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Review article

Calcium signaling in cardiac mitochondria

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ABSTRACT

Mitochondrial Ca signaling contributes to the regulation of cellular energy metabolism, and mitochondria participate in cardiac excitation–contraction coupling (ECC) through their ability to store Ca, shape the cytosolic Ca signals and generate ATP required for contraction. The mitochondrial inner membrane is equipped with an elaborate system of channels and transporters for Ca uptake and extrusion that allows for the decoding of cytosolic Ca signals, and the storage of Ca in the mitochondrial matrix compartment. Controversy, however remains whether the fast cytosolic Ca transients underlying ECC in the beating heart are transmitted rapidly into the matrix compartment or slowly integrated by the mitochondrial Ca transport machinery. This review summarizes established and novel findings on cardiac mitochondrial Ca transport and buffering, and discusses the evidence either supporting or arguing against the idea that Ca can be taken up rapidly by mitochondria during ECC. This article is part of a Special Issue entitled "Calcium Signaling in Heart".

Contents

1. Introduction: Cardiac excitation–contraction coupling and mitochondrial Ca

Cardiac contraction is regulated by beat-to-beat elevations of cytosolic calcium ($[Ca]_i$) by a process termed excitation–contraction coupling (ECC) [1] where membrane depolarization induced by an action potential leads to Ca entry through voltage-activated L-type Ca channels. Entering Ca triggers Ca release from the sarcoplasmic reticulum (SR) Ca store via ryanodine receptor (RyR) Ca release channels by a mechanism known as Ca-induced Ca release (CICR). CICR increases global $[Ca]_i$ which activates proteins of the contractile apparatus and initiates cell contraction. Subsequent relaxation occurs by removal of Ca from the cytosol via four main pathways including reuptake via the SR Ca-ATPase (SERCA), extrusion via sarcolemmal Na/Ca exchange (NCX) and the sarcolemmal Ca-ATPase. A fourth avenue of Ca sequestration potentially involves mitochondrial Ca uptake since mitochondria are equipped with an efficient machinery for Ca transport and are capable of storing large amounts of Ca. Mitochondria of cardiomyocytes are known to accumulate Ca during elevations in cytosolic $[Ca]_i$ (for reviews cf. [2–8]), however, the kinetics of mitochondrial Ca cycling and buffering during ECC have remained highly controversial [9]. The question of whether and how beat-to-beat

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changes of cytosolic $[Ca]_i$ during ECC translate into changes of mitochondrial matrix Ca concentration ($[Ca]_m$) has important ramifications for cardiac physiology and pathophysiology. First, mitochondrial Ca uptake and buffering have the potential to shape the cytosolic Ca transient and therefore contribute to the regulation of contractile activity, and second, mitochondrial Ca uptake regulates cellular metabolism and energy supplies required for contraction. The latter occurs through the Ca-dependence of key enzymes of the tricarboxylic acid (TCA) cycle and possibly also Ca-dependent regulation of various sites of the electron transport chain (ETC) and the mitochondrial F_1/F_0 ATP synthase [10–12].

In this review we will briefly summarize the elements of the mitochondrial Ca transport machinery and recent novel findings on mitochondrial Ca buffering. Furthermore, we discuss how mitochondria encode rapid beat-to-beat cytosolic Ca oscillations and critically review arguments in favor and against rapid mitochondrial Ca uptake during ECC.

2. Mitochondrial Ca transport

Mitochondria are cytosolic double-membrane organelles that have been dubbed 'power plants' of the cell [13,14] for their ability to generate ATP to satisfy cellular energy demands. Mitochondria, however, participate in a myriad of other cellular processes such as ion homeostasis, redox signaling, apoptotic and necrotic cell death, as well as the control of cell cycle and cell growth [15]. Furthermore, mitochondria undergo remodeling in cardiac disease, including arrhythmia and heart failure, that has profound effects on mitochondrial structure-function that become important determinants of the course of the disease [6,16–19]. In cardiac myocytes mitochondria occupy ~35% of the cell volume [20,21] reflecting the high energy demands of these cells. Mitochondria possess an elaborate system of Ca uptake and extrusion mechanisms and pathways (Fig. 1) that allow for a fine-tuned regulation of $[Ca]_m$ [22,23].

2.1. Mitochondrial Ca uptake

Several mechanisms for mitochondrial Ca uptake (Fig. 1A) have been described and proposed for cardiac myocytes — some well established, others still controversial or a matter of debate: the mitochondrial Ca uniporter (MCU) [24–27], a rapid mode of Ca uptake (RaM) [28–31], the mitochondrial ryanodine receptor type 1 (mRyR1) [32–35] and the recently proposed leucine-zipper-EF-hand-containing transmembrane protein 1 (LETM 1) [36–38], all, together with

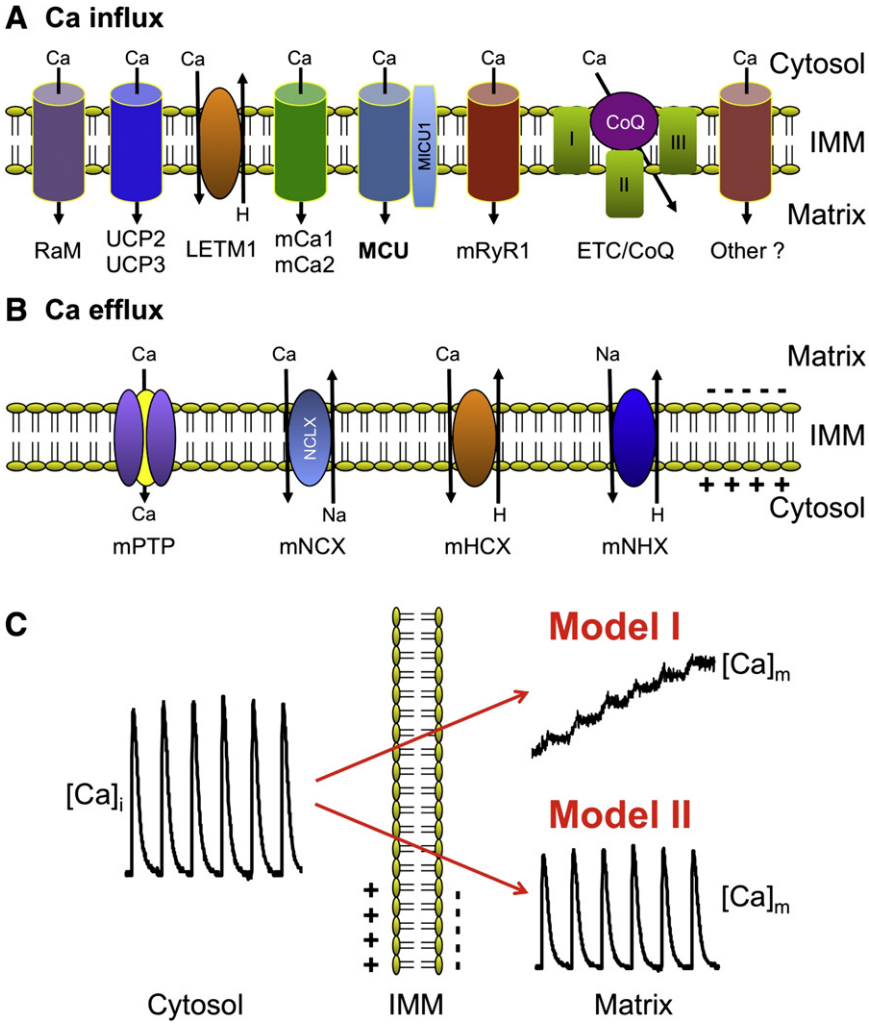

Fig. 1. Mitochondrial Ca transport and mitochondrial decoding of cytosolic Ca signals. A) Mitochondrial Ca uptake mechanisms and pathways located at the inner mitochondrial membrane (IMM). From left: RaM, rapid mode of Ca uptake; UCP2 and UCP3, uncoupling proteins 2 and 3; LETM1, leucine-zipper-EF-hand-containing transmembrane protein 1; mCa1 and mCa2, Ca-selective IMM conductances 1 and 2; MCU, mitochondrial Ca uniporter, with the associated protein MICU1; mRyR1, mitochondrial ryanodine receptor type 1; CoQ, Coenzyme Q10; ETC., electron transport chain. B) Mitochondrial Ca extrusion mechanisms and pathways located at the IMM. mPTP, mitochondrial permeability transition pore; mNCX, mitochondrial Na/Ca exchange with NCLX as suggested molecular identity; mHCX, mitochondrial proton/Ca exchange; mNHX, mitochondrial Na/proton exchange. C) Models of transmission of fast cytosolic Ca transients to matrix $[Ca]_m$: Model I, slow integration of cytosolic Ca spiking. Model II: rapid, beat-to-beat transmission of cytosolic Ca oscillations.