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MTCH2 in regulation of mitochondrial dynamics and metabolism: new insights and perspectives

Lishu Guo[1,2,*]
[1]Tongji University Cancer Center, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200072, China
[2]Department of Anesthesiology, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY 10032, USA
*Correspondence to: E-mail: guolishu@tongji.edu.cn; guolsh15@gmail.com

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ABSTRACT

Mitochondrial dynamics and metabolic plasticity bestow the adaptive flexibility to fit cellular stress and metabolic demands. Mitochondrial carrier homolog 2 (MTCH2) MTCH2 is initially recognized for its role in mediating apoptosis through the recruitment of tBID to mitochondria, triggering the outer membrane permeabilization. Recent studies reveal that MTCH2 is a regulator of mitochondrial dynamics, metabolism, protein insertion and the permeability transition pore (PTP). MTCH2's multi-faceted roles in mitochondrial homeostasis, dynamics, biogenesis, metabolism and permeability transition provide a mechanistic explanation for its association with the wide range of phenotypes and disease states.

Key words: mitochondria; MTCH2; mitochondrial dynamics; mitochondrial fusion; mitochondrial metabolism; mitochondrial permeability transition

List of abbreviations:

MTCH2	Mitochondrial carrier homolog 2
MFN1	mitofusin 1
MFN2	mitofusin 2
OPA1	optic atrophy 1
OMM	the outer mitochondrial membrane
tBID	truncated BID
MOMP	mitochondrial outer membrane permeabilization
PTP	the mitochondrial permeability transition pore
CyPD	Cyclophilin D
CsA	cyclosporin A
OXPHOS	oxidative phosphorylation
mtDNA	mitochondrial DNA
LPA	lipid lysophosphatidic acid
ER	endoplasmic reticulum
ROS	reactive oxygen species
AML	acute myelocytic leukemia
TCA	mitochondrial tricarboxylic acid cycle
PDH	pyruvate dehydrogenase
NSCLC	non-small cell lung cancer
CRPC	castration-resistant prostate cancer
PDAC	pancreatic ductal adenocarcinoma

INTRODUCTION

Mitochondria are highly dynamic, energy-transforming, biosynthetic, signaling organelles that remodel and adapt to metabolic changes or cellular stress [1,2]. Mitochondria are the primary sites of cellular respiration, converting chemical energy stored in nutrients to ATP through oxidative respiration [3]. Mitochondria dynamically undergo fission and fusion, which is crucial to maintain the healthy mitochondrial population in response to energy demands and adapt to metabolic changes [4–6]. This dynamic behavior ensures efficient ATP production and mitochondrial quality control. Mitochondrial fusion allows the spreading of metabolites, enzymes, and mitochondrial gene products throughout the entire mitochondrial compartment to optimize mitochondrial function [4,7]. Mitochondrial fission is essential for cell growth and division, providing sufficient mitochondria for ATP production, eliminating damaged mitochondria [5,8]. Cellular and organismal health relies on a delicate balance between fission and fusion, which are mediated by the core mitochondrial dynamics proteins including dynamin-related protein 1 (DRP1) that controls division, and the mitofusins 1 and 2 (MFN1, MFN2) and optic atrophy 1 (OPA1) that drive membrane fusion [9].

Mitochondrial carrier homologue 2 (MTCH2), also known as MIMP or SLC25A50, is a protein within the SLC25A family, located at the outer mitochondrial membrane (OMM) [10]. MTCH2 is a protein of 303 amino acids in humans with a molecular weight of approximately 33 kDa, which is located on chromosome 11 [11]. MTCH2 contains a single mitochondrial carrier domain and three transmembrane domains with six transmembrane α-helices. Both the N and C termini of MTCH2 are oriented towards the inner membrane space, while three long hydrophilic segments, connecting the transmembrane regions, face the matrix [12–14]. MTCH2 is initially recognized for its role in mediating apoptosis through the recruitment and integration of truncated BID (tBID), triggering mitochondrial outer membrane permeabilization (MOMP) and the release of pro-apoptotic factors [15–17]. Subsequent studies reveal that MTCH2 play a role in regulating mitochondrial and whole-body metabolism, as well as metabolic disorders [18–20]. MTCH2 has recently been shown to act as an insertase, helping to embed cytoplasmic α-helical proteins into the OMM [13], and as a scramblase, facilitating phospholipid movement between the inner and outer mitochondrial membranes [14,21].

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The recent studies show that MTCH2 is involved in the regulation of mitochondrial dynamics [22,23], and more recently, it's shown that MTCH2 regulates the opening of the mitochondrial permeability transition pore (PTP) and mitochondrial permeability transition [24]. This review will summarize the regulation of mitochondrial dynamics and metabolism by MTCH2, and propose the potential involvement of its regulatory role in PTP.

THE INTERPLAY BETWEEN MITOCHONDRIAL DYNAMICS AND MITOCHONDRIAL METABOLISM

Mitochondrial plasticity bestows the adaptive flexibility constant remodeling of the mitochondrial network to fit cellular stress and metabolic demands [4–6]. Mitochondrial dynamics, the constant process of mitochondrial fusion and fission, shape the morphology of mitochondria, resulting in a spectrum of elongated and fragmented forms within a cell [4–6]. These events are crucial for maintaining a healthy mitochondrial population and quality in response to ATP demands and metabolic stress [3]. Mitochondrial fission, the process of dividing mitochondria, can produce damaged daughter mitochondria that are then targeted for removal by mitophagy. Thus, mitochondrial fission ensures that potentially harmful components are removed, maintaining a healthy mitochondrial population [25,26]. On the other hand, mitochondrial fusion can dilute impaired components within the mitochondrial network, potentially preventing their removal [25,26]. This interplay is crucial for maintaining mitochondrial health and adapting to cellular stress [25–28].

The interplay between mitochondrial dynamics and metabolism is bidirectional: the morphology and structure of mitochondria influence their metabolic output, while the metabolic state of the cell regulates mitochondrial shape and behavior. Mitochondrial dynamics help maintain the pool of mitochondria within a cell and optimal metabolism by allowing efficient transport and distribution of mitochondrial content [7]. Mitochondrial fusion facilitates the exchange and connection of mitochondrial content, ultimately benefiting ATP production, mitigating oxidative stress, and maintaining membrane potential [29]. Mitochondrial fusion is important for optimizing oxidative phosphorylation (OXPHOS) through efficient respiratory capacity, maintenance of mitochondrial DNA (mtDNA) and cristae structure, which are essential for the proper functioning of respiratory chain [28,29]. Fission is associated with reduced OXPHOS and a shift toward glycolysis, because it allows for the segregation of damaged mitochondria and supports rapid redistribution of mitochondria during cell division or stress [5]. Mitochondrial dynamics can be regulated by the metabolic state of the cell or order to ensure efficient energy generation and removal of damaged mitochondria. High energy demand or caloric restriction triggers mitochondrial fusion, promoting ATP production and cell survival; While nutrient excess, oxidative stress, or mitochondrial damage activates fission for quality control [30,31].

MTCH2 AND MITOCHONDRIAL DYNAMICS

MTCH2 has been implicated in the regulation of mitochondrial dynamics, further expanding its functional roles in the cell [22,23]. MTCH2 is involved in stimulating mitochondrial fusion, which can be triggered by various factors including starvation, and is important for maintaining mitochondrial function and cellular survival [22,23]. MTCH2 is shown to be a direct regulator of mitochondrial fusion/elongation in mouse embryonic fibroblasts and embryonic stem cells [22]. It has been proposed that MTCH2 regulates mitochondrial fusion by modulating the pro-mitochondrial fusion lipid lysophosphatidic acid (LPA), a key lipid involved in mitochondrial fusion [23]. MTCH2 is involved in producing lipids, particularly LPA, and transporting LPA from the endoplasmic reticulum (ER) to the mitochondria, a process vital for mitochondrial fusion. Disruption of MTCH2 function leads to fragmented mitochondria and impaired mitochondrial fusion, highlighting the importance of this process [3,23]. MTCH2's function in enforcing fusion is dependent on MFN1, and mitochondrial fragmentation caused by loss of MTCH2 can be specifically counterbalanced by overexpression of MFN2 but not MFN1 [32]. While MTCH2 primarily influences fusion, its role in fission is less clear. However, some studies suggest that MTCH2 may also be involved in regulating fission, potentially contributing to the balance between fusion and fission [11,22,23,33,34]. By regulating fusion and fission, MTCH2 indirectly influences the overall shape and morphology of mitochondria. Changes in mitochondrial shape can have significant consequences for cellular function, including ATP production and cell death [3,8,9,11,22,23,33,34].

MTCH2 AND MITOCHONDRIAL METABOLISM

MTCH2 serves as a regulator of mitochondrial OXPHOS, specifically, loss of MTCH2 results in enhanced OXPHOS activity, leading to increased ATP production and elevated levels of reactive oxygen species (ROS). This suggests that MTCH2 acts as a repressor of OXPHOS and mitochondrial metabolism [18,19,35]. Loss of MTCH2 in hematopoietic stem cells disrupts the normal metabolic balance and triggers a metabolic shift, which promotes active cell cycling, increases oxidative stress and potentially leads to stem cell exhaustion [19]. MTCH2 deletion leads to a complex metabolic shift characterized by a high demand for ATP, an oxidized cellular environment, and increased utilization of various energy substrates like lipids, amino acids, and carbohydrates, alongside a decrease in certain metabolites [3]. The body tries to compensate for the energy shortfall caused by MTCH2 deficiency by ramping up metabolism across multiple pathways, often leading to an "oxidized" state due to increased OXPHOS. This increased oxidative activity creates a catabolic and oxidative environment that hinders the anabolic processes required for lipid accumulation and adipocyte differentiation [3]. In acute myelocytic leukemia (AML) cells, deletion of MTCH2 disrupts the normal flow of glucose into the mitochondrial tricarboxylic acid (TCA) cycle, forcing the cells to rely more heavily on glutamine for oxaloacetate production. This shift also leads to reduced mitochondrial pyruvate levels and increased nuclear pyruvate and pyruvate dehydrogenase (PDH) levels [16,36]. Therefore, MTCH2 plays a crucial role in regulating mitochondrial metabolism and cellular energy flow.

MTCH2 AND MITOCHONDRIAL PERMEABILITY TRANSITION

MTCH2 is a crucial facilitator of tBID recruitment to the mitochondria, which is essential for apoptosis. MTCH2 binds to tBID at the mitochondrial outer membrane (OMM), promoting tBID translocation to mitochondria and ultimately inducing MOMP to accelerate apoptosis [16,17,23,37,38]. It has been well established that Bax/Bak oligomers are required for the occurrence of MOMP [39]. MTCH2's role extends to promoting the interaction between tBID and Bax, and the tBID-Bax interaction triggers MOMP, a hallmark of apoptosis [17,37,38,40,41].

Mitochondrial permeability transition is regulated by an inner membrane channel so-called the PTP, a Ca^{2+}-dependent megachannel that plays an important role in mitochondrial physiology and cell fate [42,43]. Mitochondrial matrix Ca^{2+} overload and oxidative stress may trigger opening of the PTP, resulting in the rupture of OMM, eventually apoptotic and necrotic cell death [44]. Numerous genetic manipulation and biochemical studies have established the hypothesis that F-ATP synthase is involved in the regulation and formation of the PTP [42,45–58]. The PTP-induced mitochondrial swelling, leading to the rupture of OMM, was initially understood as a purely mechanical process [42,59]. Our recent study has demonstrated that the interplay between MTCH2 and subunit j of F-ATP synthase coordinates MOMP and PTP to mediate the occurrence of mitochondrial permeability transition [24]. Cyclophilin D (CyPD), the unique mammalian mitochondrial matrix cyclophilin, is a most well-characterized regulator of PTP [60]. A large fraction of CyPD can be enriched at OMM and interact with MTCH2, which thus stimulates the association of MTCH2 with subunit j of F-ATP synthase, allowing the cooperation between MOMP and the PTP to mediate mitochondrial permeability transition [24].

THERAPEUTIC POTENTIAL OF TARGETING MTCH2

MTCH2 plays a pivotal role in regulating mitochondrial function, apoptosis, and metabolism, and its involvement in various diseases has garnered significant attention [11,12,61,62] (Table 1). Recent research highlights MTCH2's role in metabolic diseases, neurodegenerative diseases, cancers, and embryonic development, often through its influence on mitochondrial apoptosis, metabolic shifts, and mitochondrial dynamics. This makes it a promising therapeutic target for various conditions [11,12,61,62].

MTCH2 is crucial in metabolic diseases by regulating mitochondrial apoptosis, metabolic shifts between glycolysis and OXPHOS, and mitochondrial dynamics [12]. MTCH2's regulation of mitochondrial function and apoptosis is implicated in neurodegenerative diseases, suggesting that its dysfunction can contribute to neuronal damage [12]. MTCH2-deficient hippocampal neurons display a deficit in mitochondria motility and calcium handling and impaired hippocampal-dependent cognitive functions [63].

MTCH2 is overexpressed in several cancers, including non-small cell lung cancer (NSCLC), castration-resistant prostate cancer (CRPC), ovarian cancer, and gliomas [61,64–67]. In NSCLC, elevated MTCH2 levels promote tumor growth by maintaining mitochondrial hyper-function, suggesting that targeting MTCH2 could be a novel therapeutic strategy [64]. MTCH2 generally acts to inhibit ferroptosis, and overexpression of MTCH2 leads to reduced ferroptosis and increased cell survival. Conversely, silencing or knockdown of MTCH2 increases the sensitivity of cells to ferroptosis-inducing agents and induces ferroptosis, as evidenced by increased lipid peroxidation and ROS accumulation [67–69]. MTCH2 plays a protective role against ferroptosis by regulating mitochondrial permeability transition, which allows the release of mitochondrial ROS into the cytosol and prevents ROS accumulation in the mitochondrial matrix [24]. In CRPC, the MTCH2-silenced xenografts exhibit increased apoptosis, elevated lipid peroxidation, and decreased ATP levels [61,70,71]. Knockdown of MTCH2 in human pancreatic ductal adenocarcinoma (PDAC) MIA PaCa-2 cells facilitates RSL3-induced ferroptotic cell death, which can be inhibited by MitoTEMPO [24].

The PTP acts as a channel with distinct roles depending on its opening duration. Transient PTP openings relieve mitochondrial Ca^{2+} overload or oxidative stress without collapsing membrane potential, contributing to intracellular physiological Ca^{2+} and ROS homeostasis. Conversely, persistent PTP openings may induce mitochondrial swelling followed by release of pro-apoptotic proteins from the intermembrane space, mitochondrial depolarization, loss of ATP production, and ultimately cell death [42–44,72,73]. Therefore, dysregulation of the PTP plays a significant role in various pathological conditions, making it a key area of focus for research and potential therapeutic development. Transient PTP openings can prime mitochondrial quality control and activate mitochondrial protection mechanisms *via* mild ROS signaling, potentially slowing aging and protecting against neurodegenerative stress, while persistent pore openings trigger neuronal death and exacerbate neurodegenerative diseases [74]. Transient PTP openings are required for ischemic preconditioning, allowing heart cells to survive subsequent ischemia-reperfusion by initiating protective signaling cascades, while the persistent PTP openings cause ischemia-reperfusion injury, which can be mitigated by PTP inhibitor cyclosporin A (CsA) [75]. The open states of PTP are involved in metabolic plasticity, reprogramming and cell death in tumors [44]. MTCH2 regulates the PTP opening and MTCH2 knockdown impairs transient opening of the PTP and leads to accumulation of ROS within mitochondrial matrix, resulting in peroxidation of mitochondrial lipids and eventually ferroptosis [24].

CONCLUSION AND PERSPECTIVE

Mitochondrial dynamics shape mitochondrial morphology and help maintain a healthy mitochondrial population in response to cellular

Table 1. Summary of MTCH2's roles in various disease contexts.

Disease Context	MTCH2 Function	Key Findings
Metabolic Diseases	Regulates mitochondrial metabolism, energy balance, fat storage, mitochondrial dynamics and apoptosis	MTCH2 variants linked to obesity, insulin resistance, and impaired lipid metabolism
Cancers	Modulates cell proliferation, apoptosis, and mitochondrial membrane permeability	Overexpressed in certain cancers, influencing tumor growth and survival
Neurodegeneration	Controls neuronal cell death, mitochondrial function, and synaptic maintenance	Altered MTCH2 expression associated with Alzheimer's disease and cognitive decline in animal models
Cardiovascular Disease	Influences cardiac cell apoptosis under stress, mitochondrial-mediated cell death pathways	MTCH2 deficiency worsens ischemia-reperfusion injury in mouse cardiac tissue
Immune-Related Diseases	Modulates T cell metabolism, survival, and immune responses	Essential for memory $CD8^+$ T cell development; impacts antitumor and antiviral immune responses
Liver Diseases	Controls hepatic mitochondrial function and lipid accumulation	Loss of MTCH2 in the liver leads to steatosis and mitochondrial dysfunction

stress and metabolic demands [4–7,25–29]. The molecular mechanisms that regulate mitochondrial dynamics and the roles in cell biology are only beginning to be understood. MTCH2 has been implicated in the regulation of mitochondrial dynamics and metabolism [18,19,22,23,35] (Figure 1). MTCH2 appears to be a direct regulator of mitochondrial fusion by modulating LPA [23], and MTCH2 enforces fusion in a MFN1 dependent manner [32]. Loss of MTCH2 results in fragmented mitochondria and enhanced OXPHOS activity, which triggers metabolic switch and increases oxidative stress [3,18,19,23,35]. MTCH2 functions as a mitochondrial outer membrane protein insertase and regulates mitochondrial homeostasis, particularly through its role in mitochondrial protein biogenesis and potentially in lipid transport [13]. Given its central role in mitochondrial function and its involvement in various diseases, MTCH2 presents a promising therapeutic target [11,12,61,62]. Further research is necessary to develop specific inhibitors or modulators of MTCH2 and to understand the full spectrum of its functions in various disease conditions.

MTCH2 is the mitochondrial receptor of tBID and facilitates MOMP [16]. The very recent work demonstrates that MTCH2 regulates the PTP opening by interaction with subunit j of F-ATP synthase and coordinately mediates the mitochondrial permeability transition [24]. The PTP is a nonspecific channel in the inner mitochondrial membrane, and its opening allows the release of matrix molecules including ROS, Ca^{2+} and metabolites, which are fundamental signaling molecules for many biological processes including cell metabolism, proliferation, and apoptosis [24,44,73,76–91]. More functions of MTCH2 in regulation mitochondrial biology and cellular physiology, potentially through regulation of PTP activity, await further explorations (Figure 1).

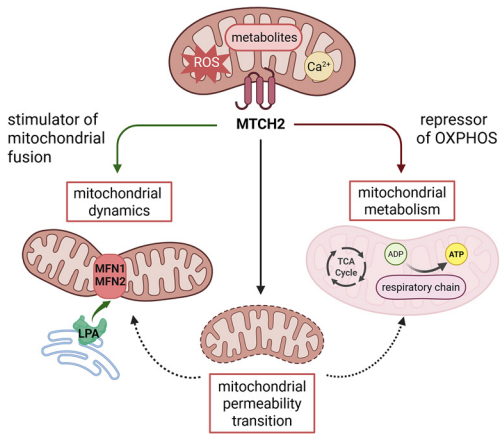

Figure 1. MTCH2 is a multifaceted regulator of mitochondrial biology. MTCH2 is a regulator of mitochondrial dynamics, metabolism and permeability transition. Mitochondria are the primary sites of cellular respiration, converting chemical energy stored in nutrients to ATP through oxidative respiration. Mitochondria dynamically undergo fission and fusion, which ensures efficient ATP production and mitochondrial quality control. MTCH2 is initially recognized to be the receptor of tBID and mediates MOMP. Subsequent studies reveal that MTCH2 plays a crucial role in regulating mitochondrial metabolism and cellular energy flow. MTCH2 is involved in producing lipids, particularly LPA, and transporting LPA from ER to mitochondria, a process vital for mitochondrial fusion. MTCH2's function in enforcing fusion is dependent on MFN1, and mitochondrial fragmentation caused by loss of MTCH2 can be specifically counterbalanced by overexpression of MFN2 but not MFN1. The most recent work demonstrates that the interplay between MTCH2 and subunit j of F-ATP synthase coordinates MOMP and PTP to mediate the occurrence of mitochondrial permeability transition. The regulatory mechanisms of mitochondrial dynamics and metabolism by MTCH2 and the involvement of its regulatory role in PTP awaits further investigations.

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