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The role of lipoylation in mitochondrial adaptation to methionine restriction

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Abstract

Dietary methionine restriction (MR) is associated with a spectrum of health-promoting benefits. Being conducive to prevention of chronic diseases and extension of life span, MR can activate integrated responses at metabolic, transcriptional, and physiological levels. However, how the mitochondria of MR influence metabolic phenotypes remains elusive. Here, we provide a summary of cellular functions of methionine metabolism and an overview of the current understanding of effector mechanisms of MR, with a focus on the aspect of mitochondria-mediated responses. We propose that mitochondria can sense and respond to MR through a modulatory role of lipoylation, a mitochondrial protein modification sensitized by MR.

KEYWORDS
cellular metabolism, lipidomics, methioinine metabolism, metabolomics, phospholipid

INTRODUCTION

Methionine is a sulfur-containing amino acid not synthesized in mammals and must be obtained from food.[1] As a proteinogenic amino acid, methionine is present in virtually any protein foods and varies widely in different types of diets.[2,3] Limiting dietary methionine intake is reportedly associated with numerous health benefits, including cardiac protection,[4,5] prevention of obesity and diabetes,[6,7] and lifespan extension.[8–10] Methionine restriction (MR) has also been used as a nutritional intervention to improve the efficacy of treatments for diseases such as cancer,[11,12] Despite the essentiality of methionine to life, the beneficial effects of MR revealed in pre-clinical studies have inspired the development of precision diets for a spectrum of health applications by formulating dietary methionine composition.[13,14] However, it is important to consider undesired, deleterious health outcomes associated with MR, including the disruption of the microbiome and immunity.[15,16] In particular, the applicability of MR during early or adolescent development is challenged due to an increased requirement for methionine at these stages.[17,18] Therefore, a better understanding of MR effector mechanisms will advance the development of nutraceuticals and dietary strategies for the prevention and treatment of human diseases.

METHIONINE AND CYSTEINE AS A DIETARY SOURCE OF SULFUR MOIETIES

Plants and microbes can synthesize methionine and other sulfur-containing metabolites by reducing sulfate, which is the most abundant sulfur source.[19,20] This sulfur assimilatory mechanism plays a key role in the sulfur cycle in nature and provides organic sulfur nutrients to animals. Unlike plants and microorganisms, mammalian cells do not have sulfate-reducing enzymes and cannot use inorganic sulfur sources.[2] Methionine and cysteine (or cystine, the oxidized disulfide form of cysteine) from dietary protein serve as predominant sulfur moieties sources in mammals, which are readily

metabolized to all sulfur-containing intermediary metabolites, such as homocysteine, glutathione, coenzyme A (CoA), hydrogen sulfide (H_2S), iron-sulfur (Fe-S) clusters.[2,21] Because cysteine can be synthesized from methionine via the transsulfuration pathway,[22] methionine can serve as the sole source of nutritional sulfur moieties, in principle. As such, MR may signal a nutritional state reflecting sulfur amino acid scarcity in mammalian cells, sensitizing the critical roles of sulfur amino acids in catalytic and electrochemical functions. However, the expression of transsulfuration enzymes varies across developmental stages and disease states, influencing cellular reliance on extracellular cystine/cysteine.[21,23] Genetic mutations in the transsulfuration pathway can result in homocystinuria, characterized by pathologies including dislocated lens, osteoporosis, and thrombosis.[24]

The sulfur amino acid restriction (SAAR) diet in animal models, which limits methionine and excludes cysteine, effectively reduces levels of both sulfur amino acids. A MR diet may also decrease both methionine and cysteine levels, mimicking the effect of the SAAR diet, especially when cysteine reduction is significant. Therefore, cysteine reduction could be responsible for some observed effects of MR treatment. For example, the anti-obesity effects of MR in rats are attributed to low cysteine levels and can be reversed by cysteine supplementation.[25] Another study in mouse model confirms that the anti-adiposity effects of SAAR are due to cysteine restriction and further shows that cysteine restriction alone is sufficient to induce hepatic *de novo* serine biosynthesis and alter adipose metabolism.[26] Nevertheless, the individual contributions of MR and cysteine restriction to SAAR-induced changes remains incompletely understood. Given that MR and cysteine restriction can lead to different biological effects, we focus herein on the effects of MR.

HOW DOES MR TRANSDUCE THE SIGNAL OF METHIONINE DEPLETION?

While some studies have observed a reduction in circulating methionine levels following consumption of an MR diet,[27,28] it is important to note that findings have not been fully consistent across different research investigations.[26,29] Discrepancies in reported methionine reductions may stem from variations in model backgrounds, dietary protocols, and sampling methods and timing. Despite these inconsistencies, hepatic methionine levels exhibit a rapid and significant decline within the first 2 days of initiating the MR diet.[30] This highlights the liver's responsiveness to MR and underscores the importance of understanding the dynamic interplay between dietary MR and hepatic metabolism. When depleting methionine in cell culture media, cellular levels of methionine, S-adenosylmethionine (SAM), and S-adenosylhomocysteine (SAH) all decline rapidly within 1 hour.[29] Similar decreases in methionine cycle metabolites are observed in *Drosophila* after 1 week of MR.[31] The low levels of homocysteine and cystathionine further suggest that MR can reduce activity in the transsulfuration pathway.[31]

A decrease in cellular methionine content triggers a cascade of changes in many methionine-derived metabolites,[27,32] such as SAM, a major methyl donor synthesized from methionine through ATP activation.[33] Metabolic alterations resulting from MR can prompt transitory adaptation to low methionine conditions. Numerous mechanisms activated during MR are driven by metabolite-dictated coordination of cellular processes, such as protein synthesis,[34–36] sulfur metabolism,[37] epigenetic modification,[29,37–40] antioxidant defense,[41–43] and signal transduction.[44,45] Responses to MR can vary significantly under different biological contexts, potentially due to variations in cellular methionine requirement among different cell types. For example, the methionine dependence is observed in cancer cells, commonly referred to as the Hoffman effect.[46] In colorectal cancer, for example, dietary MR has been shown to disrupt cellular redox balance and nucleotide metabolism through its effect on one-carbon metabolism.[11] Moreover, among all tissues, the liver, kidney, and pancreas, which exhibited higher metabolic enzyme activities, are particularly active in methionine uptake from the bloodstream.[2,47] The susceptibility of liver cancer to MR is determined by hepatocyte nuclear factor 4α (HNF4α).[48] However, SAM reduction in a healthy liver can regulate ER-mitochondria contact, β-oxidation, and ATP production.[49] Despite its benefits, MR can impair anti-tumor immunity, partly due to reduced gut microbial production of H_2S.[16] We propose that organismal fitness under MR results from physiological adaptation to a low-sulfur state. Sulfur scarcity during MR may trigger a metabolic signal that modulates cellular activities, ultimately suppressing energy production.

Methionine metabolism is intricately linked to a variety of mitochondrial biochemical processes, including bioenergetics and anabolic reactions, as sulfur atoms are extensively utilized as conduits for electron transfer. Mitochondria, being central metabolic compartments for biosynthesis and energy production, possess the capability to sense and respond to numerous cellular stresses.[50,51] However, the mechanism by which scarcity signals in sulfur moieties, such as methionine depletion, are processed within mitochondria remains largely unknown. A recent study has shown that protein lipoylation, a posttranslational modification of mitochondrial metabolic enzymes in eukaryotes, plays a pivotal role in sensing and responding to methionine depletion.[52] This leads us to hypothesize that the ability of mitochondrial lipoylation to interpret the chemistry of sulfur metabolism mechanistically underpins the physiological benefits of MR.

METHIONINE METABOLISM IS CENTRAL TO A PLETHORA OF METABOLIC PATHWAYS INVOLVING SULFUR-CONTAINING BIOMOLECULES

Methionine is readily activated by ATP in cells and transformed into the high-energy metabolite SAM through the catalysis of methionine adenosyltransferase (MAT). All chemical moieties attached to the sulfur of SAM can serve as leaving groups for nucleophilic substrates in

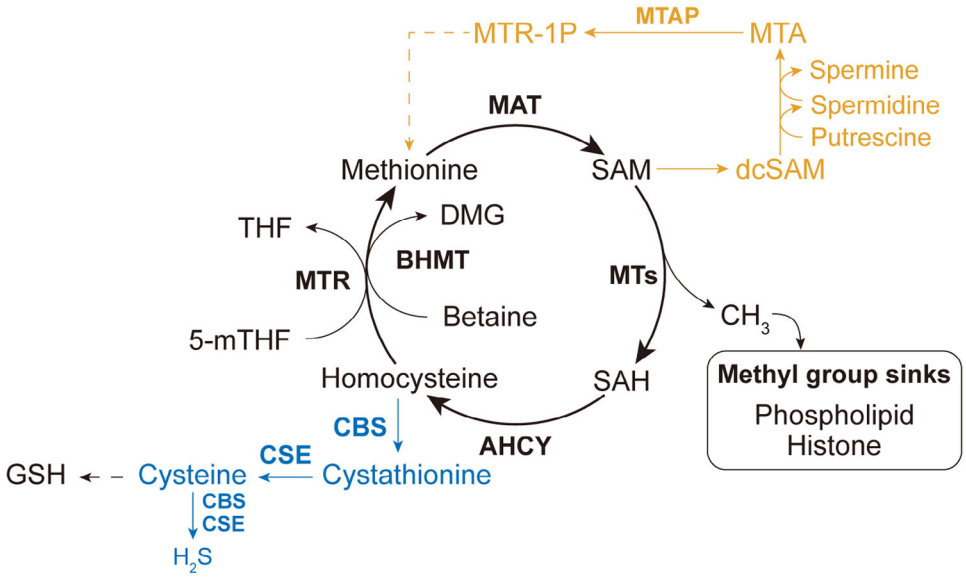

FIGURE 1 Methionine metabolism pathways. Major pathways for methionine and SAM metabolism, including the methionine cycle (black), the transsulfuration pathway (blue), and the methionine salvage pathway (orange). Key abbreviations:MT, methyltransferase; dcSAM, decarboxylated S-adenosylmethioninamine.

cellular biosynthesis and regulation,[53] showcasing its unique chemical versatility. This versatility expands the biological role of methionine beyond being solely a proteinogenic amino acid. Here, we briefly discuss recent advances related to major metabolic pathways originating from methionine and SAM, including methionine cycle, transsulfuration, and methionine salvage (Figure 1).

Methionine cycle

The metabolism of methionine begins with the synthesis of SAM catalyzed by MAT (Figure 1). In yeast cells, SAM synthesis involves two MAT genes, *SAM1* and *SAM2*.[54] Mammalian cells have three MAT genes (*MAT1A*, *MAT2A*, *MAT2B*) encoding two catalytic subunits (MATα1 and MATα2) and one regulatory subunit (MATβ), forming three isoenzymes with different tissue distribution and kinetic characteristics. The *MAT1A* gene is highly expressed in adult hepatocytes, while *MAT2A* and *MAT2B* are mainly expressed in other cell types and fetal livers.[55] Cells can switch between different forms of MAT during active liver growth and liver cancer progression,[56] suggesting the importance of regulating cellular SAM synthesis for cell growth and differentiation. While MAT enzymes are traditionally considered cytoplasmic, nuclear MAT enzymes have been found to interact with transcriptional factors, revealing a role for metabolic enzymes in locally regulating histone methylation and gene expression.[57,58] Interestingly, recent studies have identified MAT1α in the mitochondrial matrix of hepatocytes.[59,60] The cytosolic and mitochondrial pools of SAM can be exchanged via the SAM-specific transporter SLC25A26, also known as SAM carrier (SAMC).[61] However, the exchange rate may not be sufficient to meet metabolic demand in hepatocytes, considering the liver's high activity in methionine metabolism and SAM production.[62] This compartmentalization of MAT enzymes suggests a potentially overlooked role of liver mitochondria in sensing methionine and SAM availability, likely integrated with the multifaceted roles of this organelle in metabolism and stress responses.

As an essential cofactor for SAM-dependent methyltransferases, SAM donates methyl groups to various substrates, including nucleic acids, proteins, lipids, and small molecules.[33] This transmethylation reaction generates a byproduct SAH, a potent inhibitor of many methyltransferases (Figure 1). Adenosylhomocysteine hydrolase (AHCY) is a highly conserved enzyme and the sole enzyme in mammals responsible for hydrolyzing SAH to homocysteine and adenosine. Like MAT enzymes, AHCY can be recruited to chromatin during replication and active transcription, possibly for modulating methylation potential in the local environment.[63,64] In mammals, two AHCY-like proteins (AHCYL1 and AHCYL2) exist, each containing a highly conserved SAH-binding domain but lacking hydrolytic activity.[65] AHCYL1 functions as an SAH sensor via its SAH-binding domain to inhibit autophagy.[66]

The methionine cycle concludes with the remethylation of homocysteine into methionine (Figure 1). In mammals, this process is catalyzed by betaine homocysteine S-methyltransferase (BHMT) and methionine synthase (MTR). BHMT is a zinc-dependent methyltransferase that uses the choline metabolite betaine as the methyl donor,[67] and MTR is a cobalamin-dependent enzyme that employs 5-methyltetrahydrofolate (5-mTHF) as the methyl donor.[68] While MTR is expressed ubiquitously, BHMT is primarily found in the kidney and liver, contributing to ~ 50% of methionine synthesis in the liver.[69,70] Recent isotope tracing studies have shown that MTR serves as only a minor source of methionine in normal tissues and tumor cells but plays a major role in maintaining folate pools.[71,72] Deficiency in MTR, like cobalamin deficiency, leads to folate trapping as 5-mTHF, a predominant circulating folate species. As a result, loss of MTR activity disrupts

the folate cycle, resulting in nucleotide depletion and delayed cancer cell proliferation.[71,72] While MTR couples the methionine cycle and the folate cycle, its fundamental role appears to lie in modulating folate metabolism.

Transsulfuration

In the transsulfuration pathway, the transfer of a sulfur atom from homocysteine to cysteine occurs through two irreversible steps in vertebrates,[73] resulting in the production of several sulfur metabolites, such as cysteine, glutathione (GSH), and H_2S (Figure 1). Cystathionine-β-synthase (CBS) catalyzes the rate-limiting step, converting homocysteine and serine into cystathionine. CBS is a homotetrameric enzyme using pyridoxal-5′-phosphate and heme as cofactors, typically found in the cytosol. However, under ischemia and hypoxia conditions, CBS can accumulate in liver mitochondria and relocated to the nucleus upon sumoylation.[74,75] The activity and stability of CBS are regulated by SAM, which acts as an allosteric activator of the enzyme.[76]

Cystathionine is further hydrolyzed to produce cysteine by cystathionine-γ-lyase (CSE) (Figure 1). Both CBS and CSE can catalyze the production of H_2S,[77] a gasotransmitter acting in physiological processes such as blood pressure regulation and neuroprotection.[78,79] Cysteine serves as a precursor for the antioxidant GSH, synthesized through two ATP-dependent reactions. Thus, the transmethylation-transsulfuration sequence metabolically converts methionine and SAM to cysteine and GSH.[80] Studies show that the methylation of the phospholipid phosphatidylethanolamine and histones actively consumes substantial amounts of SAM.[37,40,80] Serving as methyl group sinks, these methylation reactions can quickly deplete cellular methionine and SAM upon nutrient deprivation, generating a low SAM signal indicative of nutrient scarcity.[81,82] Meanwhile, the turnover of SAM fuels the synthesis of cysteine and GSH, thereby regulating cell proliferation and antioxidant capacity.[37,40]

Methionine salvage pathway

The methionine salvage pathway, also known as the 5′-methylthioadenosine (MTA) cycle, plays a crucial role in maintaining methionine levels by recycling the sulfur moiety of MTA, a by-product generated from the biosynthesis of polyamines (Figure 1). During polyamine synthesis, the aminopropyl group of decarboxylated SAM is transferred to putrescine and spermidine as MTA is formed. In mammalian tissues, MTA phosphorylase (MTAP) is the key enzyme in the salvage pathway responsible for breaking down MTA into 5-methylthioribose-1-phosphate (MTR-1P) and adenine. Notably, MTAP deletion is frequently found in various human tumors, leading to alterations in methionine metabolism.[83,84] MTAP-deficient cancers are very sensitive to the inhibition of MAT2A and protein arginine N-methyltransferase 5 (PRMT5), likely due to the methionine dependence of tumor cells and MTA-mediated inhibition of PRMT5.[83] This vulnerability has emerged as a potential therapeutic strategy for cancer treatment.[84]

SAM DEPLETION SERVES AS A MAJOR CELLULAR MR EFFECT ENTAILING RESPONSIVE MECHANISMS

Intracellular SAM levels are maintained through a balance between synthesis and consumption. Upon MR, SAM levels decrease due to an imbalance in synthesis resulting from the lack of the precursor metabolite, methionine. SAM depletion directly suppresses SAM-dependent reactions sensitive to changes in SAM levels (Figure 2). In yeast, SAM depletion signals nutrient starvation and facilitates cellular adaptation through SAM-mediated mechanisms. These include PP2A methylation-dependent regulation of autophagy [85] and SAM-sensitive histone methylation [40,82] (Figure 2). Interestingly, recent research demonstrates that MR-induced SAM depletion modulates antitumor immunity by altering the methylation status of cyclic GMP-AMP synthase (cGAS).[86] SAM-sensitive demethylation of cGAS under MR enhances its activation by suppressing binding and sequestration to chromatin [86] (Figure 2). Moreover, SAM depletion can be directly sensed by SAMTOR, a SAM sensor transmitting an inhibitory signal to mTORC1 signaling [87] (Figure 2). In addition, MR can also lead to reductions in SAH levels, implicated in lifespan extension through the modulation of hepatic DNA methylation decrease.[88]

SULFUR METABOLISM IN MITOCHONDRIA

Mitochondrial SAM transport

SAM is essential for many mitochondrial processes such as the biosynthesis of biotin and lipoate, as well as the methylation of mitochondrial rRNA.[89] Mitochondria contain approximately 30% of the total cellular SAM content,[90] predominantly relying on a SAM-specific transporter to import SAM from the cytosol, where it is synthesized (Figure 3). Both yeast and mammalian cells possess a single SAM transporter, encoded by *SAM5*[91] and *SLC25A26*,[61] respectively. Mutations in the SAM transporter gene are associated with a disorder syndrome characterized by respiratory insufficiency, cardiopulmonary failure, and muscle weakness.[92] These mutations inhibit mitochondrial functions, including mitochondrial translation and lipoate biosynthesis.[92,93] Overexpression of the SAM transporter can lead to decreased oocyte maturation and embryonic lethality.[94] The SAM transporter, known as SAMC, functions as an antiporter, facilitating SAM import into mitochondria and SAH export in the opposite direction.[61] Regulation of this process remains unknown. However, it is likely that information regarding cytosolic SAM levels is relayed to the mitochondria via this transporter. Consequently, SAM-sensitive reactions within mitochondria can respond by modulating mitochondrial functions.

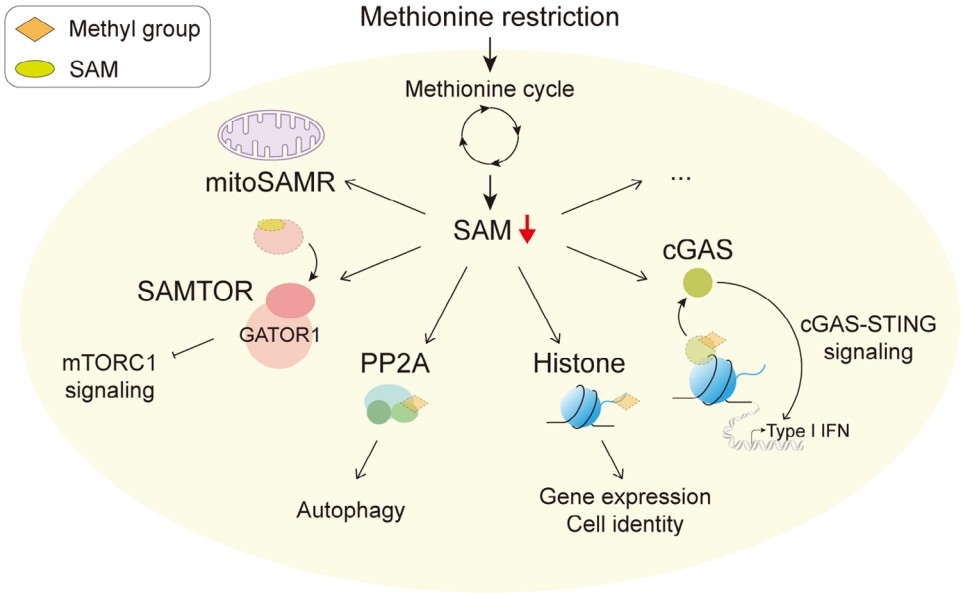

FIGURE 2 SAM depletion serves as a major cellular MR effect promoting responsive mechanisms. Cellular SAM depletion can activate various mechanisms to adapt to MR. Effectors of MR include SAM-dependent methylation substrates, such as PP2A, histones, and cGAS. SAMTOR acts as a direct sensor of SAM, inhibiting mTORC1 signaling in response to SAM depletion. Additionally, mitochondria respond to SAM depletion by activating mitoSAMR signaling to balance mitochondrial outputs between energy production and nitrogenous anabolism.

Mitochondrial GSH transport

Mitochondria lack the enzymes necessary for synthesizing GSH. Therefore, GSH molecules must be transported from the cytosol to provide protection against oxidative damage from reactive oxygen species generated in the electron transport chain.[95] Recent studies have demonstrated that *SLC25A39* is essential for importing mitochondrial GSH [96,97] (Figure 3). Genetic analyses have revealed that the loss of *SLC25A39* results in a dependence on a paralogue transporter encoded by *SLC25A40* for maintaining the activity of Fe-S clusters [96] and on the iron transporter encoded by *SLC25A37* for mitochondrial oxidative phosphorylation.[97] These findings underscore the collaborative roles of mitochondrial carriers in transmitting metabolic signals across different cellular compartments.

Biosynthesis of coenzyme (CoA) and iron-sulfur (Fe-S) cluster

CoA is an indispensable thiol compound widely used in metabolic systems. It often acts as an acyl carrier, facilitating group transfer and fatty acid β-oxidation. CoA biosynthesis occurs in both the cytosol and mitochondria, utilizing pantothenate and cysteine as precursors (Figure 3). CoA synthase, a bifunctional enzyme, catalyzes the final two steps of CoA synthesis within mitochondria.[98] Alternatively, dephosphocoenzyme A (dPCoA) is transferred to the cytosol, where it is phosphorylated by dPCoA kinase to produce CoA.[99] The biosynthesis of CoA requires coordination between compartment-specific enzymes. Mitochondrial CoA transporters further contribute to maintaining the mitochondrial pools of CoA [99] (Figure 3).

Fe-S clusters represent one of the most ancient protein cofactors present in nearly all kingdoms of life. Fe-S clusters in the forms of [2Fe-2S], [3Fe-4S], and [4Fe-4S] have a wide range of redox potentials and serve as electron transfer for a variety of biological processes.[100] The biogenesis of Fe-S proteins involves the synthesis, trafficking, and assembly into apoproteins. In eukaryotic cells, this process is catalyzed by highly conserved, complex protein machineries. Dysfunction in Fe-S protein biogenesis is associated with numerous human disorders, including the neurodegenerative disease Friedreich's ataxia.[101,102] Fe-S clusters are exclusively synthesized within mitochondria. Fe-S proteins can be assembled in the mitochondria or the cytosol by distinct machinery [103] (Figure 3). The cytosolic Fe-S protein assembly machinery uses the sulfur-containing factor generated by the mitochondrial Fe-S protein assembly machinery to produce Fe-S proteins in the cytosol and nucleus.[103] Although cysteine provides the activated sulfur atom for Fe-S cluster assembly, the mechanisms of mitochondrial cysteine transport remain poorly understood.[104] The activity of mitochondrial cysteine transport and the availability of mitochondrial sulfur moieties can influence Fe-S cluster biosynthesis, thereby regulating various biological processes dependent on Fe-S clusters, such as mitochondrial lipoate synthesis and energy production.[103]

Lipoate and lipoylation

Lipoate is a sulfur-containing fatty acid, a modified form of octanoate where one hydrogen atom at each of C6 and C8 is replaced by

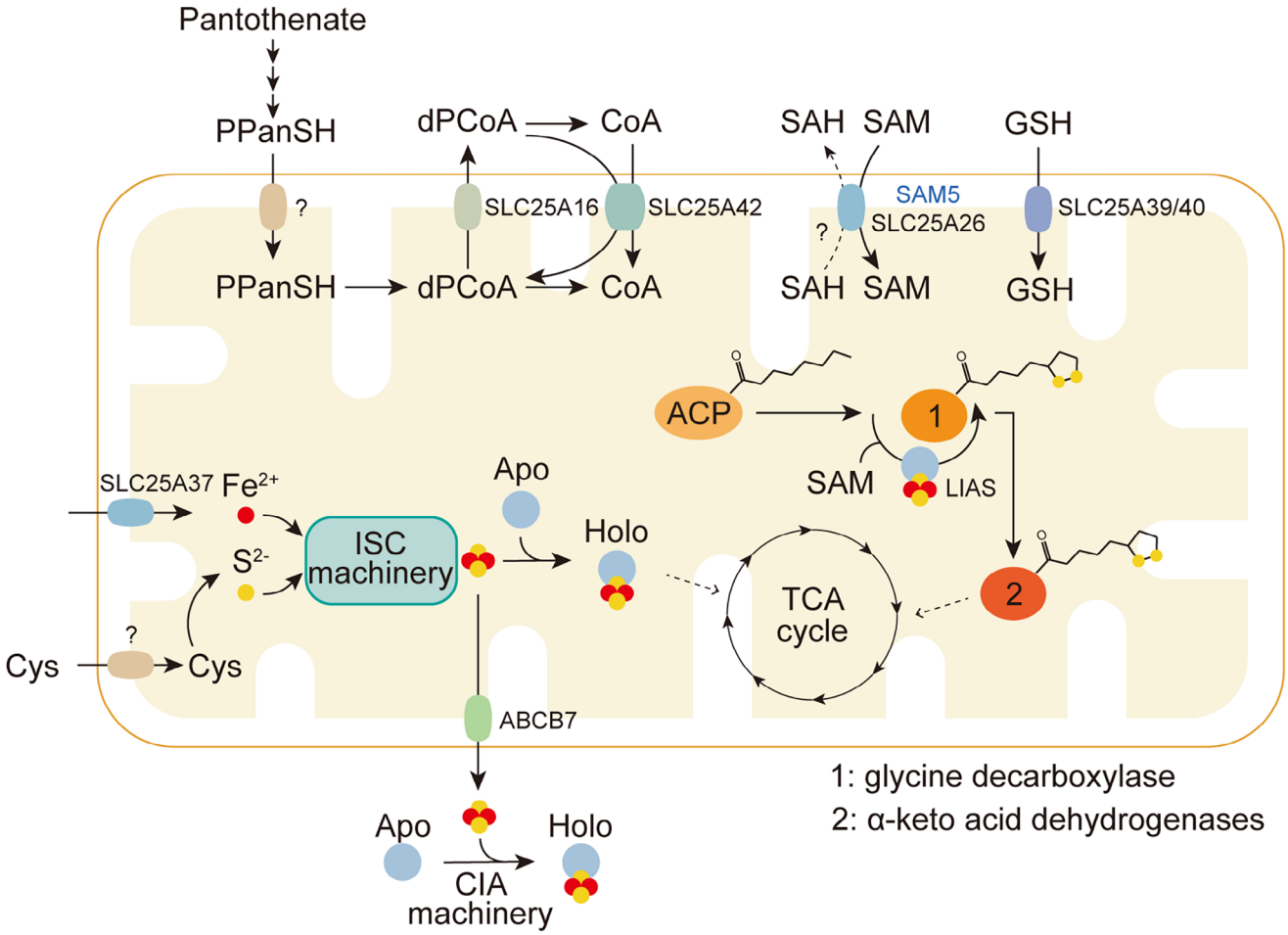

FIGURE 3 Sulfur metabolism in mitochondria. Sulfur-containing molecules such as SAM and GSH are transported across the inner mitochondrial membrane via mitochondrial carriers. Cysteine serves as the sulfur source for the biosynthesis of Fe-S clusters, which is crucial for various cellular functions. Fe-S clusters, in turn, contributes sulfur atoms to the synthesis of lipoate, a process dependent on radical SAM enzymes. Lipoylation of PDH and KDH is essential for the proper functioning of the TCA cycle. Key abbreviations: PPanSH, 4′-phosphopantetheine; dPCoA, dephosphocoenzyme A; ACP, acyl carrier protein; ISC, iron-sulfur cluster; CIA, cytosolic iron-sulfur cluster assembly; Apo, apoprotein; Holo, holoprotein.

sulfur. Lipoylation refers to the posttranslational modification of protein lysine residues with lipoate. Commonly observed lipoyl enzymes include mitochondrial metabolic enzymes such as glycine decarboxylase and α-keto acid dehydrogenases (pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase (KDH), branched-chain α-keto acid dehydrogenase). Lipoylation is crucial for the catalytic activity of α-keto acid dehydrogenases, while glycine decarboxylase acts as a carrier protein for lipoyl transfer.[105] In eukaryotes, lipoate synthesis and lipoylation occur in mitochondria via a multistep reaction requiring SAM and Fe-S clusters [106,107] (Figure 3). Lipoylation is matured from an octanoyl group attached to the glycine decarboxylase protein via a radical SAM enzyme-catalyzed sulfur insertion [108] (Figure 3). The resulting lipoyl group is then transferred to modify the α-keto acid dehydrogenases (Figure 3). While bacterial cells can use free lipoate for lipoylation,[109] eukaryotic lipoylation is highly relied on and coupled to the *de novo* synthesis of mitochondrial lipoate.[110] This is evidenced by the fact that protein lipoylation defects resulting from disruption of the *de novo* synthesis cannot be rescued by lipoate supplementation.[111–113] Thus, lipoate biosynthesis can become a limiting factor under certain metabolic environments, and the constriction of lipoylation forces cells to reprogram mitochondrial metabolism, such as the tricarboxylic acid cycle (TCA) cycle, via their catalytic reactions requiring this modification. A recent study has demonstrated that MR constrains mitochondrial lipoylation, revealing an underappreciated role of this modification in linking sulfur nutrient status with metabolic regulation.[52]

MULTIPLEXING ROLES OF MITOCHONDRIA IN CELLULAR METABOLISM AND STRESS SIGNALING

Mitochondria are double membrane-bound organelles found in most eukaryotes. During billion years' evolution of endosymbiosis, mitochondria have become the powerhouse of the cell for energy production, a metabolic hub for biosynthetic processes, and a regulation center for stress responses.[50] As a bioenergetics compartment and

a biosynthetic compartment, mitochondria catabolize sugars and fatty acids to produce energy while generating numerous cofactors like Fe-S clusters and biosynthetic precursors essential for synthesizing amino acids, nucleotides, and fatty acids. The coordination of mitochondrial functions in bioenergetics and biosynthesis is often facilitated by sentinel metabolic processes. For example, mitochondrial fatty acid synthesis (mtFAS), dependent on mitochondrial acetyl-CoA, can directly modulate mitochondrial bioenergetics by regulating the assembly of the electron transport chain.[114] This renders mtFAS a sensor for mitochondrial acetyl-CoA availability, allowing mitochondrial metabolism to adapt to changes in the metabolic status of the cell.[115]

As a center for stress responses, mitochondria undergo fusion and fission, a dynamic process adapting mitochondrial morphology and networks to metabolic needs of stressed cells.[116] Under physiological and pathological conditions, defective mitochondria can be eliminated through mitophagy to maintain cellular homeostasis. Mitochondria also serve as a platform to initiate and propagate signals from various cellular stresses [117] and have a critical role in regulating many forms of cell death.[118] The impairment of mitochondrial integrity and function activates mitochondrial unfolded protein responses (UPR^{mt}), a transcriptional program promoting mitochondrial biogenesis and metabolic adaptation.[119] Under amino acid stress, mitochondrial-derived compartments (MDC) are released to facilitate cellular adaptation by regulating nutrient transporters.[120] The multifaceted roles of mitochondria rely on their communication with the surrounding environment. However, how changes in nutrient status and the metabolism outside of mitochondria may transduce mitochondrial signaling remains largely unknown.

MR STIMULATES MITOCHONDRIAL STEPS FOR ARGININE AND LEUCINE BIOSYNTHESIS

Methionine is a vital nutrient containing organic sulfur. Cellular methionine and SAM levels are tightly regulated under MR and nutrient deficiencies, resulting in the autonomous preservation and replenishment of their cellular contents.[121–123] However, these regulatory feedback mechanisms may vary in different cultured cells and among tissues composed of different cell types. As such, many MR-responsive metabolic events are left unexplored. A study in budding yeast, utilizing genetic mutants that block cellular restoration of methionine and SAM, demonstrates a rapid accumulation of nitrogenous metabolites under MR.[52] This accumulation of amino acids is specifically attributed to an MR-induced decrease in cellular SAM content rather than methionine itself.[52] Isotopic tracing and absolute quantification of amino acid levels reveal that under MR, for the amino acids whose synthesis involves mitochondrial reaction steps, their accumulation is due to active synthesis.[52] Notably, arginine synthesis is particularly prominent, with the amount of arginine produced within 30 min exceeding 170% of all other proteinogenic amino acids.[52] Given that active synthesis of arginine promotes cell survival under MR,[52] the activation of arginine synthesis likely represents an adaptive response of mitochondria to SAM depletion.

In budding yeast, the synthesis of arginine involves the capture of mitochondrial acetyl-CoA molecules by the arginine metabolon, comprising acetyl-glutamate synthase and a dual-function enzyme responsible for catalyzing acetyl-glutamate phosphorylation and a reduction reaction.[124] The resulting product acetyl-glutamate irreversibly enters the acetyl cycle and exits to form ornithine, a precursor metabolite in arginine biosynthesis (Figure 4). Acetylation channels mitochondrial glutamate towards arginine synthesis under MR,[125] deviating α-ketoglutarate from the TCA cycle to produce glutamate (Figure 4). Therefore, MR-induced arginine synthesis occurs at the expense of fuel metabolites for energy production.[52] A serendipitous discovery is the leucine auxotrophy resulting from genetically blocking both mitochondrial SAM uptake and glutamate acetylation, revealing an unexpected hyper-activation of leucine biosynthesis in the mitochondria of MR.[52] Mitochondrial acetyl-CoA, if occluded from the TCA cycle and the arginine metabolon, readily enters the leucine biosynthesis pathway (Figure 4), synthesizing 2-isopropylmalate (2-IPM) by condensing with 2-keto-isovalerate.[126] 2-IPM directly activates the transcription of metabolic genes,[126] boosting the synthesis of branched-chain amino acids with the consumption of the end-product of glycolysis, pyruvate (Figure 4). As such, this metabolic program diverts pyruvate into branched-chain amino acid synthesis, further exacerbating incomplete glucose oxidation.[52] Under mitochondrial SAM adequacy, we propose that a general hierarchy of acetyl-CoA allocation in mitochondrial metabolism in budding yeast is as follows: the TCA cycle for energy production > the acetyl cycle for arginine synthesis > 2-IPM production for leucine synthesis.[52] By monitoring mitochondrial SAM adequacy, mediated by mitochondrial enzyme lipoylation states, acetyl-CoA hierarchically flows into energy metabolism. Upon MR, mitochonrial SAM depletion-induced response (mitoSAMR) functions to achieve a trade-off between energy metabolism and nitrogenic synthesis of amino acids by directing mitochondrial acetyl-CoA flow (Figure 4).

LIPOYLATION IS A SENTINEL MODIFICATION THAT SIGNALS CYTOSOLIC SAM DEPLETION TO MITOCHONDRIA

How is the TCA cycle sensitized and mitochondrial acetyl-CoA flow directed during MR? The answer turns out to be the regulation of lipoate metabolism.[52] Glucose oxidation in the TCA cycle requires lipoylation of the mitochondrial enzymes PDH and KDH.[52] Under MR, lipoate biosynthesis, a radical SAM-dependent process exclusive to the mitochondria, is constrained by mitochondrial SAM availability.[52] Lipoate limitation thus acts as a signal to reduce the carbon oxidation capacity of the TCA cycle, redirecting carbon flow towards the nitrogenic synthesis of amino acids, such as arginine and leucine. PDH and KDH lipoylation exhibits different sensitivities to alterations in cellular SAM levels (Figure 4). In budding yeast, KDH lipoylation is more responsive and becomes greatly restrained upon SAM depletion.[52] This is likely due to the sequential transfer of the lipoyl group from the carrier protein glycine decarboxylase to PDH and then to the

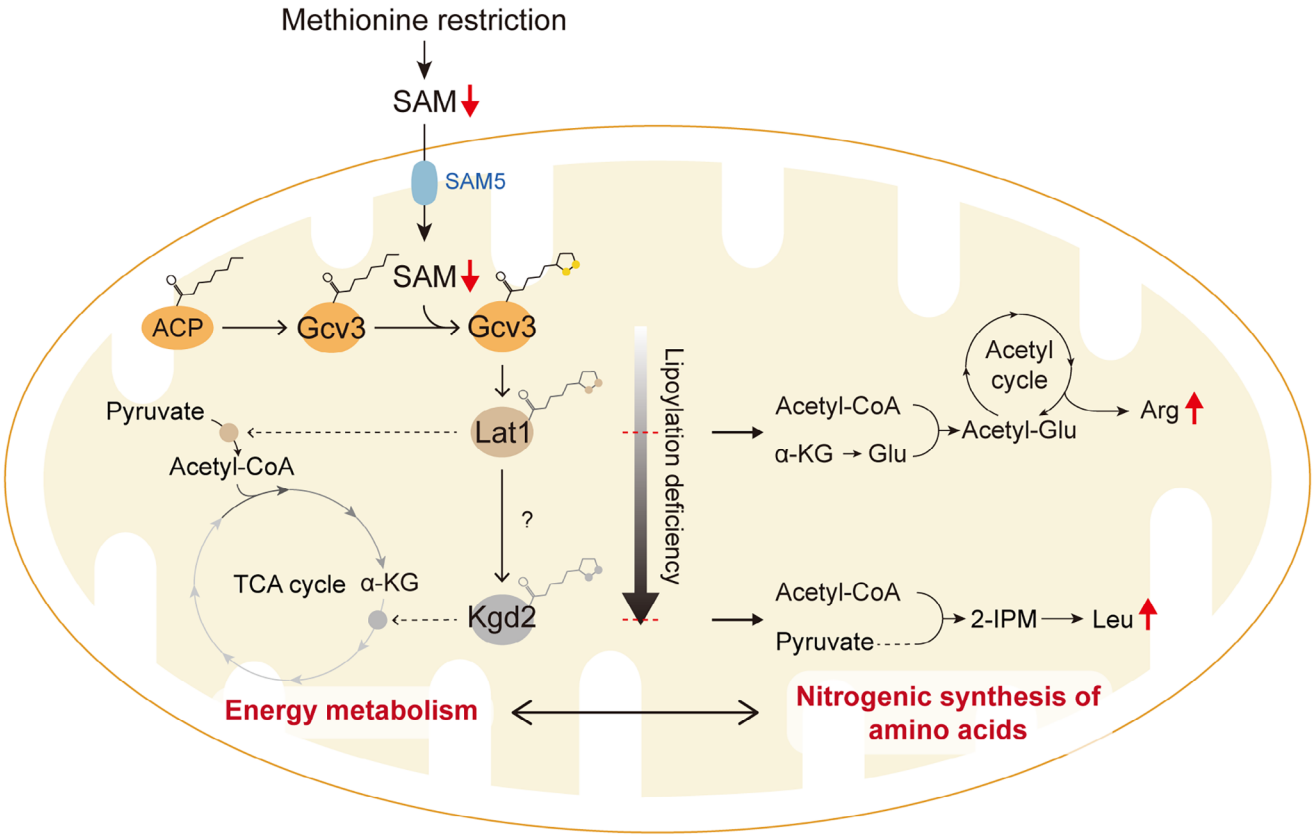

FIGURE 4 The working model of mitoSAMR. A model illustrating the mechanism of mitoSAMR signaling in budding yeast. The activation of mitoSAMR signaling under MR is characterized by differential regulation of lipoylation in the KGD complex and the PDH complex. Key abbreviations: Gvc3, glycine cleavage system H protein; 2-IPM, 2-isopropylmalate; Lat1, E2 subunit of PDH complex; Kgd2: E2 subunit of KDH complex.

final recipient KDH [52,113] (Figure 4). The differential sensitivity of lipoylation likely invokes the metabolic shunt of acetyl-CoA and α-ketoglutarate towards arginine biosynthesis under MR. However, another study shows that the lipoylation of KDH does not require the presence of PDH. The contrasting results may arise from differences in genetic backgrounds of yeast strains and culture conditions. For example, while one study utilized the prototrophic CEN.PK yeast strain, the other employed the auxotrophic BY4741 yeast strain.[127] Mutations in amino acid biosynthesis genes altering cellular metabolism could potentially influence the hierarchy of lipoyl group transfer, a process sensitive to metabolic states. Additionally, a recent study demonstrates that mitochondrial protein lipoylation is dispensable under hypoxia,[128] suggesting that the lipoylation process may be influenced by growth conditions affecting oxygen availability, such as growth stages. Nevertheless, these findings suggest that the sequential transfer of the lipoyl group may be a regulated process. Elucidating the regulation of lipoylation hierarchy is an intriguing subject of research warrants further investigations.

To form a functional α-keto acid dehydrogenase complex, each E2 subunit of the PDH and KDH complexes requires at least one lipoyl group.[129] Yeast and mammalian cells typically harbor 20~60 E2 subunits.[130,131] The abundant presence of these protein complexes in mitochondria underscores the necessity for an active flow of lipoate biosynthetic reactions within the organelle. Considering factors such as location, quantity, and SAM-responsive synthesis of lipoate, we propose that lipoylation serves as a mitochondrion-specific SAM effector, playing a key role in coordinating mitochondrial metabolism in response to fluctuations in cellular SAM levels. Serving as a sentinel modification lipoylation provides an avenue for exploring the spatial regulation of SAM homeostasis within mitochondria.

IS THE MITOSAMR SIGNALING CONSERVED IN MAMMALIAN SYSTEMS?

The lipoate-mediated mitoSAMR signaling is uncovered in the eukaryote model of budding yeast, relying on the sole mitochondrial SAM carrier to relay the information of cytosolic SAM alteration to the mitochondria. Given the similarities in lipoate biosynthesis and lipoylation between yeast and mammals, it is possible that the mitoSAMR signaling is conserved. However, there are several notable differences between yeast and mammals. While no lipoamidase has been reportedly identified in yeast, mammalian cells possess the lipoamidase SIRT4, which can remove lipoyl groups from PDH, thereby regulating its activity.[132] Therefore, in mammals, lipoylation is not solely subject to passive regulation by the constraint of cellular SAM, but

can be erased by lipoamidase. The presence of an enzyme hydrolyzing the lipoamide cofactors adds another layer of regulation to the mitoSAMR signaling in mammalian systems, likely resulting in a more complex lipoylation hierarchy. As mitochondrial anabolic processes for amino acid synthesis differ between yeast and mammals, it is unsurprising that mitoSAMR signaling, if conserved in mammals, may activate a metabolic response not identical as observed in yeast. Acetyl-glutamate acts as an obligatory allosteric activator of mammalian carbamoyl phosphate synthetase,[133] a mitochondrial enzyme required for arginine biosynthesis. Since the synthesis of acetyl-glutamate requires acetyl-CoA and occurs in mitochondria, modulation of the metabolic flow of acetyl-CoA and arginine biosynthesis can still be an important function of the lipoylation-mediated mitoSAMR signaling if conserved in mammals. To this end, we highlight several pressing questions for further exploration in the study of mitoSAMR signaling in mammals: What physiological or pathological conditions can trigger the activation of mitoSAMR signaling in mammals? What are the key players in mammalian mitoSAMR signaling, such as lipoamidase and cellular SAM levels? Is the trade-off regulation of mitochondrial functions between bioenergetics and amino acid biosynthesis still the primary outcome of mitoSAMR signaling in mammals?

CONCLUSIONS

As vital hubs for cellular metabolism, mitochondria contribute to coordinating metabolic responses to MR. In budding yeast, the characterization of mitochondrial lipoate biosynthesis and lipoylation in regulating the TCA cycle and nitrogenic synthesis of amino acids provides a promising avenue for understanding the role of mitochondria in metabolic adaptation under MR. The lipoate-mediated mitochondrial reprogramming of energy metabolism may represent a key mechanism underlying the benefits of MR. However, future research is warranted to investigate if this mitoSAMR signaling is conserved and capable of promoting metabolic fitness in mammalian systems.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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