Inter-mitochondrial communication and the pathophysiological relevance in the heart

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Mitochondria are organelles highly dynamic in most types of cells, constantly changing morphology and forming dynamically continuous networks. Defects of mitochondrial dynamics are associated with various human diseases including neurodegenerative diseases and cardiovascular diseases. Hearts are organs with high energy demands, mitochondria occupy ~40% of the volume of adult cardiomyocytes. However, cardiac mitochondria are rigidly organized between myofilaments into a crystal-like lattice pattern, it is not clear whether mitochondria communicate with each other dynamically. By target-expressing photoactivatable green fluorescent protein (PAGFP) in the mitochondrial matrix, we demonstrated that in cardiomyocytes mitochondria communicate with each other through mitochondrial nanotunneling and kissing, thus forming a dynamically continuous network. Mechanistically, we found that the outer mitochondrial membrane protein Miro2 accelerates inter-mitochondrial communication through increasing both mitochondrial nanotunneling and mitochondrial kissing events along microtubules in adult cardiomyocytes. More importantly, Miro2 is degraded during cardiac hypertrophy by Parkin-mediated ubiquitination. Miro2 transgenic mice displayed ameliorated heart function after transverse aortic constriction (TAC) surgery, accompanied with increased cardiac inter-mitochondrial communication and improved mitochondrial function. Our results provide new insights into molecular mechanisms of the regulation of cardiac inter-mitochondrial communication and further suggest potential therapeutic targets of regulating the inter-mitochondrial communication during cardiac diseases.

Keyword

Inter-mitochondrial communication, nanotube, microtubule, cardiomyocytes, hypertrophy