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Bioenergetic roles of mitochondrial fusion

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ABSTRACT

Mitochondria are bioenergetic hotspots, producing the bulk of ATP by the oxidative phosphorylation process. Mitochondria are also structurally dynamic and undergo coordinated fusion and fission to maintain their function. Recent studies of the mitochondrial fusion machinery have provided new evidence in detailing their role in mitochondrial metabolism. Remarkably, mitofusin 2, in addition to its role in fusion, is important for maintaining coenzyme Q levels and may be an integral player in the mevalonate synthesis pathway. Here, we review the bioenergetic roles of mitochondrial dynamics and emphasize the importance of the *in vitro* growth conditions when evaluating mitochondrial respiration. This article is part of a Special Issue entitled 'EBEC 2016: 19th European Bioenergetics Conference, Riva del Garda, Italy, July 2–6, 2016,' edited by Prof. Paolo Bernardi.

1. Introduction

Mitochondria are double membrane-bound organelles observed in spermatocytes more than a century ago [1]. The inner mitochondrial membrane (IMM) delimits the matrix and intermembrane space (IMS), whereas the outer mitochondrial membrane (OMM) separates the IMS from the cytosol. The cristae invaginations of the inner mitochondrial membrane house the oxidative phosphorylation system (OXPHOS) [2–4]. This system is composed of two functional entities, the respiratory chain (RC) and the phosphorylation system, which, in turn, consists of the ATP synthase and membrane carriers such as the ATP/ADP carrier and the phosphate carrier. The RC is historically defined as consisting of the mobile electron carriers coenzyme Q and cytochrome *c* and four respiratory complexes, denoted complex I–IV, which perform substrate oxidation to drive proton extrusion from the mitochondrial matrix to the intermembrane space. The proton electrochemical potential difference across the inner membrane (ΔP) is used by the ATP synthase to drive ATP synthesis hence coupling proton transport to ATP production [5]. Interestingly, complex I, III, and IV of the RC and the ATP synthase are under dual genetic control. The mitochondrial genome (mtDNA) only encodes 13 proteins that are all components of the OXPHOS system and nuclear genes encode the remaining mitochondrial respiratory proteins. The nuclear genome also encodes the mitochondrial proteome required for the maintenance and expression of mtDNA [6], protein synthesis [7], import and degradation [8,9], iron-sulfur cluster synthesis [10], citric acid and urea cycles, fatty acid oxidation, and additional metabolic pathways.

Mitochondria constantly fuse and divide in cells and thus form a dynamic cellular network and specialized transport machineries ensure their mobility and proper subcellular localizations. Due to their key energetic role, mitochondria are often positioned at intracellular sites of high-energy demand. In muscle, mitochondria are embedded between myofibrils that consume ATP during contraction. Likewise, in neurons, mitochondria are transported and accumulate in synapses to provide the energy required to maintain and regulate synaptic transmission. Thus, proper control of mitochondrial subcellular localization and network morphology is an absolute requisite to maintain energy homeostasis and cell functions. This article will review recent findings on the energetic relevance of mitochondrial dynamics, with an emphasis on mitochondria fusion.

2. Inter-relationship between mitochondrial OXPHOS bioenergetics and mitochondrial dynamics

2.1. Mitochondrial fusion and fission machinery

The term mitochondrial dynamics describes the continuous changes in the position, size, and shape of mitochondria within cells. In eukaryotic cells, mitochondria are arranged in a wide variety of shapes, ranging from long interconnected tubules to individual spheres [11–13]. The mitochondrial network morphology is in fact the result of balanced fusion and fission controlled by protein members of the dynamin-related

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protein (DRP) family. Recent microscopic, structural, and biochemical analyses led to the characterization of the core machinery of mitochondrial fusion and fission. The discovery of fuzzy onion (Fzo) in *Drosophila melanogaster* as an essential protein mediating mitochondrial fusion during spermatogenesis [14] led to rapid advances in our knowledge of the components involved in mitochondrial dynamics. The characterization of this evolutionary conserved GTPase OMM protein in budding yeast (Fzo1p) showed that it has a similar function in mitochondrial fusion [15,16] and yeast genetic screens led to the identification of additional components of the machinery involved in mitochondrial fusion and fission [17]. The core of the yeast mitochondrial fusion machinery is composed of three proteins. Fzo1p and mitochondrial genome maintenance 1 (Mgm1p) [18–20] control fusion of the outer and inner mitochondrial membrane, respectively, whereas UGO1 (UGO is Japanese for fusion) is proposed to be a two-membrane spanning protein mediating the interaction between Fzo1p and Mgm1p [21–23]. Drosophila melanogaster possesses, in addition to FZO specifically expressed in spermatocytes, another protein regulating outer mitochondrial membrane fusion named mitochondrial assembly regulatory factor (MARF), which is ubiquitously expressed. Also, the mammalian orthologs known as mitofusin 1 and mitofusin 2 (MFN1 and MFN2) [24–28] are ubiquitously expressed. The Mfn1 and Mfn2 genes are 81% identical to each other and 46% identical to Marf [13,24,26,29]. Interestingly, MARF is functionally similar to mammalian MFNs, by exhibiting both mitochondria- and ER-shaping functions [28].

In mammals, OPA1 is the main actor controlling IMM fusion [30,31] and has been shown to play a role in mitochondrial cristae structure maintenance as well as respiratory chain supercomplex assembly [32–35]. Mgm1p/OPA1 are present as multiple proteins forms generated by alternative splicing and proteolytic cleavage [18–20,36]. Alternative splicing of OPA1 generates long OPA1 proteins (L-OPA1) that can be proteolytically cleaved to short OPA1 proteins (S-OPA1). The regulated cleavage of OPA1 isoforms by the metallopeptidase OMA1 (exerts similar activity as the *m*-AAA protease) [37,38] or YME1L (mammalian ortholog of the yeast *Yme1*) [39–41] results in the loss of the transmembrane domain of the protein and modulates the activity of OPA1. In mammals, both alternative splicing of transcripts from the OPA1 gene and proteolytic processing of the OPA1 protein by OMA1 and YME1L generate the multiple protein OPA1 isoforms, whereas proteolytic processing is the only mechanism in budding yeast.

Mitochondrial morphology results from a careful orchestration between mitochondrial fusion and fission. It is therefore not surprising that yeast genetic screens looking for suppressors of fusion mutants originally identified most of the key regulators of mitochondrial fission. The dynamin-related GTPase Dnm1p is the key component of the fission machinery. Dnm1p is a cytosolic protein that can be recruited into punctuate structures on the OMM [42,43]. According to the most recent model, Dnm1p recruitment to the OMM is mediated by the mitochondrial fission protein 1 (Fis1p) [44] and causes membrane constriction through its interaction with the adaptor protein mitochondrial division 1 (Mdv1p) [45–50] and CCR4-associated factor 4 (CAF4) [51,52]. After its recruitment, DNM1 forms extended spirals [53], which undergo conformational change upon GTP hydrolysis leading to the constriction and division of mitochondria [54]. Similar studies in mammalian cells led to the identification of dynamin-related protein 1 (DRP1), also referred as DLP1 (dynamin-like protein 1) in humans, and FIS1 as components of the mammalian fission machinery [55–57]. Beyond Drp/Fis1, the fission machineries of yeast and mammals differ in their adaptors (Mdv/Caf for yeast and Mff/Mid for mammals [58,59]). Mitochondrial fission is highly regulated and controlled. For instance, DRP1 undergoes several posttranslational modifications such as phosphorylation [60–63], S-nitrosylation [64,65], ubiquitination [66–68], and sumoylation [69–71]. These modifications control the activity and subcellular localization of DRP1 [13]. Furthermore, unlike mitochondrial fusion, the core of the mitochondrial fission machinery plays a similar role in peroxisomes [72,73].

2.2. Metabolic role of mitochondrial dynamics

The mitochondrial network is highly dynamic and is usually remodeled under stress or modification of cell fate and metabolism to adapt the energetic needs of the cell [74]. For instance, the mitochondrial network morphology changes depending on growth on respiratory [75,76] or glycolytic carbon sources [77,78]. Furthermore, mitochondrial network interconnections are greatly enhanced under starvation. This increase in connectivity of the mitochondrial network has been proposed to prevent mitochondrial degradation by autophagy [79,80]. In contrast, mitochondrial network fragmentation under apoptotic conditions promotes mitochondrial fragmentation [81–83] followed by release of pro-apoptotic factors from mitochondria mediated by BCL2-Antagonist/Killer (BAK) and BCL2-Associated X Protein (BAX) [84].

It has become increasingly clear that mitochondrial bioenergetics and mitochondrial fusion are closely related and modulate each other. The IMM fusion through OPA1 not only depends on GTP but also requires a membrane potential ($\Delta\Psi$) across the IMM [85–88]. Dissipation of the mitochondrial membrane potential by an uncoupler inhibit IMM fusion through L-OPA1 cleavage by metalloproteases [20,37,38,40,89,90]. However, further studies are needed to understand the mechanism whereby the membrane potential modulates OPA1 processing in order to determine if proteolysis of OPA1 depends directly on the membrane potential or indirectly via alterations in the dNTP/dNDP pools [91]. The interdependency between mitochondrial bioenergetics and mitochondrial fusion is further supported by the observation that mitochondrial bioenergetics defects impair mitochondrial dynamics [92] through proteolytic processing of OPA1 [93]. Moreover, OXPHOS defects observed in mtDNA depleted cells (ρ^0 cells) affects IMM fusion [94]. In contrast, both OMM fusion and fission seem grossly insensitive to OXPHOS defects and membrane potential impairment [78,94]. It has become increasingly clear that OPA1-mediated IMM fusion and bioenergetics are closely interrelated and modulate each other. In the following section, we will review how mitochondria IMM and OMM fusion modulate and impact OXPHOS.

2.3. The role mitochondrial fusion in mitochondrial genome maintenance

Mounting evidence supports the critical role played by mitochondrial dynamics in controlling mitochondrial OXPHOS activity through the maintenance of the mitochondrial genome. The yeast OPA1 orthologs *mgm1* [95,96] and *msp1* [97] were described in *Saccharomyces cerevisae* and *Schizosaccharomyces pombe*, respectively, as genes required for the maintenance of the mitochondrial genome. The complete loss of IMM or OMM fusion is associated with a loss of the mitochondrial genome in yeast and with a depletion of mtDNA in mammals [16,95,98–101]. Moreover, the mtDNA maintenance defect observed in mitochondrial fusion-deficient skeletal muscle has been reported to be associated with accumulation of mtDNA point mutations and deletions [101]. However, the loss of mitochondrial fission has no deleterious effect on mtDNA levels [43,102,103]. This is surprising because emerging data indicate that the majority of mitochondrial fission sites are located in close proximity to endoplasmic reticulum (ER)-mitochondria contact sites [104] and mtDNA molecules [105,106]. Yet, the loss of mtDNA as well as the aberrant mitochondrial network morphology observed in Fzo1p deficient yeast cells could be efficiently prevented by the additional loss of Dnm1 [43]. Altogether these observations show that mitochondrial genome maintenance requires a tight control over the balance between mitochondrial fusion and fission. Unfortunately, the molecular mechanisms causing mitochondrial genome depletion in response to impaired fusion remain mostly unknown despite more than a decade of intense research.

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2.4. Loss of mitofusin 2 in mammals causes mitochondrial dysfunction without affecting mtDNA

As mentioned earlier, mammals have two Fzo homologues called MFN1 and MFN2 that control OMM fusion. MFN1 and MFN2 are functionally redundant in their role in mitochondrial fusion and can physically dimerize through homotypic or heterotypic interactions. Thus, whereas FZO1 is a unique mediator of OMM fusion in yeast, loss of MFN1 or MFN2 only partially impairs OMM fusion process and is not causing depletion of mtDNA [13]. Ubiquitous knockout of the *Mfn1* or *Mfn2* genes impairs placental function [13,107] and results in embryo lethality in mid-gestation [13]. Remarkably, when the placental dysfunction is prevented by using a conditional knockout allele in conjunction with cre-recombinase expression only in the embryo, *Mfn1* or *Mfn2* knockout mice are viable [107]. Moreover, mice ubiquitously lacking MFN1 are apparently healthy, whereas loss of MFN2 causes mouse lethality in the early postnatal period and triggers cerebellar atrophy causing severe defects in movement and balance [107]. Besides the placental defects and the partial impairment of mitochondrial fusion, loss of MFN1 has no gross metabolic impact on embryos and mouse tissues. In contrast, partial impairment of mitochondrial fusion by the loss of MFN2 in different mammalian tissues severely impacts metabolism and physiological function. Thus, apart from its well-established role in mitochondrial fusion, a growing body of evidence suggests that MFN2 has additional functions potentially required to sustain cellular energy demand. Many reports implicate MFN2 in tethering of mitochondria with the endoplasmic reticulum [108], lipid droplets [109], melanosomes [110], and with the Miro/kinesin system [111,112]. Although a scientific consensus has been reached regarding the involvement of MFN2 in ER-mitochondria communication [108,113–117], its role as a pro-tethering agent was recently reconsidered [118,119]. The functional divergence between MFN1 and MFN2 are further supported by *in vivo* studies in mice, showing that MFN2 is required for normal glucose homeostasis [46–49,117], steroidogenesis [109,120], cerebellar development, and function [107] and for maintaining axonal projections of dopaminergic neurons [121,122]. The additional roles of MFN2 have been studied in several organisms and in various tissues, but a common mechanism that could explain the pleiotropic and tissue-specific metabolic defects attributed to the loss of MFN2 was missing until recently.

Interestingly, the bioenergetic impact caused by the loss of MFN2 are pleiotropic and tissue specific. In Purkinje or dopaminergic neurons and skeletal muscle, loss of MFN2 is associated with a loss of complex IV activity [107,117,121]. In contrast, loss of MFN2 in liver only mildly impairs complex I–III and II–III activities [117]. Loss of MFN1 or MFN2 in heart is associated with a mild OXPHOS dysfunction that cannot be explained by reduced levels of the OXPHOS protein complexes or loss of their enzymatic activities [123,124]. Loss of MFN2 in heart has been reported to protect mitochondria from Ca^{2+}-induced permeability transition pore (PTP) opening [123]. Altogether, numerous studies show that mitochondrial bioenergetics defects observed in absence of MFN2 cannot be attributed to marked loss of OXPHOS subunits or reduced mtDNA levels [117,125,126].

3. Material and methods

3.1. Mouse embryonic fibroblast (MEFs)

Immortalized *Mitofusin 1*, *Mitofusin 2*, *Mitofusin 1-2*, and *Optic atrophy 1* homozygous knockout MEFs were a gift from Thomas Langer at the University of Cologne, Germany and David Chan at California Institute of Technology, Pasadena, California. MEFs were maintained in Dulbecco's modified eagle medium (DMEM) with GlutaMax™ (Thermo Fischer Scientific cat.no. 31966) containing 25 mM glucose, 1 mM sodium pyruvate, 10% fetal bovine serum (FBS, Thermo Fischer Scientific, cat.no. 10270–106), 50 μg/ml uridine (Sigma–Aldrich U3003), 1% penicillin and streptomycin (Pen/Strep, Thermo Fischer Scientific, cat.no. 15070–063), and 1% non-essential amino acids (NEAA, Thermo Fischer Scientific, cat.no. 11140-50). In certain experiments, 1% dialyzed FBS (v/v) was used to supplement the media (Thermo Fischer Scientific, cat.no. 26400-036).

3.2. Growth curves

To assess the growth rate of cells, MEFs were plated at a density of 9000 cells/ml in a 6-well dish in 3 ml of media containing 25 mM glucose and supplemented with 1 mM sodium pyruvate, 50 μg/ml uridine, 1% Pen/Strep, and 1% NEAA. Concentration of FBS (v/v) was set to either 10% or 1%. Cells were collected each day after seeding and total number of viable cells was counted with an automatic Vi-Cell XR analyzer (Beckman Coulter).

3.3. Mitochondrial respiration

The flux of mitochondrial oxygen consumption was measured using an Oxygraph-2K (Oroboros instruments) at 37 °C using 1 million cells diluted in 2 ml of mitochondria respiration buffer (120 mM sucrose, 50 mM KCl, 20 mM Tris-HCl, 4 mM KH_2PO_4, 2 mM $MgCl_2$, and 1 mM EGTA pH7.2). Cells were permeabilized with 0.02 mg/ml digitonin. The oxygen consumption rate in state 3 was assessed using 10 mM succinate, and 5 mM glycerol-3-phosphate in presence of 2.5 mM ADP and the nonphosphorylating state using 0.5 μg/ml oligomycin. Mitochondrial respiration was uncoupled by successive addition of up to 0.4 μM CCCP to reach maximal oxygen consumption.

3.4. Measurement of coenzyme Q content

MEFs were grown for 1 week in complete DMEM media containing either 10% FBS or 1% dialyzed FBS. Coenzyme Q levels in MEFs were determined as detailed previously [126]. The following MRM transitions were used for Q9 m/z 795.58–196.95 (quantifier) collision 30V, 795.58–95.02 (qualifier) collision 50V, 795.58–106.46 (qualifier) collision 64V, cone was in all cases 31V for Q10 m/z 863.67–196.94 (quantifier) collision energy 36V, m/z 863.67–95.02 (qualifier) collision 54V, m/z 863.67–80.97 (qualifier) collision 66V, cone was in all cases 35V.

4. Results

4.1. Mitofusin 2 is required to maintain the mevalonate pathway and coenzyme Q synthesis

We recently reported that conditional *Mfn2* heart knockout mice are respiratory chain deficient despite having normal mtDNA levels and normal enzyme activities of individual respiratory chain complexes, consistent with previous studies of fibroblasts from Charcot-Marie-Tooth type 2A patients carrying *Mfn2* mutations [125,127]. We further showed that the impaired respiratory chain function in the absence of MFN2 is explained by a deficiency of coenzyme Q. A continuous cellular supply of coenzyme Q requires *de novo* synthesis from the mevalonate pathway, a multistep process that has been reported to involve many subcellular compartments [128]. We found that loss of MFN1 and MFN2 is associated with down-regulation of enzymes of the mevalonate biosynthesis pathway and reduced levels of specific metabolites. It is known that the condensation of the long isoprenoid side chain to the para-hydroxybenzoic acid can occur in mitochondria [129,130]. However, the exact subcellular localization of components involved in mevalonate and coenzyme Q biosynthetic pathways remain undetermined and the mechanisms that govern the intracellular transport of metabolites in these pathways are also undefined [128], although some enzymes of the mevalonate biosynthesis pathway have been found in different organelles such as mitochondria, ER, and peroxisomes [131–133]. Interestingly, MFN2 was previously reported to play an important role in high-level steroid production in trophoblast and

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Leydig cells [120,134]. Our results suggest that the previously observed steroidogenesis defects of trophoblast and Leydig cells lacking MFN2 is likely to originate from a deficiency in the mevalonate synthesis pathway.

In vitro, loss of MFN2 in mouse and human fibroblasts grown in glucose and supplemented with a high concentration of fetal bovine serum show no gross bioenergetics defects [13,119,135]. In line with these previous reports, our own experiments cultivating *Mfn1* and *Mfn2* knockout MEFs with medium containing glucose and high serum over weeks show that these cells do not exhibit any bioenergetics deficiency or loss of coenzyme Q (Fig. 1 A, C, E). However, it is important to take into account that coenzyme Q is a lipid soluble antioxidant present in fetal bovine serum (FBS), which is dialyzed and non-dialyzed and widely used to supplement cell culture media. In this work, we investigated the impact of cell culture conditions on *Mfn1* and *Mfn2* knockout MEFs phenotype. In order to minimize exogenous supplementation of coenzyme Q, we cultivated *Mfn1* and *Mfn2* knockout MEFs in glucose medium containing low levels (1%) of dialyzed fetal bovine serum (Fig. 1 B, D, F). Under these specific conditions, the growth rate of MEFs lacking either of the MFNs is affected (Fig. 1 B). However, only *Mfn2* knockout MEFs displayed markedly reduced coenzyme Q levels and cellular respiratory chain deficiency (Fig. 1 D, F). These metabolic and bioenergetic defects could only be observed when cells were grown for 1 week in glucose medium supplemented with low serum. Thus, our assessment of classical cell culture conditions shows that the high serum condition is not suitable to reveal the bioenergetics defects associated with loss of MFN2. It is likely that low serum conditions stress *Mfn2* knockout MEFs and thereby causes respiratory chain and coenzyme Q deficiency,

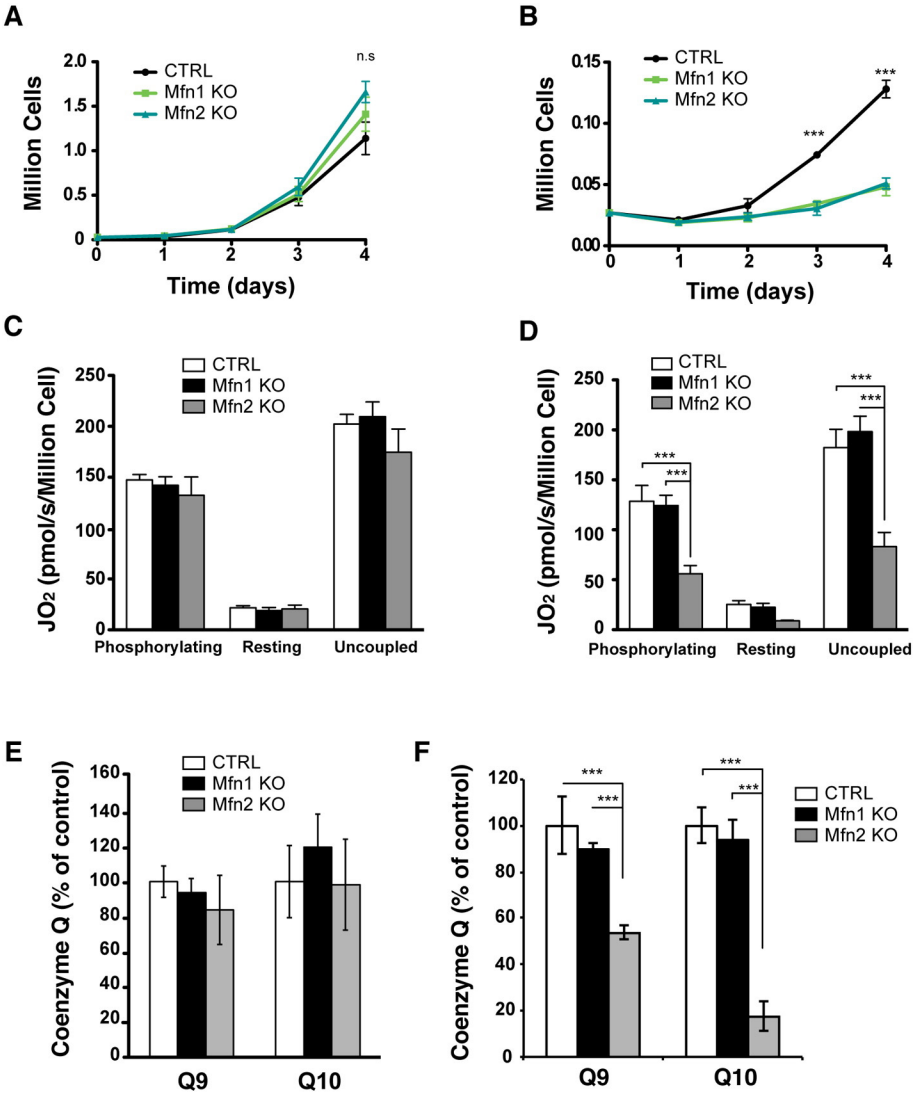

Fig. 1. Bioenergetic properties of *Mfn1* and *Mfn2* knockout MEFs under different cell culture conditions. (A) Growth curve was assessed in control (black line, n = 4 independent experiments), *Mfn1* KO (green line n = 4 independent experiments), *Mfn2* KO (turquoise line n = 4 independent experiments) MEFs grown in glucose medium supplemented with 10% FBS. No statistical significance (n.s). (B) Growth curve of control (black line, n = 5 independent experiments), *Mfn1* KO (green line, n = 5 independent experiments), *Mfn2* KO (turquoise line, n = 5 independent experiments) MEFs grown in glucose medium supplemented with 1% dialyzed FBS. (C) Assessment of cellular respiration in control (white bars, n = 4 independent experiments), *Mfn1* KO (black bars, n = 4 independent experiments), *Mfn2* KO (gray bars, n = 6 independent experiments) MEFs that were grown in glucose medium supplemented with 10% FBS. MEFs were permeabilized and analyzed in the presence of succinate and glycerol-3-phoshate. (D) Assessment of cellular respiration in control (white bars, n = 5 independent experiments), *Mfn1* KO (black bars, n = 5 independent experiments), *Mfn2* KO (gray bars, n = 6 independent experiments) MEFs that were grown for 1 week in glucose medium supplemented with 1% dialyzed FBS. MEFs were permeabilized and analyzed in the presence of succinate and glycerol-3-phoshate. (E) Quinone quantification performed on whole cell extracts isolated from control (white bar, n = 4 independent experiments), *Mfn1* KO (black bar, n = 4 independent experiments), *Mfn2* KO (gray bar, n = 4 independent experiments) MEFs grown in glucose medium supplemented with 10% FBS. (F) Quinone quantification performed on whole cell extracts isolated from control (white bar, n = 4 independent experiments), *Mfn1* KO (black bar, n = 4 independent experiments), *Mfn2* KO (gray bar, n = 4 independent experiments) MEFs grown for 1 week on glucose medium supplemented with 1% dialyzed FBS. For all experiments, the error bars indicate ±SEM and statistical analysis was performed by one-way ANOVA with Turkey multiple comparisons. $^{***}P < 0.001$.

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similar to the observation in mice lacking MFN2 in the heart [126]. This interesting observation demonstrates that bioenergetic defects associated with loss of mitochondrial fusion are not only related to mitochondrial genetic impairments, ER-mitochondria stress or cristae remodeling but can directly originate from perturbations in anabolic pathways.

5. Conclusion

The fact that mitochondrial bioenergetics status cannot be systematically linked to specific mitochondrial morphologies show that the mitochondrial network morphology is a poor marker of OXPHOS activity. However, beyond mitochondrial network morphology, mitochondrial bioenergetics and OPA1-mediated IMM fusion are reportedly linked. Furthermore, mitochondrial genome maintenance defects observed in yeast and mammalian cells presenting abolished IMM or OMM fusion cannot on its own account for the OXPHOS defects observed in *Mfn2* knockout models presenting only partial OMM fusion impairment. We recently reported the novel and unexpected finding that MFN2 has an essential role in regulating the mevalonate biosynthesis pathway, which, in turn, is required to maintain mitochondrial coenzyme Q levels for optimal function of the respiratory chain. Our work showed that the coenzyme Q deficiency and the respiratory chain deficiency could be partially rescued by coenzyme Q10 supplementation. This finding could have direct clinical importance because mutations in MFN2 are known to cause human disease. Indeed, a recently published case report indicates that coenzyme Q supplementation may have a positive effect in a patient with pathogenic *Mfn2* mutations [136]. Interestingly, the mevalonate pathway deficiency could account for the disparity of previously unrelated molecular and tissue-specific phenotypes associated with the loss of MFN2. *In vivo* studies of Mfn2 deficient models have shown that MFN2 is required to maintain mitochondrial function [117], steroidogenesis activity [120], autophagy [137], and coenzyme Q homeostasis [126]. Interestingly, both steroidogenesis and mitochondrial dysfunction caused by coenzyme Q deficiency could be the direct effect of mevalonate synthesis defects. Furthermore, impairment of the mevalonate pathway has been also associated with deregulation of autophagy [138], likely caused by impaired protein prenylation [139]. Our future research aims to decipher the exact molecular role of MFN2 in maintaining the mevalonate synthesis pathway. It is important to note that the role for coenzyme Q deficiency in explaining bioenergetics defects in cells lacking MFN2 has been missed for a long time due to the fact that FCS contains coenzyme Q and thereby cause complementation, as we demonstrate here. These findings make it important to reassess the role for coenzyme Q deficiency as an explanation for the many phenotypes associated with deficiency of MFN2.

Transparency document

The transparency document associated with this article can be found, in online version.

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