*Journal of Zhejiang University-SCIENCE B 2026 27(3):225-235*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
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**Review**

https://doi.org/10.1631/jzus.B2400202



# Recent research advances in the biological function and molecular mechanism of methylmalonic acid

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**Abstract:** The abnormal accumulation of methylmalonic acid (MMA), the leading cause of methylmalonic acidemia, can cause irreversible damage to the brain, kidney, and cardiovascular system. In addition, the accumulation of MMA in the blood has recently been associated with the occurrence of cancer, restricted bodily movement, and growth retardation. In this review, recent studies on the relationship between the metabolic abnormality of MMA and disease occurrence were summarized, concerning the brain, kidney, cardiovascular system, cancer, and skeletal muscles. It provides a theoretical basis and reference for further research and the treatment of MMA-related pathophysiological changes.

**Key words:** Methylmalonic acid (MMA); Mitochondrial dysfunction; Oxidative stress; Post-translational modification of protein; Muscle atrophy

## 1 Introduction

Methylmalonic acid (MMA) is a metabolite of methylmalonyl-coenzyme A (CoA) in the catabolic pathways of isoleucine, valine, methionine, threonine, cholesterol, and odd-chain fatty acids. The enzyme methylmalonyl-CoA mutase (MCM) and its cofactor, coenzyme cobalamin (also known as vitamin B12 (VitB12)), participate in the production of free radicals and catalyze the reversible isomerization of methylmalonyl-CoA into succinyl-CoA, which subsequently enters the tricarboxylic acid (TCA) cycle (Takahashi-Iñiguez et al., 2012). Mutations in the MCM (encoded by the *MMUT* gene) or impaired metabolic activation of its cofactor, VitB12, lead to the abnormal accumulation of metabolites such as MMA, 3-hydroxypropionic acid, and methylcitrate (Rosenberg et al., 1968; Baumgartner et al., 2014). Dysregulated MMA metabolism results in the accumulation of MMA, causing elevated concentrations of MMA in various tissues and organs via the bloodstream. This abnormal accumulation contributes to mitochondrial damage, oxidative stress, and aberrant intracellular signaling pathways, ultimately causing cellular metabolic disorders and multiple organ damage, particularly affecting the brain, liver, kidney, and heart.

## 2 Relationship between abnormal MMA metabolism and diseases

### 2.1 Methylmalonic acidemia

Methylmalonic acidemia is an autosomal recessive metabolic disease characterized by disrupted MMA metabolism (Fig. 1). Under normal circumstances, methylmalonyl-CoA is converted into succinyl-CoA by the enzymes MCM and VitB12, for succinyl-CoA to enter the TCA cycle. However, mutations in the *MMUT* gene or defects in VitB12 metabolism can cause MMA accumulation in the body. This often leads to severe intermittent ketoacidosis, elevated MMA levels in the blood and urine, and high mortality rates, particularly in newborns and young children.

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Received Apr. 22, 2024; Revision accepted Nov. 2, 2024; Crosschecked Oct. 31, 2025; Published online Nov. 21, 2025

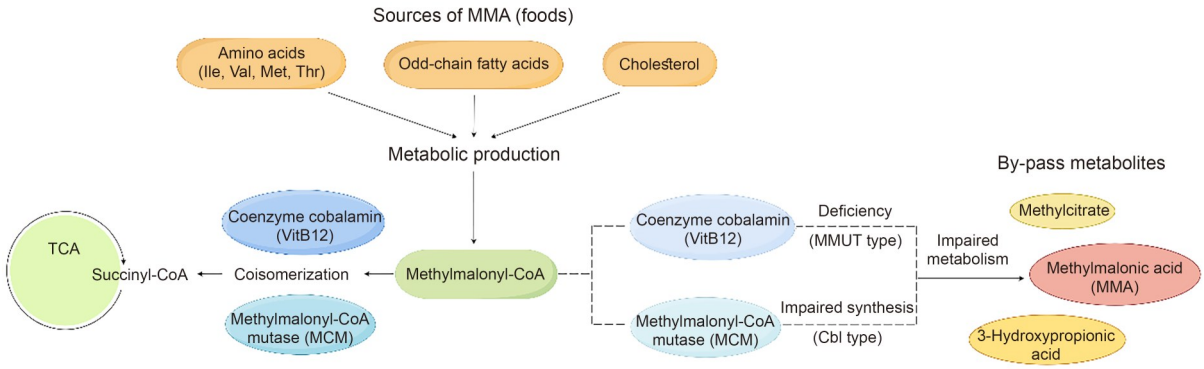


**Fig. 1 Metabolic processes of methylmalonic acid (MMA). The process of abnormal MMA metabolism in patients with methylmalonic acidemia is shown here. The main sources of MMA in patients are isoleucine (Ile), valine (Val), methionine (Met), threonine (Thr), odd-chain fatty acids, and cholesterol in foods. Normally, they are metabolized as succinyl-coenzyme A (CoA) into the tricarboxylic acid (TCA) cycle, and the deletion of some enzymes leads to abnormal accumulation of by-pass metabolites in patients, of which MMA is a typical metabolite. The lower left of the figure shows the metabolic process in normal people; the lower right of the figure shows the abnormal metabolic processes in patients with methylmalonic acidemia. VitB12: vitamin B12; MMUT: methylmalonyl-CoA mutase; Cbl: cobalamin.**

Methylmalonic acidemia can be classified into two major types based on the underlying cause: the MMUT type, caused by mutations in *MMUT* gene, and the cobalamin (Cbl) type, which results from defects in VitB12 metabolism. The MMUT type is further subdivided into Mut0 (completely inactive) and Mut$^-$ (partially active), depending on the degree of MCM enzyme deficiency. The Cbl type is more complex, encompassing multiple subtypes, including cblA, cblB, cblC, cblD, cblF, and cblH. Specifically, cblA and cblB are mitochondrial defects that impair adenosyl-cobalamin metabolism, while cblC, cblD, and cblF involve cytosolic and lysosomal defects in methylcobalamin metabolism and are associated with abnormal homocysteine levels (Ribes et al., 1984; He et al., 2021). Methylmalonic acidemia can also be categorized into isolated or combined methylmalonic acidemia, based on whether there is an accompanying elevation of homocysteine levels. Despite the differing underlying causes, both forms share a common pathological mechanism: disruption of the isomerization of methylmalonyl-CoA into succinyl-CoA results in the accumulation of MMA, propionic acid, methylcitrate, and other toxic metabolites in the bloodstream, which manifests clinically as feeding difficulties, intellectual disability, psychomotor retardation, dystonia, seizures, and drowsiness.

## 2.2 MMA and its association with brain and neurological disorders

The primary damage caused by MMA involves the brain and the nervous system, with its hallmark being the accumulation of MMA in the brain, including the central nervous system (Cudré-Cung et al., 2016). A limited efflux of dicarboxylic acids through the blood–brain barrier can lead to higher levels of MMA accumulation in brain tissue. This elevated accumulation has been directly linked to neurological deterioration in affected patients (Kölker et al., 2006). Early-onset cases, as observed in a brain magnetic resonance imaging-based analysis of 37 children with methylmalonic acidemia, typically present with ventricular dilation, brain atrophy, reduced white matter volume, thinning of the corpus callosum, cortical atrophy, and abnormal myelination (Yang et al., 2020; Dilber and Eyüboğlu, 2022). Hydrocephalus and white matter reduction are among the most frequently observed abnormalities (Cheng et al., 2019). In late-onset cases, spinal cord atrophy and other deviations were also documented (Martinelli et al., 2011). These manifestations are strongly associated with abnormal myelination and neuronal apoptosis, signifying that MMA impairs brain function by damaging both the myelin sheath and neurons (Rossi et al., 2001).

The brain damage caused by abnormal MMA accumulation is further reflected in several age-related neurological diseases, such as Alzheimer's disease and stroke (Serot et al., 2005; Pascoe and Linden, 2016). Recent studies have demonstrated a correlation between elevated MMA levels and systemic nerve damage (peripheral neuropathy), suggesting a potential link between increased MMA and other diseases characterized by neuronal damage (Stein et al., 2021). For

example, higher MMA levels have been linked to cognitive impairment in older adult stroke survivors, suggesting that serum MMA levels are more closely associated with long-term cognitive decline in older adults than previously thought, surpassing the role of VitB12 levels (Pascoe and Linden, 2016). A cross-sectional study revealed that plasma MMA levels were significantly higher, exceeding 360 nmol/L, in patients with dementia than in control subjects with elevated MMA levels, but not plasma VitB12 levels, suggesting the link to pathologically confirmed Alzheimer's disease (Smith and Refsum, 2009; Bednarska-Makaruk et al., 2016). In an Alzheimer's disease case-control study, the case group exhibited significantly higher MMA levels than the control group ($P$=0.027) (Refsum and Smith, 2003). Additionally, cblC disease, characterized by elevated MMA levels, demonstrated protein changes similar to those seen in Alzheimer's disease cases (Hannibal et al., 2011). Interestingly, while serum MMA levels increase with age, those in cerebrospinal fluid are significantly decreased in older adults with Alzheimer's disease, suggesting that MMA-related neurological damage may be caused by the interplay of associated small molecules rather than by MMA accumulation alone (Serot et al., 2005).

The mechanism of brain injury in methylmalonic acidemia involves mitochondrial dysfunction and increased oxidative stress. These processes contribute to neuronal apoptosis, which is closely associated with the abnormal accumulation of MMA. MMA induces neuronal damage, particularly in chick embryo neuron cells, and the extent of this damage is directly correlated with both the concentration and the exposure time of MMA (Kölker et al., 2000). Moreover, MMA impacts metabolism and function in neuronal-associated cells, further contributing to neuronal damage. For example, astrocytes, which are essential cells in the central nervous system, perform numerous adaptive functions to maintain brain homeostasis, such as regulating energy metabolism, supplying glucose to neurons, countering oxidative stress, and reducing inflammation. They also play a protective role against reactive oxygen species (ROS)-mediated damage (Souza et al., 2019). As cells that safeguard neurons, astrocytes are critical to the pathology of methylmalonic acidemia (da Costa et al., 2021).

In a study using the human neuroblastoma SH-SY5Y cells as a neuronal model, exposure to pathological concentrations of MMA (>0.5 mmol/L) revealed that MMA could induce coenzyme $Q_{10}$ ($CoQ_{10}$) deficiency, reduce the activity of mitochondrial respiratory chain complex II/III, and inhibit succinate dehydrogenase, all of which impair mitochondrial electron transport chain function in neuronal cells (Proctor et al., 2020). Furthermore, the protective myelin sheath surrounding neurons can also be damaged by MMA (Brismar and Ozand, 1994). Chronic MMA treatment in young rats resulted in deficiencies in important structural lipids in the brain (Brusque et al., 2001). If extrapolated to humans, these findings suggest that MMA can impair myelin biosynthesis, leading to hypomyelination or demyelination, which may be associated with central nervous system myelination disorders in methylmalonic acidemia. In conclusion, MMA-associated neuronal damage not only directly affects neurons but also causes synergistic harm through cells related to neuronal activity, ultimately leading to neuronal death and contributing to brain injury.

### 2.3 MMA and renal dysfunction

Methylmalonic acidemia is primarily associated with interstitial nephritis and renal failure (Morath et al., 2008). In addition to its neurotoxic effects, MMA is toxic to the kidneys, causing kidney DNA damage and contributing to kidney failure in patients with methylmalonic acidemia (Singh et al., 1988; Andrade et al., 2014).

Zsengellér et al. (2014) analyzed the kidneys of a 19-year-old patient with methylmalonic acidemia who underwent a combined kidney–liver transplant. Light microscopy revealed extensive interstitial fibrosis, chronic inflammation, and proximal tubular atrophy in the kidney tubules. Electron microscopy revealed that the proximal renal tubules had disturbed cristae, giant mitochondria (megamitochondria), and a loss of cytochrome C oxidase activity. The metabolic signatures of elevated toxic organic acids were also detected in urinary excretions and kidney biopsies from patients with methylmalonic acidemia, suggesting a strong link between MMA accumulation and the development of interstitial nephritis and renal failure. However, whether MMA can cause renal failure directly remains unclear.

It is essential to establish whether elevated MMA levels in patients with kidney disease are a cause or consequence of the condition. Understanding the pathogenesis of kidney disease requires further investigation into small molecular substances, such as MMA (Nielsen et al., 2022; Delgado et al., 2023).

### 2.4 MMA and cardiovascular disease

MMA-induced diseases have been strongly linked to the disruption of mitochondrial energy metabolism and increased oxidative stress, both of which are also key factors in the pathophysiology of cardiovascular disease (CVD). Numerous studies have confirmed that the abnormal accumulation of MMA is closely associated with cardiovascular injury. For example, Wang et al. (2020) used Cox regression models to analyze data from 23 437 adults in the United States National Health and Nutrition Examination Survey (NHANES). The NHANES 1999–2004 and 2011–2014 datasets were used as primary and validation subsets, respectively, to investigate the impact of MMA levels. They found that elevated circulating levels of MMA were strongly associated with increased all-cause and cardiovascular mortalities, suggesting that MMA may exacerbate cardiovascular damage.

Coronary atherosclerotic heart disease, also known as coronary heart disease (CHD), is a type of CVD that predominantly affects individuals over the age of 40 years and is linked to high mortality rates (Figtree et al., 2022). Studies have shown that in patients with CHD, an increased blood concentration of MMA is closely correlated with higher mortality (Vermorken et al., 2021). Similarly, elevated plasma MMA has been linked to a greater risk of acute myocardial infarction and mortality in patients with CHD (Dhar et al., 2023). Furthermore, serum MMA levels increase with age and are significantly correlated with CVD risk (Wang XY et al., 2022). In the study by Zhu et al. (2023), data from 9934 hypertensive adults enrolled in NHANES were analyzed using Cox regression and restricted cubic spline (RCS); based on their serum VitB12 levels during two periods ten years apart (1999–2006 vs. 2011–2014), high concentrations of circulating MMA were linearly correlated with increased mortality in hypertensive adults. Among patients with CHD from the NHANES cohort, MMA accumulation was also found to be associated with elevated cardiovascular mortality risk (Guo et al., 2023). Interestingly, neither serum nor dietary VitB12 levels had a significant effect on reducing mortality in these patients. The above findings collectively indicate that the abnormal MMA accumulation in the blood contributes to the progression of heart disease and can ultimately result in death.

A recent study revealed that MMA activates oxidative stress and ROS generation, which induces ferroptosis and exacerbates cardiomyocyte injury in an ischemia–reperfusion model (Guo et al., 2024). Additionally, MMA accumulation leads to the significant sequestration of mitochondrial CoA in cardiomyocytes, increasing myocardial oxygen consumption and impairing normal cardiac function (Wang et al., 2018). These observations suggest that abnormal MMA accumulation is closely linked to heart failure and cardiac hypertrophy, and the mechanism of heart damage caused by MMA may be similar to other diseases related to mitochondrial dysfunction.

### 2.5 MMA and cancer

The concentration of metabolites in the blood can cause the onset and progression of various diseases, including cancer. Previous studies have shown that MMA levels are significantly elevated in the blood of older adults, compared with younger individuals. In a study analyzing blood metabolites in 30 young individuals (aged ⩽30 years) and 30 older adults (aged ⩾60 years), MMA concentration was found to be significantly higher in the latter (Gomes et al., 2020). Similarly, using data from 22 812 participants aged ⩾20 years in NHANES, Tang et al. (2024) found that MMA levels were positively correlated with most indicators of biological aging. These studies suggest that metabolic alterations occurring with age create a systemic environment conducive to tumor progression and aggressiveness. Specifically, MMA is upregulated in the serum of older individuals and serves as a mediator of tumor progression, potentially reducing cancer-related survival rates.

Further research revealed that cancer cells themselves can increase MMA levels by altering propionate metabolism, particularly in highly aggressive cancers like triple negative breast cancer (Gomes et al., 2022). In these types of cancer, MMA accumulation occurs due to the inhibition of methylmalonyl-CoA epimerase (MCEE), which blocks propionate metabolism. In addition, MMA can activate stromal fibroblasts into cancer-associated fibroblasts, inducing a secretory phenotype, as demonstrated in a mouse model exposed to high local concentrations of MMA (Li et al., 2022). These cancer-associated fibroblasts, in turn, secrete extracellular vesicles containing interleukin-6 (IL-6) and other factors, promoting epithelial-to-mesenchymal transition (EMT) in tumor cells. This transition facilitates the acquisition of invasive traits such as drug resistance and increased metastasis. These findings indicate that during

the aging process, an elevated serum MMA level, potentially exacerbated by tumor production, shapes the tumor microenvironment, thereby enhancing cancer cell invasion and therapeutic resistance, which ultimately leads to poorer clinical outcomes.

Recent studies have also found a significant link between elevated serum MMA levels and cancer-related mortality (Wang J et al., 2022; Liu et al., 2024). For example, for each one-unit increase in natural log-transformed MMA levels, the risks of all-cause, CVD, and cancer-related mortalities increased 2.652 times, 3.153 times, and 4.514 times, respectively (Wang J et al., 2022). These data underscore that MMA accumulation is a critical factor in cancer development. Furthermore, several studies have linked elevated MMA levels to the progression of breast cancer, colorectal cancer (CRC), and osteosarcoma (Santamaría et al., 2023; Wu et al., 2024). For instance, Hu et al. (2023) found that the treatment of human CRC cells (HCT116 and SW480) with MMA promoted CRC progression both in vivo and in vitro, suggesting that MMA activates EMT via the Wnt/β-catenin signaling pathway. As such, MMA holds great potential for cancer research, offering valuable insights into tumor biology and therapeutic targets. Investigating small-molecule metabolites like MMA could open new avenues for understanding cancer progression and developing novel treatment strategies.

### 2.6 MMA and skeletal muscle function

Skeletal muscle, a critical metabolic and motor tissue, plays a pivotal role in maintaining physiological homeostasis and supporting essential life activities. Clinical studies have shown that patients with methylmalonic acidemia frequently exhibit motor and growth dysfunctions, including muscle weakness, dystonia, and abnormal muscle development (el Hasbaoui et al., 2021; Yuan et al., 2024). Similarly, mouse models of methylmalonic acidemia display significant phenotypes, such as weight loss and growth retardation (Forny et al., 2016). As a tissue with a high abundance of mitochondria, skeletal muscle provides substantial energy for the body. Muscle function and growth are intrinsically linked to mitochondrial health, while the abnormal accumulation of MMA can lead to mitochondrial dysfunction. These findings suggest a potential relationship between MMA and the regulation of muscle growth and function.

MMA levels are elevated in the blood of patients with myasthenic mitochondrial encephalomyopathy. Østergaard et al. (2005) reported a case of methylmalonic acidemia associated with reduced maximal muscle load, impaired oxygen consumption, and subsarcolemmal mitochondrial accumulation, as observed in a muscle biopsy, suggesting that MMA inhibits mitochondrial energy metabolism (Østergaard et al., 2005). Furthermore, de Keyzer et al. (2009) found respiratory chain defects in patients with methylmalonic acidemia, characterized by a predominance of type I muscle fibers and the atrophy of type II muscle fibers in patients' muscles, indicating that type II muscle fibers are more susceptible to MMA-induced damage.

Under normal conditions, skeletal muscle serves as a significant source of MMA in circulation, highlighting its roles as an essential metabolic tissue for MMA (Østergaard et al., 2005; Chandler et al., 2007). However, with aging, muscle mass and function gradually decline. After the age of 60 years, muscle protein degradation accelerates, leading to sarcopenia and impaired muscle function. MMA levels in the blood of older adults (over 60 years old) are significantly higher than those in younger individuals (under 30 years old), suggesting a reduced capacity for MMA metabolism in this age group (Gomes et al., 2020). Pannérec et al. (2018) found that the level of VitB12, a crucial coenzyme in MMA metabolism, is significantly decreased in the blood, muscles, and livers of older adults, resulting in impaired MMA metabolic pathway activity. This allows MMA to accumulate in muscle tissue, contributing to sarcopenia. Regarding the impact of MMA on muscle function, there is currently no direct in vivo or in vitro experimental evidence available. However, exploring the relationship between MMA and muscle growth and function could represent a novel strategy for treating methylmalonic acidemia and sarcopenia (Fig. 2).

## 3 MMA and the molecular mechanisms of diseases

### 3.1 MMA and mitochondrial dysfunction

Mitochondria, the primary energy-producing organelles within cells, play a vital role in supporting cellular metabolism and function (Fig. 3). Mitochondrial dysfunction has been associated with metabolic

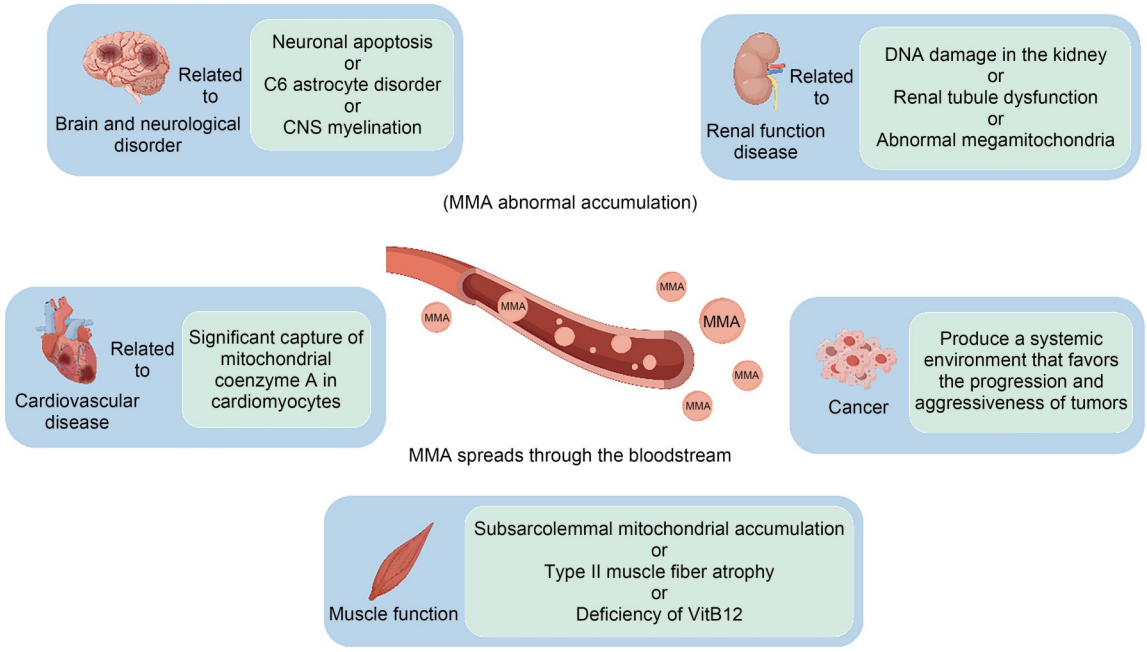


**Fig. 2 Relationships between abnormal accumulation of methylmalonic acid (MMA) and related diseases. Since the pathogenesis of MMA in cerebral, renal, and cardiovascular diseases has been demonstrated, the term "related to" is used to indicate its correlation with the brain, renal, and cardiovascular diseases. However, the pathogenesis of MMA in cancer or muscle function is not clear, so the "related to" is not used. CNS: central nervous system; VitB12: vitamin B12.**

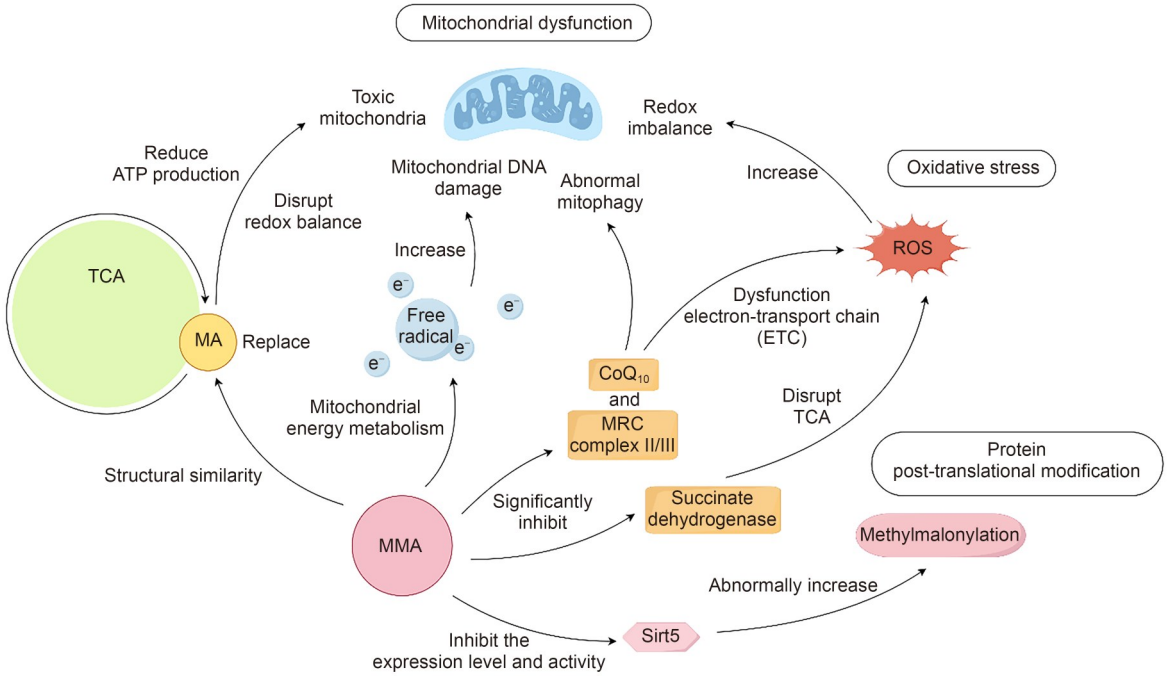


**Fig. 3 Molecular mechanism of methylmalonic acid (MMA)-causing diseases. The mechanism of abnormal accumulation of MMA leading to disease can be classified into three categories: mitochondrial dysfunction, oxidative stress, and protein post-translational modification. Mitochondrial dysfunction can be classified into four types: toxic mitochondria, mitochondrial DNA damage, abnormal mitophagy, and redox imbalance according to different mechanisms. Significant inhibition of $CoQ_{10}$ and MRC complex II/III, due to MMA, will lead to not only abnormal mitophagy but also oxidative stress. TCA: tricarboxylic acid; ATP: adenosine triphosphate; MA: malic acid; $CoQ_{10}$: coenzyme $Q_{10}$; MRC: mitochondrial respiratory chain; Sirt5: silent mating-type information regulation 2 homolog 5; ROS: reactive oxygen species.**

disturbances in the body and various associated diseases. MMA shares structural similarities with malic acid, which is known to inhibit the respiratory chain complex II. Consequently, MMA can disrupt the redox balance by inhibiting electron transport complex II and affecting polyproteins within the TCA cycle; therefore, it has been considered as a mitochondrial toxin (Wajner and Coelho, 1997). Under normal circumstances, MMA is metabolized into the TCA cycle via propionyl-CoA and methylmalonyl-CoA, generating a significant amount of adenosine triphosphate (ATP). However, elevated MMA levels in tissues and biological fluids can impair mitochondrial energy metabolism, resulting in increased intracellular free radical production. This in turn leads to mitochondrial DNA damage, creating a detrimental feedback loop (Indo et al., 2007). Pathological concentrations of MMA (>0.5 mmol/L) were associated with abnormal accumulation and a significant inhibition of $CoQ_{10}$, a critical electron carrier in the mitochondrial respiratory chain. This inhibition has been shown to result in a notable ($P$=0.0087) reduction of approximately 75% in the $CoQ_{10}$ level and a significant decrease ($P$=0.0099) in mitochondrial respiratory chain complex II/III activity when elevated MMA levels exceeded 2 mmol/L (Proctor et al., 2020). Mitochondrial dysfunction and abnormalities in autophagy caused by high MMA concentrations are primary contributors to diseases affecting the heart, kidney, muscles, and other organs. MMA has been shown to inhibit the transport of malate and succinate in mitochondria via dicarboxylic acid carriers (Halperin et al., 1971). Additionally, MMA disrupts redox balance and compromises mitochondrial antioxidant defenses by inhibiting glutathione transport via dicarboxylate carriers (Lash, 2006). Therefore, understanding the complex relationship between MMA and mitochondrial function is essential for deciphering the pathophysiology of MMA-related diseases.

### 3.2 MMA and oxidative stress

Oxidative stress refers to an imbalance between oxidation and antioxidation in the body, favoring oxidation. This condition results from the harmful effects of free radicals and is recognized as a significant contributor to aging and various diseases. Oxidative stress elevates the level of ROS throughout the body, leading to an excessive oxidation of intracellular compounds. This disruption impairs the normal functioning of mitochondria and cells, ultimately resulting in related diseases (Filomeni et al., 2015).

MMA has emerged as a promising biomarker for oxidative stress, with various diseases induced by MMA linked to cellular oxidative stress (Okun et al., 2002; Atkuri et al., 2009; Polytarchou et al., 2020). Numerous studies, including animal models and patient reports, have indicated the presence of oxidative stress in methylmalonic acidemia. For instance, Viegas et al. (2014) found that MMA injection into the rat brain disrupts redox homeostasis.

The sources of oxidative stress include the accumulation of toxic metabolites and the generation of ROS in metabolic disorders, as well as reactive nitrogen species associated with the pathogenesis of various diseases (Stepien et al., 2017). In methylmalonic acidemia, mitochondrial ROS production due to dysfunction in the electron transport chain is considered the primary cause of oxidative stress. Increased ROS production activates the nuclear factor-κB (NF-κB) and transforming growth factor-β (TGF-β) signaling pathways. Notably, MMA can induce ROS generation in fibroblasts, and this ROS activation drives metastatic reprogramming in tumor cells through TGF-β and NF-κB signaling (Li et al., 2022).

### 3.3 MMA and post-translational modification of proteins

Post-translational modifications (PTMs) of proteins introduce a vast functional diversity to the proteome through the covalent attachment of functional groups or proteins, proteolytic cleavage of regulatory subunits, and degradation of entire proteins. PTMs play crucial roles in various biological processes, including carcinogenesis, DNA damage response, cell proliferation, metastasis, and apoptosis (Chen et al., 2020; Shu et al., 2023).

Research involving *MMUT* mutant mice and patients with methylmalonic acidemia has revealed significantly elevated levels of methylmalonylation in the liver tissue. This modification inhibits several enzymes in the urea cycle and glycine cleavage pathway, ultimately leading to MMA accumulation (Head et al., 2022). In turn, MMA can inhibit the expression and activity of silent mating-type information regulation 2 homolog 5 (*Sirt5*), resulting in an abnormal increase in methylmalonylation levels. To investigate this further, researchers constructed a highly active

*Sirt5* expression vector and injected it into *MMUT* mutant mice via an adeno-associated virus (AAV). The injection of a highly active *Sirt5* vector gained the body weight of *MMUT* mutant mice and significantly reduced the level of methylmalonyl modification in vivo, effectively mitigating the symptoms of MMA mice and providing a novel therapeutic approach for MMA treatment.

## 4 Summary

This review primarily elucidates the metabolic functions and action mechanism of MMA and how its abnormal accumulation leads to various types of bodily damage. These effects involve multiple organs, resulting in conditions such as brain disorders, renal dysfunction, CVD, and cancer. Findings to date indicate that ROS, redox imbalance, and mitochondrial damage are the primary mechanisms driving most organ injuries associated with MMA. Moreover, muscle damage is closely linked to ROS, redox disturbances, and mitochondrial dysfunction, which may also be related to the abnormal accumulation of MMA. Numerous studies have found a connection between MMA accumulation in skeletal muscle and muscular dystrophy, muscle weakness, and impaired motor function. Therefore, future research should focus on how MMA influences muscle growth and function, as well as the underlying mechanisms in medical contexts.

Additionally, an increasing body of evidence underscores that MMA can activate various signaling pathways, including the TGF-β and NF-κB pathways highlighted in this study. Recent research has also indicated that MMA directly influences protein methylation modifications. These findings suggest that MMA exerts its effects through multiple biological mechanisms. Furthermore, small molecules like MMA typically bind to specific protein targets, affecting their function and thereby exerting direct biological roles. Due to its structural similarity to succinate, MMA can target succinate receptor 1 (SUCNR1), activating the downstream inflammatory signaling pathways. Exploring whether MMA can directly interact with certain proteins to influence their function represents a promising new avenue for MMA research.

The occurrence of MMA diseases is primarily attributed to mutations in the *MMUT* gene, along with biallelic pathogenic variants in the methylmalonic aciduria type A (*MMAA*), methylmalonic aciduria type B (*MMAB*), methylmalonic aciduria and homocystinuria type D (*MMADHC*), *MCEE*, succinate-CoA ligase GDP/ADP-forming subunit alpha (*SUCLG1*), and succinate-CoA ligase ADP-forming subunit beta (*SUCLA2*) genes (Tejero et al., 2024). In recent years, advancements in gene editing technologies, particularly single-base editing, have shown great promise in treating genetic mutation disorders. Spinal muscular atrophy (SMA) is a severe inherited neuromuscular disease caused by homozygous deletions or mutations in the *SMN1* gene, which encodes the survival motor neuron (SMN) protein. The absence of the SMN protein in patients with SMA results in the rapid degeneration of motor neurons, leading to a progressive loss of muscle function, paralysis, and ultimately death; the majority of patients with type 1 SMA do not survive beyond two years. Recent study has demonstrated that the adenine base editor ABE8e can convert a T·A base pair in the *SMN2* gene to a C·G pair, effectively transforming the gene into a functional copy of the *SMN1* gene (Arbab et al., 2023). This innovative treatment approach increases SMN protein levels by 40 times, restoring them to the levels comparable to those in healthy cells, effectively treating SMA. McAuley et al. (2023) applied adenine base editing to treat CD3δ severe combined immune deficiency (SCID), a devastating inherited immune disorder, in mouse models. The development of single-base editing technology has emerged as a vital research direction for addressing congenital gene mutation diseases. Therefore, utilizing this technology to alleviate MMA diseases may become a viable option in the future.

### Acknowledgments

This work was supported by the Natural Science Foundation of Shanxi Province (No. 2023-JC-QN-0243), the National Natural Science Foundation of China (No. 31900448), and the Fundamental Research Funds for the Central Universities (No. Z1010422004), China.

### Author contributions

Zi'ang WANG, Wenhui CHENG, Teng WANG, and Yidi ZHANG were involved in writing – original draft and editing. Xin'e SHI, Yuqi LV, and Jianjun JIN were involved in writing – review and editing. All authors have read and approved the final manuscript.

## Compliance with ethics guidelines

Zi'ang WANG, Wenhui CHENG, Teng WANG, Yidi ZHANG, Xin'e SHI, Yuqi LV, and Jianjun JIN declare that they have no conflicts of interest.

This review does not include any study with human or animal subjects performed by any of the authors.

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