

Advantages and disadvantages of mitochondrial mechanism (mitophagy) for cancer treatment

Amir Herić, Amar Silajdžić * and Tarik Zubčević

Department of Genetics and Bioengineering, International Burch University, Sarajevo, Bosnia and Herzegovina.

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Abstract

Mitochondrial organelles are crucial organelles for the energy supply of the whole cell. Also, mitochondria are beneficial for the production of ATP, a byproduct of the stabilization of nutrients in the TCA cycle, and FADH and NADH are reducing equivalents. Defects in mitochondria impair the energy supply, metabolite production, and redox reactions. Also, a crucial point for cell survival is to maintain mitochondrial quality rather than quantity. Qualitative mitochondria are required to produce the proper amount of ATP, degrade p53, and decrease reactive oxygen species (ROS) production. All of these factors lead to mitochondrial dysfunction. Dysfunctional mitochondria are „eaten“ by autophagosomes through the process of mitophagy. Mitophagy is crucial since it prevents the build-up of poorly/affected mitochondria, and prevents excess production of ROS and mtDNA mutation. Also, mitophagy shows positive effects on cancer, since mitophagy promotes pro-apoptotic signals for cancer stem cells (CSC). Due to all the advantages of mitophagy, this organelle can be used as a beneficial assistant for chemotherapy in cancer treatment. The authors of these papers provide a pathway for using mitophagy combined with cancer treatment. This claim is confirmed within the paper, with tables provided. Our results show the importance of mitophagy in human organisms and its importance in cancer.

Keywords: Mitochondria; Mitophagy; Cancer; Mitochondrial dysfunction; Chemotherapy

1. Introduction

Mitochondria is a cellular organelle crucial for the supply of cell energy supply. Defects in mitochondria are not only limited to cellular homeostasis but also cellular bioenergetics, redox reactions, and cell death [1, 2, 3, 4]. The main cellular energy contributor is ATP (adenosine triphosphate), produced via oxidative phosphorylation. Mitochondria contains an independent (own) genome (mtDNA), which consists of 13 proteins. Since the proteins are produced in the mitochondria, this organelle is more prone to mutation compared to the nuclear genome due to a lack of repair mechanisms in the organelle. Also, mitochondria are located near the production site of reactive oxygen species (ROS) [5, 6]. The ROS mechanism behaves as a signaling molecule needed for cellular homeostasis [7]. Nutrients are metabolized and produced in the tricarboxylic acid (TCA) cycle, and through a series of iterations, the electrons are stored as NADH and FADH₂ as reducing equivalents. These equivalents are represented as electrons and placed in the inner part of the mitochondrial membrane. The process results in proton production and ATP synthesis as a source of cellular biosynthetic processes [8]. In addition, cellular bioenergetics and changes in mitochondrial metabolism are associated with cell fates, decisions, and injury [2, 7].

As mentioned before, mitochondria contain only 13 proteins, which could seriously disrupt mitochondrial function, injury, and cellular bioenergetics. Most mitochondrial mutations are either deletions or point mutations and are

*Corresponding author: Amar Silajdžić

correlated with myopathy, ataxia, and neuropathy. Since mitochondria lack introns, histones, and non-histone proteins, they are more susceptible to endogenous and exogenous mutagens exposure.

In cancer, the term „mitochondrial dysfunction" refers to the mitochondrial incapability to produce cellular energy, metabolic reprogramming, and glucose and lactose [7]. The autophagic systems target impaired mitochondria into the lysosome for degradation. This process is called mitophagy. Mitophagy is crucial since a majority of tissues utilize ATP as a source of energy, such as the brain, skeletal muscle, heart, liver, and kidney [9]. In response to the mitochondrial depolarization, PINK1 (PTEN-induced putative kinase 1) serine/threonine kinase 1 is bound to the mitochondrial surface, after mitochondrial damage due to various factors such as ROS or mitochondrial DNA damage, mitochondria may recruit the autophagy receptors (OPTN and NDP52) which bind to LC3 of autophagosome and fuse with lysosome and results in a mitochondrial degradation [10, 11, 12]. The activation of PINK1 is dependent on TIM23 [13]. When mitochondria are damaged, PARL blocks PINK1 cleavage on TIM23 receptors, so that PINK1 accumulates on the surface of mitochondria and promotes autophagy. The surface of mitochondria is ubiquitinated with protein channel VDAC1 (voltage-dependent anion channel 1) in affected mitochondria and recognized with signal adapter proteins that bind to the Atg8 family of proteins on the surface of damaged mitochondria. Also, NIP3 and NIX are proapoptotic BH3 proteins present on the outer structures of mitochondria and bind to the LC3 (protein 1 light chain 3) to induce the mitochondrial binding to the autophagosome [13]. Autophagosomes prevent the mitochondria from producing excess amounts of ROS and damage the cell [13]. Inhibitions of PINK1 and other genes listed above prevent the mitochondrial removal and accumulation of damaged mitochondria [13, 14]. Considerable modification has been made to the concept of the mitochondria as an organelle suspended in the cytoplasm that produces ATP. As we all know, mitochondria have a variety of roles in cell physiology, including ion buffering, lipid metabolism, antiviral response, apoptosis, and cell division. Over the past 20 years, much evidence has shown that mitochondria can communicate directly with other intracellular organelles. Perhaps the most well-studied connection of this type is between the mitochondria and the endoplasmic reticulum, which is essential for lipid metabolism and Ca²⁺ regulation among other processes [87].

In addition to their obvious role in oxidative phosphorylation, which generates cellular ATP, mitochondria also play critical roles in ion homeostasis, many metabolic pathways, apoptosis and programmed cell death, and the generation and consumption of reactive oxygen species. Each of these roles could be important in disease and/or aging. Mitochondria damage can lead to the accumulation of malfunctioning parts. Radicals that the mitochondria themselves create may be the direct cause of this damage. As a result of a variety of internal or external stressors, such as skin exposure to UV radiation, it may be brought on by sequence or regulatory mistakes that follow mutation of nuclear or mitochondrial DNA [88, 89]. Degradation of the quality control mechanisms that typically prevent the accumulation of malfunctioning mitochondria by focusing on low-performing components of the mitochondrial network for elimination can worsen these effects [90, 91]. Although the molecular complexities of how mitochondria travel across the cell are still being worked out, it is known that proper movement of mitochondria inside the cell is necessary for them to send signals to the right places [92]. One way to illustrate hypoxia is to consider a situation in which the release of reactive oxygen species into the nucleus facilitates the clustering of mitochondria into the perinuclear area, providing the best conditions for hypoxic gene expression [86]. In healthy cells, this powerhouse of the cell is more likely to be stretched and fused to form filamentous structures. Mitochondrial fusion and fission rates are strictly regulated [93]. These filamentous networks are upset by excessive fission, which causes a punctate pattern and malfunctioning mitochondria. A recent study demonstrates how biological outcomes are determined by the integration of cellular signaling and the fission/fusion machinery. The disruption of fusion in the mouse embryonic heart and embryonic stem cells hinders the development of the mouse heart and the differentiation of embryonic stem cells into cardiomyocytes because of increased Ca²⁺-dependent calcineurin activity and Notch1 signaling [94]. Mitochondria attach themselves to particular endoplasmic reticulum subdomains known as mitochondria-associated membranes, or MAMs. Originally, it was demonstrated that MAMs were required to quickly transmit calcium signals to control intracellular calcium levels between the ER and mitochondria [95, 96]. Other research studies have shown that membranes connected to the mitochondria control ATP synthesis, reactive oxygen species, autophagy, ER stress, and immunological signaling. They also control mitochondrial movement and shape [97].

As already mentioned, cancer is produced after an uncontrollable mutation in the genomic or epigenetic makeup of the cell, this change is induced through the signal transduction that leads to cell proliferation [21]. Signal transduction is a biological reaction that enables the transmission of signals through organisms and cells [22]. Environmental signals are transduced through the cells to the cytoskeleton or nucleus enabling the changes in cell biology and metabolism [23]. Stimulation of signal transduction is induced through activation of cell surface receptors [23, 57]. Cell surface receptors are proteins found on the cell surface that are important for the recognition of environmental changes. In a multicellular organism, the cells communicate with the release of molecules found on neighboring proteins on the cell membrane [24]. Cellular signaling starts as a first messenger (ligand) binds to receptors on the membrane or transmembrane in cell structure. This binding activates the second messenger and transduces the signal to induce conformational, structural,

or genetic changes (expression). Signaling can either be: endocrine (long-range communication), paracrine (short-range), juxtacrine (contact-dependent signaling), autocrine, or neuro-transmitter mediated. After the signal is induced the ligand binds to the receptor. The receptor is either located on the cell surface or the intracellular surface of the cell [26]. According to different hydrophilicity, sphingolipids are classified into sphingomyelin, cerebroside, and ganglioside categories. Fatty acid chains are densely packed and located on the phospholipid bilayer. Also, the plasma lipid is composed of cholesterol, enhancing the membrane fluidity and diffusion rate [25]. The receptor undergoes a conformational change that suits the ligand binding upon ligand binding to the lipid cell surface protein. This binding activates the domain-linked kinases, phosphatase, and adaptors. This activation promotes the activation of secondary messenger and transduction of signals [26]. Apoptosis is crucial to maintain cell homeostasis [41, 42, 58, 59]. A fundamental function of apoptosis is performed through the action of a series of caspases, which act as cysteinyl proteases on cytoplasmic structures [27]. The catalytic subunit called „caspase" is associated with cysteine-dependent aspartate protease molecules that can cleave the specific subunits [28]. They are present as single zymogens that require highly strict activation mechanisms [60, 29]. The caspases that are produced as inactivated zymogens undergo dimerization and oligomerization for their activation. After activation, the caspase domain procaspase undergoes cleavage to large and small subunits and forms an enzymatic complex [30]. The activation of apoptosis is either due to intrinsic or extrinsic pathways [61, 62, 63, 64]. The extrinsic stimuli are mediated through the membrane surface within the FAS receptor. The ligand that binds to the FAS receptor induces the receptors oligomerization [31]. FAS receptor (CD95) is receptor important „death receptor" for programmable cell death (apoptosis) [52]. The signal received on the FAS receptor leads to changes in the receptor and the formation of a death-inducing signaling complex (DISC), combined with FADD and activation of pro-caspase-8 and caspase-10 [50, 53, 65]. Through this process the DISC gain the enzymatic ability to cleave the caspase 8 and form a hetero-tetrameric enzyme. This enzyme targets the effector caspase and pro-apoptotic BH3-only protein [32, 33]. Another pathway of activation is the intrinsic pathway. This pathway is induced through the mitochondrial respiratory chain component, cytochrome c. Cytochrome c interacts with an adaptor protein (Apaf-1), forms the apoptosome complex, and attracts the activation of caspase 9 [31, 68]. This pathway is initiated due to oxidative stress, irradiation, and treatment with cytotoxic drugs [34]. This activation is inhibited with (BCL-2, BCL-X, BCL-w, MCL-1, or BFL-1/A1) proteins. Activation is activated due to the activation of pro-apoptotic proteins BAX (BCL-2-associated X protein) or BAK (BCL-2 antagonist or killer), which leads to membrane permeability and release of cytochrome c. The release of cytochrome c produces the complex called apoptosome and recruits the Caspase-3 (CASP3) and Caspase-7 (CASP7). The final form of caspase activity is the executioner phase. The most common executioner caspase is CASP3 which activates the CAD, which induces breaking points in nuclei [35]. Generally, the prevention of initiation of apoptosis onset can be due to: a disrupted balance of pro and anti-apoptotic proteins, reduced caspase activity, and death receptor signaling [36]. As the tumor grows the cancerous cells become isolated from the blood supply and become hypoxic [37, 56]. Hypoxia is defined as a state of oxygen deficiency, that results in disrupting the normal health of the cell [54]. One of the key activation processes in oxygen deficiency is hypoxia, with hypoxia-induced factor 1 (HIF - 1) [55]. Hypoxia is a state of continuous lack of oxygen supply, for short or long periods [38]. Oxygen exchange occurs in the alveoli regions of the lungs and circulates through the body via capillary veins to maintain the proper function of each cell [38]. Impaired oxygen consumption and delivery is one of the features of cancer sites [38]. Also one of the keys to tumor growth is blood supply for nutrient delivery, waste removal, and chemical delivery. Angiogenesis is described as the process of creating new blood vessels [43, 44, 45, 46, 47, 48, 49]. When both angiogenic switches are in balance then the angiogenesis and epithelium are not proliferating, proliferation occurs when the balance of pro-angiogenic factors is bigger than anti-angiogenic factors, which leads to the production of new vessels [40, 39].

2. Review methodology

This review paper included peer-reviewed articles, reviews, and research papers relevant to mitophagy serving as a mechanism for cancer treatment. This review paper was primarily focused on investigating the role of mitophagy in cancer therapy. Included studies for this review paper were those only written in English, as well as research articles that provided insights into mechanisms of mitophagy and in vivo and in vitro experiments.

Exclusion criteria were fulfilled with studies not related to mitophagy as a cancer treatment; also the non-English publications and publications without clear evidence and experimental data were excluded. Keywords such as „mitophagy“, „cancer“, and „treatment“, were utilized to refine research on databases such as NCBI, PubMed, and Google Scholar. This materials and methods section outlines the systematic approach taken to review and select relevant literature on mitophagy in the context of cancer onset. Both the inclusion and the exclusion part criteria were put to ensure the quality and relevance of the chosen studies, contributing to a reliable foundation for understanding the role of mitophagy in cancer development.

3. Results and discussion

Table 1 Advantages and disadvantages of mitochondrial mitophagy in cancer treatment

Mitophagy and cancer	
Advantages	Disadvantages
Decrease of ROS production (reactive oxygen species) [15].	Insufficient Mitophagy results in the build-up of damaged and poorly functioning mitochondria [18].
Inhibition of Mitophagy can lead to drug resistance in cancer cells [16].	Incomplete Mitophagy has a decreased ability to synthesize adenosine triphosphate, which raises superoxide production [18].
Maintain the number of quality mitochondria rather than quantity [17].	Defective Mitophagy may change the cellular pools of intermediate metabolites, which could have harmful effects [18].
Promote p53 degradation [17].	This process's relative activity is important since too much of it could negatively deplete the mitochondrial pool [19].
Promote pro-apoptotic signaling for cancer stem cells (CSCs) [17].	mtDNA mutations [10].

Table 2 Advantages and Disadvantages of the utilization of mitophagy with chemotherapy against cancer progression

Mitophagy and chemotherapy	
Advantages	Disadvantages
Autophagy minimizes organ damage [66, ; 67].	Unauthorized autophagy can be beneficial for tumor progression in late stages of cancer [76, 77].
Minimizes toxic features of chemotherapy [68, 69, 70].	It can be destructive if healthy nutritious food is not implemented [78, 79, 80].
Minimizes the immunosuppression [71, 72].	It can make tumor cells more resistant to cancer drugs if not implemented at the right time [81, 82, 83].
Lowers rate of chemotherapy-induced death [73, 74, 75].	In early stages, it can be very beneficial but in later stages can serve as a mechanism for minimizing the side effects of chemotherapy [84, 85].

The majority of the paper includes either the advantageous or disadvantageous aspects of mitophagy in cancer. This type of approach can exclude the perception of duality and its role in cancer. Including both aspects can provide evidence of the harmfulness and benefits of mitophagy as a potential cancer treatment. This is important for patients and clinicians since it provides both aspects and takes into account all treatment benefits. The general aim is to present the advantages and disadvantages of mitophagy in cancer treatment, the role of mitophagy in the cancer environment, and a review of apoptosis and cell signaling.

4. Conclusion

A fully functional mitochondrial organelle enables the proper function of cells and prevents the accumulation of free radicals and other molecules. This mechanism is crucial to the quality rather than quantity of the mitochondria. Several studies have shown the great importance of mitochondria in cancer treatment. By including and understanding these important mitochondrial mechanisms mitophagy can be used with a combination of drugs for cancer treatment. Both advantages and disadvantages of this method enable a precise and clear picture for the patient and clinicians, to measure the possible beneficial or harmful effects of this method. Overall, understanding both perspectives, this mechanism can become a key target for prevention or aid in the treatment of the most serious diseases.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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