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Mitochondrial quality control: An emerging therapeutic approach to heart disease

We previously reported that the homeostatic intracellular repair response (HIR²) or adaptive autophagy is activated in patients undergoing heart surgery. [Jahania et al. *J Am Coll Surg*. 2013.] We suggested HIR² represents an important protective response to cardiac stress and that its enhancement during ischemia/reperfusion (I/R) injury may represent an important therapeutic goal. Mitophagy clears mitochondria with low membrane potential to limit production of reactive oxygen species (ROS) leaving behind a pool of robust mitochondria resistant to I/R-induced damage. Damaged mitochondria are targeted for elimination through the accumulation of PINK1 and subsequent recruitment of the E3 ubiquitin ligase Parkin and autophagy adapter protein p62 to the mitochondria. Concurrently there is initiation of an intracellular isolation membrane, elongation, and closure of the isolation membrane around a ubiquitin and p62 decorated mitochondrion, giving rise to an autophagosome loaded with its mitochondrial cargo. Fusion of a lysosome with the autophagosome is followed by degradation of the cargo and export of the breakdown products (amino acids and free fatty acids) into the cytosol. Preliminary evidence indicates that the elimination of dysfunctional mitochondria by mitophagy is balanced by the generation of new mitochondria through mitochondrial biogenesis; this dynamic regulation is essential for mitochondrial quality control. Mitochondrial biogenesis proceeds by expansion of existing mitochondria followed by division. The new mitochondria formed balance the loss of mitochondria via mitophagy, preserving tissue homeostasis. The process is regulated at the transcriptional and post-transcriptional levels via the master transcription factor co-regulator PGC-1 α . This protein is controlled in part by mTOR and AMPK, the same energy sensing molecules that regulate mitophagy. Likewise, increased cardiac workload, exercise, and fasting are all potent inducers of mitophagy as they are for PGC-1 α . Moreover, it now appears that mitophagy is linked to mitochondrial biogenesis, suggesting that a better understanding of mitochondrial quality control will lead to new insights into the therapeutic potential of harnessing HIR² and, in turn, lead to the development of new strategies for the treatment of I/R injury, pathological remodeling, and heart failure in humans.

Biography

Robert M Mentzer is a renowned cardiovascular transplant surgeon known for his expertise in the areas of ischemia-reperfusion injury, myocardial protection, and organ preservation for transplantation. He is currently Professor of Cardiothoracic Surgery and Physiology at Wayne State University School of Medicine and is a member of the WSU Cardiovascular Research Institute in Detroit, MI. He also holds an Acting Professor appointment at the Cedars-Sinai Heart Institute in Los Angeles California. His current research investigates novel compounds that protect the heart from ischemia reperfusion injury when administered prior to ischemia or at the time of reperfusion. He has over 30 years of continuous peer-reviewed research NIH funding, has served on numerous NIH and AHA study sections, and conducted multi-institutional and multi-national industry-sponsored clinical research trials.

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