Mitochondrion xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Different approaches to modeling analysis of mitochondrial swelling

Sabzali Javadov[a,*], Xavier Chapa-Dubocq[a], Vladimir Makarov[b]

[a] Department of Physiology, School of Medicine, University of Puerto Rico, San Juan, PR, USA
[b] Department of Physics, Rio Piedras Campus, University of Puerto Rico, San Juan, PR, USA

ARTICLE INFO

Keywords:
Modeling analysis
Mitochondria
Matrix volume
Ion transport
Permeability transition pore
Calcium

ABSTRACT

Mitochondria are critical players involved in both cell life and death through multiple pathways. Structural integrity, metabolism and function of mitochondria are regulated by matrix volume due to physiological changes of ion homeostasis in cellular cytoplasm and mitochondria. Ca^{2+} and K^+ presumably play a critical role in physiological and pathological swelling of mitochondria when increased uptake (influx)/decreased release (efflux) of these ions enhances osmotic pressure accompanied by high water accumulation in the matrix. Changes in the matrix volume in the physiological range have a stimulatory effect on electron transfer chain and oxidative phosphorylation to satisfy metabolic requirements of the cell. However, excessive matrix swelling associated with the sustained opening of mitochondrial permeability transition pores (PTP) and other PTP-independent mechanisms compromises mitochondrial function and integrity leading to cell death. The mechanisms of transition from reversible (physiological) to irreversible (pathological) swelling of mitochondria remain unknown. Mitochondrial swelling is involved in the pathogenesis of many human diseases such as neurodegenerative and cardiovascular diseases. Therefore, modeling analysis of the swelling process is important for understanding the mechanisms of cell dysfunction. This review attempts to describe the role of mitochondrial swelling in cell life and death and the main mechanisms involved in the maintenance of ion homeostasis and swelling. The review also summarizes and discusses different kinetic models and approaches that can be useful for the development of new models for better simulation and prediction of in vivo mitochondrial swelling.

1. Introduction

Mitochondria are subcellular organelles that originated from primitive bacterial invasion of primordial eukaryotic cells (Sagan, 1967). Mitochondria are the powerhouse of the cell; ~90% of oxygen consumed by mammalian cells are used by mitochondria to produce ATP through oxidative phosphorylation (Rolfe and Brown, 1997). In addition to ATP production, mitochondria maintain a myriad of metabolic pathways such as ion homeostasis, cell growth, lipid oxidation and synthesis, and redox signaling. Mitochondria play a central role not only in cell life but also cell death (Balaban et al., 2005; O'Rourke et al., 1994; Tan et al., 1998). Due to their ability to store Ca^{2+} and respond to cytosolic Ca^{2+} signals, mitochondria together with endo (sarco) plasmic reticulum, participate in the regulation of intracellular Ca^{2+} homeostasis. Under normal conditions, mitochondrial Ca^{2+} (Ca_m^{2+}) regulates energy metabolism, whereas, at high concentrations, it stimulates mitochondria-mediated cell death pathways. Mitochondria respond to many different types of stress including oxidative and metabolic stresses. They are the main source of reactive oxygen species (ROS), a side product of respiration generated mainly at the electron transport chain (ETC) complexes I and III. Ca^{2+} overload along with high ROS and P_i, result in changes in mitochondrial membrane permeability and induces the opening of non-selective and high-conductance permeability transition pores (PTP) in the inner mitochondrial membrane (IMM). The PTP opening further compromises bioenergetics function and structural integrity of mitochondria leading to cell death (Halestrap et al., 1998; Petronilli et al., 2001; Rasola and Bernardi, 2011).

Abbreviations: AQP8, aquaporin-8; Ca_m^{2+}, mitochondrial Ca^{2+}; CICR, Ca^{2+}-induced Ca^{2+} release; CypD, cyclophilin D; ETC, electron transport chain; mHCX, mitochondrial H^+/Ca^{2+} exchanger; IMM, inner mitochondrial membrane; IMS, intermembrane space; KHE, K^+/H^+ exchanger; Kv1.3, voltage regulated K^+ channel; mBK_{Ca}, mitochondrial Ca^{2+} regulated K^+ large conductance channel; mK_{ATP}, mitochondrial ATP activated K^+ channels; mKv1.3, mitochondrial voltage-activated K^+ channel of the Kv1.3 type; MCU, mitochondrial Ca^{2+} uniporter; mRyR, mitochondrial RyR; $\Delta\Psi_m$, mitochondrial membrane potential; mSK_{Ca}, mitochondrial small-conductance Ca^{2+}-activated potassium channel; mNCX, mitochondrial Na^+/Ca^{2+} exchanger; mNHE, mitochondrial Na^+/H^+ exchanger; OMM, outer mitochondrial membrane; pH_m, mitochondrial matrix pH; PTP, permeability transition pore; RaM, rapid mode of Ca^{2+} uptake; ROS, reactive oxygen species; mRyR, mitochondrial ryanodine receptor; TCA, tricarboxylic acid; UCP, uncoupling proteins

* Corresponding author at: Department of Physiology, University of Puerto Rico, School of Medicine, San Juan, PR 00936-5067, USA.
E-mail address: sabzali.javadov@upr.edu (S. Javadov).

http://dx.doi.org/10.1016/j.mito.2017.08.004
Received 19 April 2017; Received in revised form 21 July 2017; Accepted 8 August 2017

Importantly, under physiological conditions, the mitochondrial volume is regulated by ion fluxes, mainly by K^+ and Ca^{2+} fluxes across the IMM (Garlid and Paucek, 2003; Szabo and Zoratti, 2014). Mild increases in matrix volume over the physiological range stimulate mitochondrial function and metabolism (Halestrap, 1989). Beneficial effects of matrix volume changes on mitochondrial metabolism and function may be due to structural and functional remodeling of the IMM, particularly, the fluidity of the membrane although precise mechanisms of these effects remain unknown.

Excessive mitochondrial swelling, which occurs mostly due to PTP opening, is a central player that can induce cell death through apoptosis or necrosis depending on availability of ATP. Notably, mitochondrial swelling is involved in the pathogenesis of many human diseases associated with oxidative stress such as ischemia (infarction)-reperfusion, hypoxia, inflammation and diabetes among others. Therefore, it is important to elucidate the mechanisms of mitochondrial swelling for understanding mitochondria-mediated cell death and development of new therapeutic strategies by targeting the mitochondrion. Regulation of the mitochondrial matrix volume may provide relief to stress, which would allow mitochondria to maintain their functional and morphological integrity (Kaasik et al., 2007); aiding in sustaining cellular life. As mentioned above, PTP opening induces mitochondrial swelling. However, inhibition of the PTP does not prevent mitochondrial swelling completely, suggesting a role of PTP-independent mechanisms are involved in the swelling (Eliseev et al., 2002; Gogvadze et al., 2004). The mechanisms of swelling are not clear, though ions, pH_i, and membrane potential ($\Delta\Psi_m$) are the major players that regulate matrix swelling. Particularly, the concentration of K^+ and Ca^{2+} across the IMM have been known to play a central role in creating the electrogenic transition leading to mitochondrial swelling (O'Rourke, 2007).

In this review, we discuss previous studies on the potential mechanisms of mitochondrial swelling as well as a variety of theoretical approaches to modeling mitochondrial swelling. Modeling analysis of mitochondrial swelling, particularly, the mechanisms of transition from physiological (reversible) to pathological (irreversible) swelling is important for understanding mitochondria-mediated cell death and organ/tissue dysfunction in human diseases.

2. Mitochondrial swelling: causes and consequences

Mitochondrial swelling begins with changes in ion homeostasis of the matrix, which induces an osmotic imbalance between the cytosol and the matrix. As a result, increased colloidal osmotic pressure enhances the water influx leading to matrix swelling. Notably, changes in matrix volume have an important role in regulating mitochondrial function and metabolism under physiological conditions. However, an extensive increase of the matrix volume or matrix swelling compromises mitochondrial function and initiates mitochondria-mediated cell death. Main transport mechanisms that regulate ion homeostasis and matrix volume in mitochondria are shown in Fig. 1.

2.1. Physiological role of changes in matrix volume

2.1.1. Role of K^+ and Ca^{2+} fluxes

Under physiological conditions, mitochondria maintain the matrix volume within a narrow range through the regulation of influx/efflux mechanisms for ions across the IMM. One of the main mechanisms regulating the matrix volume in unstressed mitochondria includes the movement of K^+ in or out of the matrix (reviewed in (Garlid and Paucek, 2003; Halestrap, 1994)). In 1986, Halestrap et al. (Halestrap et al., 1986) found that Ca^{2+} stimulated an energy dependent K^+ uptake that provoked a swelling response in rat liver mitochondria. Under physiological conditions, K^+-dependent Ca^{2+} influx induces an increase in matrix volume (Halestrap et al., 1986). Although the precise role of PTP in physiological swelling remains unclear (Mnatsakanyan et al., 2017), under pathophysiological conditions (e.g. oxidative

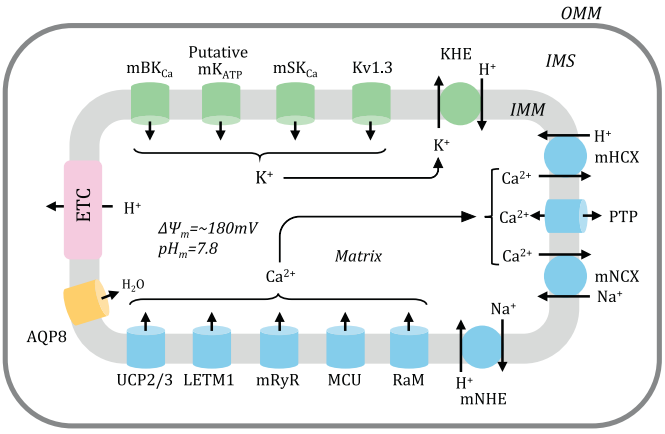

Fig. 1. Main ion flux mechanisms that regulate ion homeostasis and matrix volume in mitochondria. A schematic diagram represents the main Ca^{2+} (blue) and K^+ (green) influx and efflux mechanisms that regulate the mitochondrial volume. Main Ca^{2+} influx mechanisms include the mitochondrial Ca^{2+} uniporter (MCU), rapid mode of Ca^{2+} uptake (RaM), mitochondrial ryanodine receptor (mRyR), leucine zipper-EF-hand-containing transmembrane protein 1 (LETM1) and uncoupling proteins 2 and 3 (UCP2/3). Ca^{2+} efflux mechanisms are important for balancing of Ca^{2+} as well as ion homeostasis in the matrix, and include Na^+/Ca^{2+} exchange (mNCX), H^+/Ca^{2+} exchange (mHCX) and mitochondrial permeability transition pore (PTP). Transport of K^+ is equally important for mitochondrial metabolism and function and changes in K^+ correlate with changes in matrix volume. K^+ influx mechanisms include the mitochondrial Ca^{2+} regulated K^+ large conductance channel (mBK$_{Ca}$), mitochondrial ATP activated K^+ channel (mK$_{ATP}$), mitochondrial small-conductance Ca^{2+}-activated potassium channel (mSK$_{Ca}$), and a voltage-activated K^+ channel of the Kv1.3 type (mKv1.3), whereas K^+ efflux mechanisms are limited to the K^+/H^+ exchanger (KHE). Additionally, the mitochondrial Na^+/H^+ exchanger (mNHE) and aquaporin 8 (AQP8) have been included in the regulation of ion homeostasis in mitochondria. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

stress), the PTP presumably stimulates a shift in osmotic pressure that leads to matrix swelling.

The main K^+ influx mechanisms are the mitochondrial Ca^{2+} regulated K^+ large conductance channel (mBK$_{Ca}$), a voltage-activated K^+ channel of the Kv1.3 type (mKv1.3) and mitochondrial ATP activated K^+ channels (mK$_{ATP}$). The K^+/H^+ exchanger (KHE) is responsible for K^+ efflux from the matrix. Opening of the mBK$_{Ca}$ increases the permeability of the IMM to K^+ and which, in turn, decreases the mitochondrial Ca^{2+} buffering capacity due to membrane depolarization. The latter reduces the driving force for mitochondrial Ca^{2+} uptake and thereby, prevents Ca^{2+} overload (Giorgi et al., 2012). In favor of this, K^+ influx mediated by the mBK$_{Ca}$ improved respiratory function of mitochondria (Aon et al., 2010; Heinen et al., 2007a, 2007b). The beneficial effects of increased K^+ influx on respiratory function were dependent on mitochondrial swelling with maintained $\Delta\Psi_m$ (Aon et al., 2010). On the other hand, increased matrix K^+ influx due to stimulation of mBK$_{Ca}$ increased the ETC activity and mitochondrial respiration without altering $\Delta\Psi_m$ (Heinen et al., 2007a, 2007b). The K^+ entry into the matrix occurs mostly through the electrogenic putative mK$_{ATP}$ channel, whereas K^+ efflux mediated by KHE equilibrates the osmotic pressure across the IMM (Diwan, 1987). Hence, activation of the putative mK$_{ATP}$ channel facilitates K^+ influx and increases the matrix volume whereas stimulation of the K^+ efflux through the KHE, in contrast, decreases the volume (Garlid, 1980). A myriad of intra- and extra-mitochondrial factors are involved in the regulation of the balance between K^+ influx and efflux mechanisms in order to maintain matrix volume homeostasis. The molecular identities of the putative mK$_{ATP}$ and the KHE have not been established. The mKv1.3 was initially discovered in mitochondria of lymphocytes (Szabo et al., 2005). Later, it was identified in the IMM of different cells, where, similar to other K^+ channels, it likely participate in regulation of $\Delta\Psi_m$, matrix volume and ion homeostasis (Reviewed in (Szabo and Zoratti, 2014). A precise role of mKv1.3 under physiological conditions is not clear,