



Review

# A Review of the Role of Endo/Sarcoplasmic Reticulum-Mitochondria $\text{Ca}^{2+}$ Transport in Diseases and Skeletal Muscle Function

Shuang-Shuang Zhang <sup>1,2</sup>, Shi Zhou <sup>2</sup> , Zachary J. Crowley-McHattan <sup>2</sup> , Rui-Yuan Wang <sup>1,\*</sup> and Jun-Ping Li <sup>1</sup>

<sup>1</sup> School of Sport Science, Beijing Sport University, Beijing 100084, China; s.zhang.27@student.scu.edu.au (S.-S.Z.); doctorljp@126.com (J.-P.L.)

<sup>2</sup> Faculty of Health, Southern Cross University, East Lismore, NSW 2480, Australia; shi.zhou@scu.edu.au (S.Z.); zac.crowley@scu.edu.au (Z.J.C.-M.)

\* Correspondence: wangruiyuan2018@sina.com



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**Abstract:** The physical contact site between a mitochondrion and endoplasmic reticulum (ER), named the mitochondria-associated membrane (MAM), has emerged as a fundamental platform for regulating the functions of the two organelles and several cellular processes. This includes  $\text{Ca}^{2+}$  transport from the ER to mitochondria, mitochondrial dynamics, autophagy, apoptosis signalling, ER stress signalling, redox reaction, and membrane structure maintenance. Consequently, the MAM is suggested to be involved in, and as a possible therapeutic target for, some common diseases and impairment in skeletal muscle function, such as insulin resistance and diabetes, obesity, neurodegenerative diseases, Duchenne muscular dystrophy, age-related muscle atrophy, and exercise-induced muscle damage. In the past decade, evidence suggests that alterations in  $\text{Ca}^{2+}$  transport from the ER to mitochondria, mediated by the macromolecular complex formed by  $\text{IP}_3\text{R}$ , Grp75, and VDAC1, may be a universal mechanism for how ER-mitochondria cross-talk is involved in different physiological/pathological conditions mentioned above. A better understanding of the ER (or sarcoplasmic reticulum in muscle)-mitochondria  $\text{Ca}^{2+}$  transport system may provide a new perspective for exploring the mechanism of how the MAM is involved in the pathology of diseases and skeletal muscle dysfunction. This review provides a summary of recent research findings in this area.

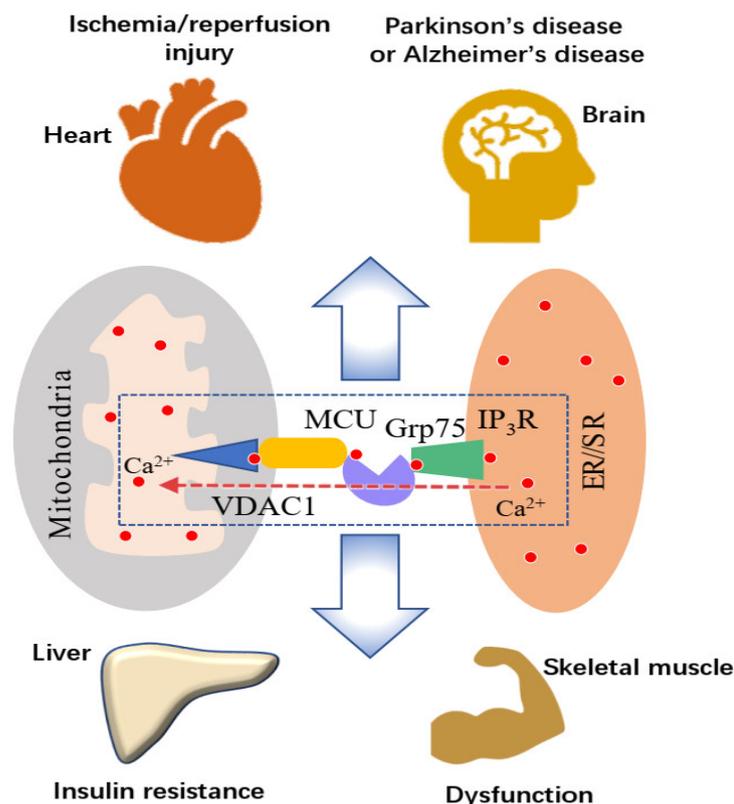
**Keywords:** mitochondria-associated membrane; endo/sarcoplasmic reticulum-mitochondria  $\text{Ca}^{2+}$  transport; mitochondrial calcium overload; skeletal muscle function

## 1. Introduction

Mitochondria and endoplasmic reticulum (ER) are two organelles in a cell that play essential roles in cellular survival and stress responses. The mitochondrion is the powerhouse of the cell. The ER is involved in protein synthesis, modification, secretion, lipid and steroid synthesis, and modulation of  $\text{Ca}^{2+}$  signalling. Sarcoplasmic reticulum (SR) is a special form of ER in striated muscle; it is specialised in the lipid synthesis,  $\text{Ca}^{2+}$  modulation, and excitation–contraction coupling. Structurally and functionally, these two organelles are connected via the mitochondria-associated membrane (MAM), a contact site that acts as a platform for inter-organelle communication [1]. In particular, the MAM is involved in a multitude of cellular processes [2], among which the  $\text{Ca}^{2+}$  transport from the ER to the mitochondrion (ER-mitochondria  $\text{Ca}^{2+}$  transport) is the focus of this review. This process is mediated by the molecular complex inositol 1,4,5-triphosphate receptor ( $\text{IP}_3\text{R}$ )–glucose-regulated protein 75 (Grp75)–voltage-dependent anion channel 1 (VDAC1), which works as a hub for cellular survival and death based on its role in regulating mitochondrial physiology and cellular  $\text{Ca}^{2+}$  homeostasis [3,4]. During the past decade, alterations of ER-mitochondria  $\text{Ca}^{2+}$  transport have been observed in diabetes, obesity, cancer, neurodegenerative diseases like Alzheimer's disease and Parkinson's dis-

ease, and ischemia/reperfusion injuries in which the integrity or number of MAMs are changed [2,5].

Skeletal muscle is a high energy-consuming organ in which adequate energy supply is essential for muscle performance. Changes in mitochondrial  $\text{Ca}^{2+}$  homeostasis could cause  $\text{Ca}^{2+}$ -dependent damage to mitochondrial structure and function. Conjecture exists that these changes contribute to the age- and disease-related attenuation in muscle performance [6]. There are also some indications that these changes may contribute to exercise-induced muscle damage [7–9]. The  $[\text{Ca}^{2+}]$  variations on either the outer mitochondrial membrane (OMM) surface or within mitochondria ( $[\text{Ca}^{2+}]_{\text{mt}}$ ), in response to stimulation of the  $\text{IP}_3\text{R}$ , are frequently measured for exploring the  $\text{Ca}^{2+}$  communication between the ER and mitochondria in the liver and brain [10–12]. However, few studies have been undertaken on skeletal muscle in this regard. The MAM's role concerning impaired skeletal muscle function has been confirmed in muscular dystrophy, ageing, and insulin resistance, with the evidence that there is a reduction in the number of MAMs in these conditions [13–15]. A reduced MAM number has also been implicated in heavy-load endurance exercise that may be caused by SR stress and an increased mitochondrial division rate [16–18]. Furthermore, according to the studies investigating MAM and ER-mitochondria  $\text{Ca}^{2+}$  transport in response to ER stress [13], mitochondrial dynamics [19], and insulin resistance [20], speculation has arisen that this transport system plays an essential role in mitochondrial  $\text{Ca}^{2+}$  overload in response to intensive exercise (Figure 1).



**Figure 1.** The changes in ER/SR-mitochondrial  $\text{Ca}^{2+}$  transport mediated by  $\text{IP}_3\text{R}$ -Grp75-VDAC1 that are involved in diseases and skeletal muscle dysfunction. Under normal physiological conditions, parts of the mitochondrial membrane are physically connected to the ER/SR. The ER/SR-mitochondria  $\text{Ca}^{2+}$  transport is mediated by the macromolecular complex  $\text{IP}_3\text{R}$ -Grp75-VDAC1 and supplies  $\text{Ca}^{2+}$  to mitochondria for ATP production. However, an increase in ER/SR-mitochondria  $\text{Ca}^{2+}$  transport is involved in diseases such as Alzheimer's disease, hepatic diabetes, heart ischemia/reperfusion injury, and skeletal muscle impairment. A decrease in the ER/SR-mitochondria  $\text{Ca}^{2+}$  transport is also a contributing factor for Parkinson's disease, insulin resistance in the liver, and muscle performance reduction.

The aims of this review are (1) to summarise the current literature on the function of the MAM and  $\text{Ca}^{2+}$  transport from the ER (or SR) to mitochondria, mediated by the  $\text{IP}_3\text{R-Grp75-VDAC1}$  complex, in regulating mitochondrial  $\text{Ca}^{2+}$  homeostasis; and (2) to discuss the changes in the MAM and ER/SR-mitochondria  $\text{Ca}^{2+}$  transport concerning diseases and skeletal muscle function.

## 2. Mitochondria-Associated Membrane: A Platform for ER-Mitochondria $\text{Ca}^{2+}$ Transport

The calcium ion ( $\text{Ca}^{2+}$ ) in the mitochondrial matrix is required to stimulate oxidative metabolism by regulating three rate-limiting enzymes in the tricarboxylic acid cycle (TCA): isocitrate dehydrogenase,  $\alpha$ -ketoglutarate dehydrogenase, and pyruvate dehydrogenase. It works as a booster in the synthesis of the reduced oxidative phosphorylation substrates (NADH and  $\text{FADH}_2$ ) [21]. Physiologically, mitochondrial  $\text{Ca}^{2+}$  accumulation is required for enhancing mitochondrial bioenergetics and cellular processes in response to cell stress. However, an excessively high  $[\text{Ca}^{2+}]_{\text{mt}}$ , i.e., mitochondrial  $\text{Ca}^{2+}$  overload, could cause a constant opening of the mitochondrial permeability transition pore (mPTP). This may subsequently lead to mitochondrial swelling, rupture of the OMM, and the collapse of the mitochondrial membrane potential, resulting in structural and functional damage to mitochondria [22].

### 2.1. High $\text{Ca}^{2+}$ Microdomain between the ER and Mitochondria

Under resting conditions, the OMM [23] is permeable to ions and small proteins. Predominantly this is due to the facilitation by the voltage-dependent anion channel 1 (VDAC1) for the diffusion of succinate, pyruvate, ATP, etc., across the OMM [24]. The voltage-dependent anion channel is also permeable to some ions, e.g.,  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Ca}^{2+}$ , and it has higher permeability to  $\text{Ca}^{2+}$  in a high potential state (so-called “closed” state) than in a low potential state (so-called “opened” state). It has been reported that the VDAC1 possesses  $\text{Ca}^{2+}$ -binding sites, and its closure promotes  $\text{Ca}^{2+}$  influx into mitochondria, which causes the opening of the mitochondrial permeability transition pore. Consequently, closure of the VDAC1 is recognised as a pro-apoptotic signal [25]. At the physiological state,  $[\text{Ca}^{2+}]$  in the mitochondrial intermembrane space is indistinguishable from that in the cytoplasm ( $[\text{Ca}^{2+}]_c$ ) (around 100 nM) [26]. Mitochondrial  $\text{Ca}^{2+}$  uptake is driven by the electrochemical gradient across the inner mitochondrial membrane (IMM) (−150 to −180 mV, negative inside) [27], while the mitochondrial calcium uniporter (MCU) on the IMM is responsible for mitochondrial  $\text{Ca}^{2+}$  uptake. The MCU is characterised by a low  $\text{Ca}^{2+}$  affinity ( $\text{KD} = 20\text{--}30 \mu\text{M}$ ), which makes it hard to understand how mitochondria uptake  $\text{Ca}^{2+}$  at such a low level of  $[\text{Ca}^{2+}]$  under resting conditions or even in response to physiological stimulation (approximately 1  $\mu\text{M}$ ) [28]. This paradox is explained by the widely accepted “ $\text{Ca}^{2+}$  microdomain” hypothesis, in which mitochondrial  $\text{Ca}^{2+}$  accumulation is effectively favoured by the high  $\text{Ca}^{2+}$  microdomain close to the ER  $\text{Ca}^{2+}$  release channels [29]. The  $[\text{Ca}^{2+}]$  at the ER–mitochondrial interface is much higher than that in bulk cytoplasm. This unique  $[\text{Ca}^{2+}]$  localisation has been directly demonstrated by monitoring the local  $[\text{Ca}^{2+}]$  at the ER–mitochondrial interface by fluorescent interorganelle linkers [10], or GFP-based  $\text{Ca}^{2+}$  probe localised on the cytosolic surface of the OMM [29]. Upon the  $\text{Ca}^{2+}$  mobilisation from the ER, the  $[\text{Ca}^{2+}]$  in local regions near the mitochondrial surface is 5–10-fold higher than that in bulk cytoplasm [30]. The local  $[\text{Ca}^{2+}]$  at the ER–mitochondrial interface may then rise to several tens of micromolar during the activation of the  $\text{IP}_3\text{R}$ . There are two important types of  $\text{Ca}^{2+}$  release channels at the ER membrane, ryanodine receptor (RyR) and  $\text{IP}_3\text{R}$ . While  $\text{IP}_3\text{R}$  is mainly for forming the high  $\text{Ca}^{2+}$  microdomain [11,12,31], the RyR has a major role in the excitation–contraction coupling processes in skeletal muscle [32].

### 2.2. Endoplasmic Reticulum-Mitochondrial $\text{Ca}^{2+}$ Transport

The  $\text{IP}_3\text{R}$  is predominantly localised on the ER membrane and is one of the important  $\text{Ca}^{2+}$  release channels of ER. There are three  $\text{IP}_3\text{R}$  isoforms,  $\text{IP}_3\text{R1}$ ,  $\text{IP}_3\text{R2}$ , and  $\text{IP}_3\text{R3}$  in mammalian cells. The ion permeability of the  $\text{IP}_3\text{R}$  could be regulated by inositol 1,4,5-

triphosphate (IP<sub>3</sub>), cytosolic Ca<sup>2+</sup>, and ATP. Upon receiving a stimulus, IP<sub>3</sub> is produced by the cleavage of phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>). In response to the presence of IP<sub>3</sub>, the IP<sub>3</sub>R releases Ca<sup>2+</sup> from the ER [33]. The ER is a major organelle for storage of intracellular Ca<sup>2+</sup>. The efficiency of mitochondrial Ca<sup>2+</sup> uptake depends on the close localisation of mitochondria to Ca<sup>2+</sup> release channels at the ER membrane that is essential to Ca<sup>2+</sup> diffusion from the ER to mitochondria (ER-mitochondria Ca<sup>2+</sup> transport) [29]. The IP<sub>3</sub>R is required for increasing [Ca<sup>2+</sup>]<sub>mt</sub>, and at times activation of this protein can result in [Ca<sup>2+</sup>]<sub>mt</sub> 20 times higher than the global increase in [Ca<sup>2+</sup>]<sub>c</sub> [31]. Additionally, the activation of IP<sub>3</sub>R may evoke a large [Ca<sup>2+</sup>] change at the ER–mitochondrial interface even when the increase in [Ca<sup>2+</sup>]<sub>c</sub> is suppressed in bulk by the ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA)/Ca<sup>2+</sup> buffer [10]. These findings suggest that IP<sub>3</sub>R plays a vital role in mediating ER-mitochondria Ca<sup>2+</sup> transport. The VDAC1 protein is also required for the control of ER-mitochondria Ca<sup>2+</sup> transport. Recombinant expression of the VDAC1 could enhance the transfer of Ca<sup>2+</sup> from the microdomains to mitochondria [34]. Moreover, a recombinant expression of IP<sub>3</sub>R-LBD<sub>224–605</sub> increases the ER-mitochondria Ca<sup>2+</sup> transport, and this phenomenon can be inhibited by the downregulation of Grp75 [35]. The Grp75 is a 75 kDa glucose-regulated protein and molecular chaperone that belongs to the heat shock protein 70 (Hsp70) family. Predominantly, Grp75 is localised in the mitochondrial matrix, while it is also found in cytoplasm or other subcellular compartments [35]. This protein is demonstrated to tether the N-terminal domain of the IP<sub>3</sub>R to VDAC1 and enhance mitochondrial Ca<sup>2+</sup> accumulation by stabilising the conformation or coupling of IP<sub>3</sub>R and VDAC1 [36].

The physical link between the ER and mitochondria is necessary for normal ER-mitochondrial Ca<sup>2+</sup> transport, with the [Ca<sup>2+</sup>]<sub>mt</sub> being increased by moving the ER closer to the mitochondria [37]. Additionally, the ER-mitochondria Ca<sup>2+</sup> transport may depend on an appropriate distance between the ER and mitochondria. One study reported that a distance of ~20 nm or shorter between the two organelles is required for proper ER-mitochondria Ca<sup>2+</sup> transport [30]. Although the optimal or average width of the MAM that coordinates efficient ER-mitochondria Ca<sup>2+</sup> transport is still unknown, it is hypothesised that the width can impact the Ca<sup>2+</sup> transfer by regulating the assembly of the IP<sub>3</sub>R-Grp75-VDAC1 complex [30].

During the past decade, the function of the IP<sub>3</sub>R-Grp75-VDAC1 complex in transporting Ca<sup>2+</sup> has attracted a great deal of attention [4,13,38]. Numerous proteins, like DJ-1 [39], transglutaminase type 2 (TG2) [35], FUN14 domain-containing protein 1 (FUNDC1) [19], glycogen synthase kinase-3β (GSK3β) [5], pyruvate dehydrogenase kinase 4 (PDK4) [15], etc., are found to regulate the integrity of MAM, or interact with the complex IP<sub>3</sub>R-Grp75-VDAC1, influencing Ca<sup>2+</sup> transport from ER to mitochondria. Abnormal transmission of Ca<sup>2+</sup> between the ER and mitochondria has been implicated in several pathological conditions [2,5,40–43]. According to the current literature, maintaining the structural integrity of the MAM and ER-mitochondria Ca<sup>2+</sup> transport within normal physiological ranges may be essential to retarding either the pathogenesis or the progression of these diseases.

### 3. Effects of the MAM and SR-Mitochondria Ca<sup>2+</sup> Transport on Skeletal Muscle Function

Over the past 40 years, the idea that mitochondrial dysfunction contributes to muscle function impairment has been hypothesised and tested [6]. It is now understood that the disruption of mitochondrial Ca<sup>2+</sup> homeostasis is a general mechanism for mitochondrial function impairment [44]. Mitochondria-associated membranes were found in skeletal muscle about 30 years ago [45], adding to the evidence that the MAM contributes to regulating mitochondrial Ca<sup>2+</sup> homeostasis. As the SR is a large Ca<sup>2+</sup> store regulating intracellular and mitochondrial Ca<sup>2+</sup> concentrations, the Ca<sup>2+</sup> cross-talk between SR and mitochondria has attracted increased attention in the recent past [23].

### 3.1. Mitochondria-Associated Membrane in Cardiac and Skeletal Muscle

Close localisation between the SR and mitochondria was first demonstrated in frog skeletal muscle using scanning electron microscopy in 1987 [45]. More recently, Ainbinder et al. (2015) found that mitochondria were located close to the I-band in the flexor digitorum of mice, and that the OMM was linked to the terminal cistern of SR by MAMs. They additionally found that the MAMs in the skeletal muscle were established and maintained during postnatal maturation. At the same time, mitochondria shifted from a longitudinal cluster to a transversal orientation and moved from the H-band to the I-band [46]. Furthermore, protein analysis showed that SR membrane fractions contained proteins involved in oxidative phosphorylation and the TCA [47]. These findings indicate that these proteins in mitochondria are connected with proteins in the cell's SR, and that the SR and mitochondria are also functionally connected through MAMs [47].

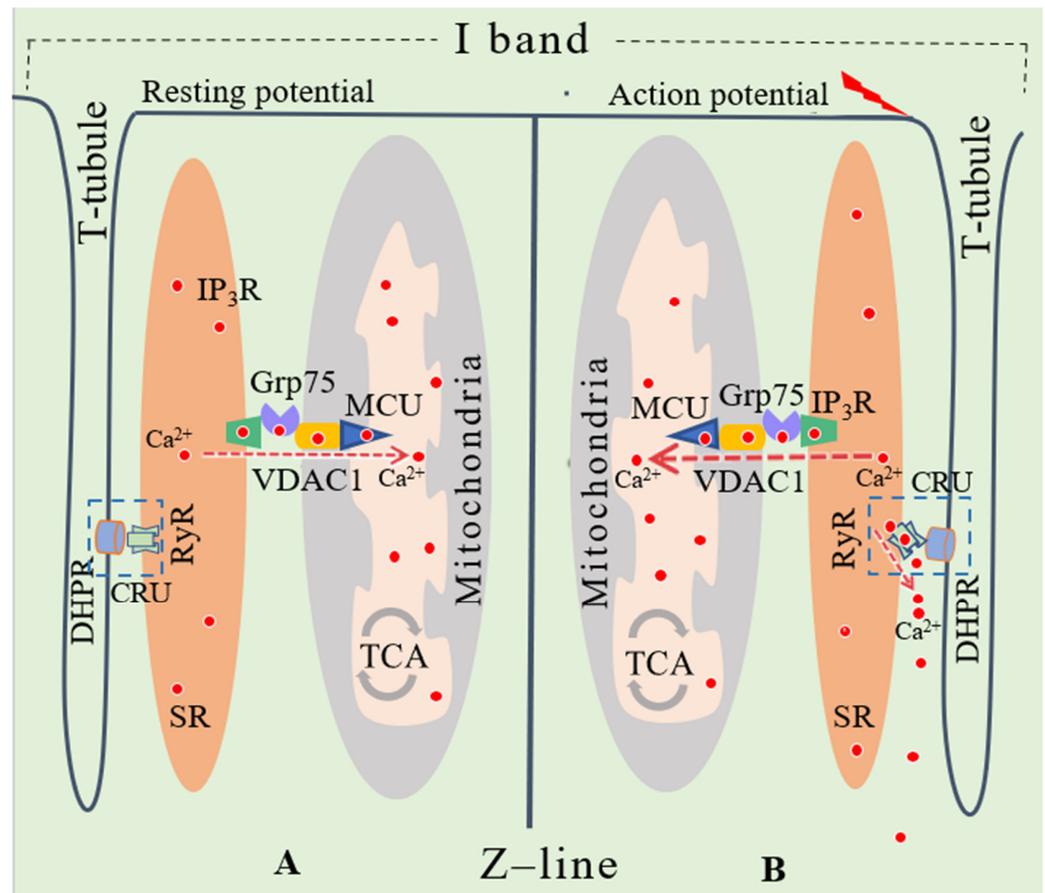
There is currently limited experimental research demonstrating the molecular composition of SR–mitochondria interaction and its specific functions in skeletal muscle. However, numerous studies have investigated MAM formation proteins and their functional relevance in the brain, liver, and cardiac muscle [48–50]. A protein analysis of the MAM in skeletal muscle has identified 459 proteins, including 101 membrane proteins, in which VDAC1, VDAC2, and VDAC3 might participate in the formation of the tethers between SR and mitochondria [51]. Among the MAM constitutive proteins, mitofusin 2 (Mfn2) is most commonly recognised as a molecule for regulating the structure of the MAMs [52,53]. However, in other studies, Mfn2 is demonstrated to be a physical tether protein [54] or a tethering antagonist [55]. In skeletal muscle, Mfn2 may work as a tether protein because its depletion leads to mitochondrial migration away from the I-band towards the A-band, resulting in reduced MAMs [46]. Moreover, proteins that are involved in  $\text{Ca}^{2+}$  transport from the ER to mitochondria, like  $\text{IP}_3\text{R}$  and Grp75, have been attracting increased investigative attention in the recent past. Additionally, the investigations suggest these 'emerging factors' being directly involved in the changes of mitochondrial  $\text{Ca}^{2+}$  homeostasis [15,56].

### 3.2. $\text{Ca}^{2+}$ Release by SR in Skeletal Muscle Fibres

It is well known that  $\text{Ca}^{2+}$  is essential in the excitation–contraction coupling process during muscle contraction [57]. Calcium ions required for skeletal muscle contraction are predominantly released from the SR via the  $\text{Ca}^{2+}$  release unit (CRU). The CRU consists of the L-type  $\text{Ca}^{2+}$  channels (dihydropyridine receptors, DHPRs) on the exterior membrane and the RyRs on the SR [58]. The major type of RyR in skeletal muscle is RyR1. The RyR1 on the SR membrane is positioned facing the voltage-dependent L-type  $\text{Ca}^{2+}$  channels (Cav1.1) that are located on the transverse tubules (T-tubules, Figure 2). This position is the key factor for  $\text{Ca}^{2+}$  being released by the RyR upon T-tubule membrane depolarisation, causing a conformational change of the DHPRs [59].

Furthermore,  $\text{Ca}^{2+}$  is also required by the mitochondrial matrix in the energy (ATP) supplying processes for muscle contraction [60]. These processes require  $\text{Ca}^{2+}$  to be under precise physiological control within the mitochondria of skeletal muscle [61]. In skeletal muscle, mitochondria are located close to the CRU [14]. This localisation might be due to the inhibitory effect of  $\text{Ca}^{2+}$  on mitochondria motility so that mitochondria are kept around the  $\text{Ca}^{2+}$  intracellular stores [62]. In addition to  $\text{Ca}^{2+}$  release by RyR's from the SR to the cytosol, the cellular membrane depolarisation could also cause  $\text{Ca}^{2+}$  release via the  $\text{IP}_3\text{R}$  protein [63]. The  $\text{Ca}^{2+}$  cross-talk between SR and mitochondria was demonstrated by comparing the  $[\text{Ca}^{2+}]_{\text{mt}}$  with the  $[\text{Ca}^{2+}]_{\text{c}}$  in response to caffeine when using a fast  $\text{Ca}^{2+}$  buffer BAPTA (1, 2-bis(2-aminophenoxy)ethane-N, N, N', N'-tetraacetic acid) in the cytosol, with the mitochondrial  $\text{Ca}^{2+}$  concentration increasing and cytosolic  $\text{Ca}^{2+}$  showing little change [64]. This finding indicates that the  $\text{Ca}^{2+}$  could be transported from the SR to mitochondria directly, not depending on the increased cytosolic  $\text{Ca}^{2+}$  concentration. According to Csordás et al. (2010),  $\text{Ca}^{2+}$  cross-talk between the SR and mitochondria is likely caused by activation of  $\text{IP}_3\text{R}$  and depends on the close location between the SR and mitochondria. It was found that mitochondrial  $\text{Ca}^{2+}$  concentration changes in

skeletal muscle may depend on the mitochondrial location being close to the CRU's [65]. Furthermore, overexpression of VDAC1 can increase  $\text{Ca}^{2+}$  transport into mitochondria from the high  $\text{Ca}^{2+}$  microdomain around SR [34].



**Figure 2.** SR-mitochondria  $\text{Ca}^{2+}$  transport in skeletal muscle. The terminals of the SR are located near the T-tubules. Mitochondria are located close to the CRU on both sides of the Z-line within the I-band. (A) At rest, RyR releases no  $\text{Ca}^{2+}$ . (B) Upon membrane depolarization, the conformational change of RyR causes  $\text{Ca}^{2+}$  release from the SR to cytosol (triggering muscle contraction) and hypothetically transported to mitochondria via the  $\text{IP}_3\text{R}$ -Grp75-VDAC1 pathway (required by ATP production).

It is known that  $\text{Ca}^{2+}$  can be transported from the ER/SR to mitochondria via the  $\text{IP}_3\text{R}$ -Grp75-VDAC1 complex in cardiac muscle and other types of cells. However, whether this is a major pathway and how the mitochondrial and cellular function is affected by this pathway in skeletal muscle are currently not clear and require further investigation.

#### 4. Sarcoplasmic Reticulum-Mitochondrial $\text{Ca}^{2+}$ Transport in Relation to Skeletal Muscle Dysfunction

Mitochondria-associated membranes have been shown to affect the metabolic adaptation and cellular function in response to physical environmental changes [66]. Evidence suggests that changes in the MAM and ER/SR-mitochondria  $\text{Ca}^{2+}$  transport are related to several health conditions and impaired skeletal muscle function, such as insulin resistance [40], Duchenne muscular dystrophy (DMD), or age-related muscle dystrophy [67]. Insulin resistance is a metabolic disorder, and the MAM has been shown to be a hub for insulin resistance in three key insulin-targeting tissues or cells: the liver [68], adipocytes [69], and skeletal muscle [70]. Reorganisation of the MAMs and mitochondrial  $\text{Ca}^{2+}$  overload has been shown in the liver of obese animals. A downregulation of MAMs and the ER-mitochondria  $\text{Ca}^{2+}$  transport has been demonstrated to improve glucose metabolism [71].

Additionally, it has been found that a reduction in ER-mitochondria  $\text{Ca}^{2+}$  transport may contribute to insulin resistance in liver cells and adipocytes [40,72]. The disruption of the MAMs in hepatocytes plays a central role in developing insulin resistance [72]. This was demonstrated by using sulforaphane for treating insulin resistance, with insulin resistance being improved along with a reduced MAM disruption and impaired interaction between VDAC1 and  $\text{IP}_3\text{R1}$  [56]. Moreover, in adipose tissue of obese mice and humans who were suffering from type 2 diabetes mellitus,  $[\text{Ca}^{2+}]_{\text{mt}}$  was found to be increased, but  $[\text{Ca}^{2+}]_{\text{c}}$  showed no change, with an accompanying rise in MCU expression and activity [73].

Skeletal muscle is an important regulator for whole-body glucose homeostasis and has been extensively studied concerning insulin resistance pathologies [74]. Tubbs et al. (2018 b) showed that the gastrocnemius muscle of obese mice with type 2 diabetes exhibited a significant disruption of SR-mitochondria interaction, which is compatible with experimental findings in human patients with obesity and type 2 diabetes [70]. These patients showed a reduction in VDAC1/ $\text{IP}_3\text{R}$  interaction, indicating that the  $\text{Ca}^{2+}$  communication between the SR and mitochondria is likely to play a key role in altered glucose homeostasis in type 2 diabetes [70]. One study by Zhe et al. (2020) investigated the improvement of glucose intolerance induced by swimming. The findings suggested that decreased MAM quantity might help in understanding the mechanism of type 2 diabetes mellitus [75]. However, contrary to the findings mentioned above, there has been evidence suggesting that the increased formation of MAMs is a contributor to insulin resistance. For example, one study found that mitochondrial  $\text{Ca}^{2+}$  accumulation in skeletal muscle with insulin resistance may be caused by augmented MAM formation [15]. This is because insulin signalling can be improved by preventing MAM-mediated mitochondrial  $\text{Ca}^{2+}$  accumulation and mitochondrial dysfunction through inhibiting pyruvate dehydrogenase kinase 4 [15]. The opening of mitochondrial permeability transition pores is a necessary contributor to skeletal muscle insulin resistance because it prevents the insulin-induced translocation of glucose transporter 4 into the cytoplasm [76]. Additionally, mitochondrial  $\text{Ca}^{2+}$  overload is commonly regarded as a central contributor to the opening of mitochondrial permeability transition pores [6,24]. As shown above, controversy still exists regarding the relationship between insulin resistance and changes in the MAMs, SR-mitochondria  $\text{Ca}^{2+}$  transport, and mitochondrial  $\text{Ca}^{2+}$  homeostasis in skeletal muscle. It is also far from clear whether the alterations in MAM and  $\text{IP}_3\text{R-Grp75-VDAC1}$  result from or are the cause of muscular insulin resistance.

Muscle weakness and wasting have long been confirmed as pathogenic DMD symptoms [77]. It is accepted that the defective gene dystrophin is involved in the DMD pathology [78], and it has been suggested that the increase in  $\text{Ca}^{2+}$  release by the sarcoplasmic reticulum is involved in calcium dysregulation in DMD myotubes. In DMD foetal muscle, myopathology begins with a significant delay of foetal muscle differentiation at an early foetal stage. This phenomenon is related to the activation of the PLC/ $\text{IP}_3\text{R}$ /calcium/PKC $\alpha$  pathway, which may be induced by the absence of dystrophy [79]. An increased  $\text{IP}_3\text{R}$  activity negatively regulates autophagy and elevates the  $[\text{Ca}^{2+}]_{\text{c}}$  and  $[\text{Ca}^{2+}]_{\text{mt}}$  [80]. However, the increase in  $\text{IP}_3\text{R}$  expression does not enhance mitochondrial  $\text{Ca}^{2+}$  uptake because of the reduction of the complex quantity of  $\text{IP}_3\text{R-Grp75-VDAC1}$  [80]. Thus, the reduced ER-mitochondria  $\text{Ca}^{2+}$  transport is a suspected contributor to the reduced  $[\text{Ca}^{2+}]_{\text{mt}}$  in DMD [13].

Disrupted SR-mitochondria  $\text{Ca}^{2+}$  transport may also potentially play a role in muscle dysfunction in ageing through mitochondrial  $\text{Ca}^{2+}$  homeostasis impairment. Further, tetanic stimulation on the flexor digitorum brevis of mice was reportedly the cause of reduced mitochondrial  $\text{Ca}^{2+}$  uptake, along with a decrease in the association between mitochondria and CRUs in aged mice [14]. In aged mice with knockdown of mitofusin 2, repetitive high-frequency tetanic stimulation reduced an impaired association between CRUs and mitochondria. This was caused by a shift of mitochondria away from the triadic positions, which may explain the declined muscle performance associated with ageing [14]. Gill et al. (2019) reported that the SR-mitochondria  $\text{Ca}^{2+}$  transport proteins  $\text{IP}_3\text{R1}$ , Grp75,

and VDAC were downregulated and that the  $IP_3$  gene expression reduced in the skeletal muscle of aged mice [81]. An ameliorated age-dependent skeletal muscle dysfunction was reported to be related to a reduced SR  $Ca^{2+}$  release and increased SR  $Ca^{2+}$  load [82]. Exercise-induced muscle function improvement is hypothesised to be attributed to the increase in  $[Ca^{2+}]_{mt}$  caused by the increased MCU expression [83], which is probably related to the improved/maintained association between CRUs and mitochondria [84]. Based on these findings, the increasing loss of  $Ca^{2+}$  homeostasis in the SR and mitochondria are said to cause the functional decline of skeletal muscle in ageing. The defective SR-mitochondria  $Ca^{2+}$  cross-talk may precede muscle function impairment in age-related dystrophy, but further studies on molecular mechanism and  $Ca^{2+}$  signalling are required to understand this explanation better.

### 5. Sarcoplasmic Reticulum-Mitochondria $Ca^{2+}$ Transport and Mitochondrial $Ca^{2+}$ Overload

It is commonly accepted that ER stress, which can be caused by ageing, genetic mutations, or environmental factors, can result in various diseases, including those mentioned above [85]. The increased ER  $Ca^{2+}$  release through  $Ca^{2+}$  channels is an essential cause of ER stress, and ER stress can be attenuated by the cone-specific gene deletion of  $IP_3R1$  [86]. The disturbance of mitochondrial  $Ca^{2+}$  homeostasis, mostly through mitochondrial  $Ca^{2+}$  overload, also occurs in the diseases mentioned above, and it is probably due to the increased ER-mitochondria  $Ca^{2+}$  transport. In the early phase of ER stress, mitochondria were found to migrate to the ER's periphery [18,87], while in the later phase, mitochondrial  $Ca^{2+}$  overload was shown to be caused by mitochondrial migration to the ER surface, resulting in mitochondria-dependent apoptosis [88]. In addition, according to a recent study on macromolecular complex  $IP_3R$ -Grp75-VDAC1,  $Ca^{2+}$  transport from the ER to the mitochondria is likely to contribute to podocyte apoptosis by facilitating mitochondrial  $Ca^{2+}$  overload [4]. As can be seen from the evidence discussed above, the  $Ca^{2+}$  transport from the ER to the mitochondria may contribute to the ER stress and mitochondrial  $Ca^{2+}$  overload at the same time, but this speculation needs further experimental evidence.

### 6. Conclusions

This review focused on the mitochondria-associated membrane's role, particularly the  $IP_3R$ -Grp75-VDAC1 pathway, in calcium ion transport from the endoplasmic/sarcoplasmic reticulum to mitochondria, in relation to normal and abnormal cellular functions. Current evidence suggests that the distance between the ER/SR and mitochondria, and the modulation of the  $IP_3R$ , Grp75, and VDAC1 activities, play a critical role in regulating mitochondrial  $Ca^{2+}$  homeostasis. A disruption in this pathway and subsequently  $Ca^{2+}$  homeostasis (such as mitochondrial  $Ca^{2+}$  overload or insufficient mitochondrial  $Ca^{2+}$ ) is believed to be a common causative factor in some health conditions, such as neurodegenerative diseases, obesity, insulin resistance, cancer, and ischemia/reperfusion damage, as well as in age-related muscle dystrophy and intensive exercise-induced reduction of skeletal muscle function. However, the exact cause-and-effect relationship and the potential physiological/pathological mechanisms under specific conditions require further investigation to shed light on potential therapeutic targets or interventions for such conditions.

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### Abbreviations

ER, endoplasmic reticulum; MAM, mitochondria-associated membrane; SR, sarcoplasmic reticulum, IP<sub>3</sub>R: inositol 1,4,5-trisphosphate receptor; Grp75, glucose regulated protein 75; VDAC1, voltage-dependent anion channel 1; [Ca<sup>2+</sup>]<sub>i</sub>, Ca<sup>2+</sup> concentration; TAC, tricarboxylic acid cycle; IMM, inner mitochondrial membrane; MCU, mitochondrial calcium uniporter; [Ca<sup>2+</sup>]<sub>mt</sub>, mitochondrial Ca<sup>2+</sup> concentration; [Ca<sup>2+</sup>]<sub>c</sub>, cytosolic Ca<sup>2+</sup> concentration; DHPR, dihydropyridine receptor; RyR, ryanodine receptor; Tubule, transversal tubule; CRU, calcium release unit.

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