Mitophagy: New Insight into the Cardiovascular Aging

Fatemeh Safari 1, 2*

1. Biotechnology Research Center, International Campus, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
2. Department of Physiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

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The incidence and prevalence of cardiovascular diseases and related risk factors increases with ageing; the most important cause of mortality in elderly people is cardiac diseases. Many theories have been developed to explain pathological changes of the heart due to aging such as accumulation of radical oxygen species (ROS) and advanced glycation end-product, telomere shortening, calcium mishandling, and metabolic switching. One of the theories that has attracted a lot of attention in recent years is disturbance in cellular phenomenon, known as “autophagy”. Autophagy is a regulated removal/recycling process that sequesters deteriorating organelles and toxic proteins, afterward the residue is delivered to lysosomes for degradation; therefore, it plays a principle role in the homeostasis of aged cardiomyocytes (1, 2).

One of the substantial and vital organelles in cardiomyocytes is “mitochondrion” that provides adequate amount of energy in the form of Adenosintriphosphate (ATP) through oxidative phosphorylation. Although electron transport chain in the inner membrane of mitochondria is the original location of the ATP production, this site is regarded for generation of ROS such as superoxide anions. Cardiomyocytes are recognized as long-lived cells with high metabolic activity; so this organ is significantly dependent on its mitochondrial function.

Studies have clearly shown that aging is associated with mitochondrial dysfunction in myocardial tissue. The aged mitochondria are characterized by impaired metabolic function and ROS overproduction. Old and damaged mitochondria release free radicals which attack structural components of the normal mitochondria and lead to further disruption in the function of the others, which indeed represents a positive feedback and deleterious cycle. Also, damaged mitochondria release large amount of calcium and proapoptotic factors through pores in membrane (mTOR) that eventually activates the apoptotic pathways and conducts the cardiac cells to cellular death. Another interesting fact is increased possibility of mutations in mitochondrial DNA (mtDNA) during aging; which in turn leads to impaired ATP production. ROS by targeting mDNA can increase the likelihood of mutations (3, 4).

Therefore, the entity of a mechanism seems to be necessary to remove old and effete mitochondria from cardiomyocytes; one of the main ways for eliminating damaged organelles is autophagy that is named “mitophagy”, exclusively for mitochondria. This term was proposed for the first time in 2005 by Lemastars (5).

In fact, mitochondrial clearance has been done selectively and cautiously by mitophagy phenomenon to prevent dysfunctional mitochondria accumulation in cardiac cells. The exact molecular and cellular mechanisms responsible for the mitophagy are still unknown and need to be investigated in details. Parkin- PINK (Pten- induced putative kinase 1) mediated mitophagy is one of the key signaling pathways for mitophagy. PINK is a mitochondrial serine-threonine kinase that is localized on inner membrane of intact mitochondria. But in old and damaged mitochondria the placement process on the inner membrane faces with problems resulting in PINK embedding on the outer membrane; accumulation of PINK on outer membrane causes recruitment of cytosolic ubiquitin ligase which is called Parkin toward mitochondria. Parkin ubiquitinates other proteins in the outer membrane of mitochondria and evokes trigger factors of mitophagy into mitochondria to initiate the process.

Receptor-mediated mitophagy is another type of mitophagy that is mediated by receptors localized in the outer membrane of mitochondria consisting of BCL-2 (B-cell lymphoma 2) related proteins BNIP3 (BCL2 Interacting Protein 3) and BNIP3L/Nix. Proapoptotic complex BAX/BAK (Bcl-2-associated X protein/ Bel-2 homologous antagonist killer) is activated by BNIP3 leads to increase of mitochondrial permeability. Mitochondrial apoptotic signaling is also activated by NIX. Furthermore, BNIP3 and NIX act as the receptors for targeting mitochondria to autophagosomes (6).

Studies have shown following mitochondrial dysfunction in aged heart increase the risk of cardiac arrhythmias and ventricular dysfunction makes the old

* Corresponding Author: Department of Physiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Tel: +989131093652, Email address: sa.physiol@gmail.com
heart more vulnerable against damages such as ischemia. Thus mitophagy impairment which leads to inadequate elimination of dysfunctional mitochondria may contribute to the pathogenesis of age-related heart disease.

Mitophagy enhancement and clearance of damaged mitochondria pave the way to increase the production of new mitochondria in cells, so mitophagy is able to affect mitochondrial biogenesis and controls both the quantity and quality of mitochondria. Considering the importance of the mitophagy phenomenon for maintaining homeostasis of old heart, there is possibility to target the signaling factors for protection of the normal heart function in old ages. In other words, there is an opportunity to introduce proteins which are involved in mitophagy process as a novel therapeutic target to treat age-related cardiovascular diseases.

For instance, caloric restriction is known to postpone aging and promotes mammalian cell survival by inducing antioxidant system and improvement of mitochondrial metabolic function (7). It is interesting to note that caloric restriction can prevent aging-induced autophagy suppression. It has been shown that mice undergone caloric restriction have greater ratio of mitophagy and smaller percentage of damaged mitochondria which was accompanied by low level of aging markers (8).

Mitophagy induction in mice can also improve mitochondrial function and prevent arterial wall stiffness (9). The natural phenol Resveratrol with the ability to extend life span was shown to activate mitophagy in heart tissue through PINK1-Parkin pathway (10).

Recent scientific evidences reveal that, mitophagy is intimately involved in cardiomyocytes survival during aging. More detailed studies are needed to identify the regulatory factors of mitophagy in aged heart to propose effective ways to prevent age-associated cardiac dysfunction.

In conclusion, considering the emerging importance of the “mitophagy” as a crucial mechanism to counteract the adverse effects of aging in the cardiovascular system is of great interest. Based on this view and taken altogether, mitophagy represents a new potential therapeutic target for development of more efficient and specific interventions to mitigate the human age-related heart disease.

References

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