REPLACEMENT OR REPAIR

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Research Abstract

? DESCRIPTION (provided by applicant): Mitochondria are the essential sources of most ATP that fuels excitation-contraction coupling in the heart. They are also major sources of toxic reactive oxygen species (ROS). To maintain overall mitochondrial and metabolic health, cells

rely upon surveillance, pre-emptive sequestration, and targeted removal of damaged organelles while retaining healthy mitochondria. Selective mitochondrial culling in this manner utilizes the cellular autophagy apparatus, and is therefore designated “”mitophagy.”” The integrated process of identification, sequestration, and mitophagic removal of damaged mitochondria is commonly referred to as “”mitochondrial quality control.”” The best understood cellular mechanism for mitochondrial quality control depends upon mitochondrial localization of, and protein ubiquitination by, the Parkinson’s disease factor Parkin. The novel concept underlying this proposal is that “”mitochondrial quality”” is not a specific condition. Because metabolic demands and substrate availability fluctuate based on cardiac developmental and pathophysiological status, the highest quality mitochondria in one condition may be sub-optimal or detrimental in another. Examples of mitochondrial plasticity include the normal perinatal transition from glycolytic to fatty acid metabolism, and the pathological reversal of this metabolic transition in diseased adult hearts. Conventional wisdom is that mitochondria are genetically “”reprogrammed”” during these metabolic transformations, but we believe this to be overly simplistic. Our intercurrent experimental data reveal that pre-existing mitochondria must first be removed in a Parkin-dependent manner before biogenesis and mitochondrial fusion can accomplish their replacement by metabolically distinct successors. Thus, we hypothesize that the Parkin mitophagy pathway serves two distinct roles in hearts: the canonical function of selecting and removing individual damaged mitochondria, and a previously undescribed function evoking generalized mitochondrial turnover essential to biogenic mitochondrial replacement during metabolic transitions. Our research efforts have produced a completely novel approach to modulating Parkin signaling specifically at its mitochondrial molecular interface by expressing dominantly active or inhibitory mitochondrial outer membrane Parkin receptors (PINK1-phosphorylated Mfn2). We will use this approach to manipulate Parkin signaling in the in vivo mouse heart and evaluate the consequences on mitochondrial quality and metabolic remodeling during the normal perinatal transition to fatty acid metabolism, after surgical induction of cardia pressure overload (TAC), and during hypertrophy reverse remodeling in TAC/de-TAC studies. If our hypothesis is correct, then enhancing Parkin signaling will facilitate early culling of damaged organelles at the cost of accelerating delayed metabolic remodeling back to the glycolytic fetal phenotype, whereas interrupting Parkin-mediated mitophagy will cause early accumulation of damaged organelles, but delay the maladaptive reversion to fetal-like metabolism. Thus, we will establish the optimal times, relative to disease progression, for conditional enhancement or suppression of Parkin-mediated mitophagy to best complement mitochondrial function and metabolism in different pathophysiological states. Together, our studies will rigorously evaluate the concept that manipulating Parkin signaling at its mitochondrial receptor (an interaction that i pharmacologically targetable) can both promote culling of damaged organelles and correct mismatches between mitochondrial metabolic preference and myocardial demand.

Further information available at:

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