PERSPECTIVE

Perspective: Methionine Restriction–Induced Longevity—A Possible Role for Inhibiting the Synthesis of Bacterial Quorum Sensing Molecules

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ABSTRACT

Methionine restriction (MR) extends lifespans in multiple species through mechanisms that include enhanced oxidative stress resistance and inhibition of insulin/insulin-like growth factor I (IGF-I) signaling. Methionine and *S*-adenosylmethionine (SAM) are the essential precursors of bacterial quorum sensing (QS) molecules, and therefore, MR might also affect bacterial communication to prevent enteric bacterial infection as well as chronic inflammation, which contributes to lifespan prolongation. Here, we discuss the influence of MR on oxidative stress resistance and inhibition of insulin/IGF-I cell signaling and further propose a potential mechanism involving bacterial QS inhibition for lifespan extension. Unraveling the connection between MR and inhibition of QS provides new strategies for combating infectious diseases, resulting in enriched understanding of MR-induced lifespan extension. *Adv Nutr* 2020;11:773–783.

Keywords: methionine restriction, lifespan, oxidative stress, insulin/IGF-I, quorum sensing

Introduction

Methionine is an essential amino acid that promotes growth (1), improves immunity (2, 3), enhances antioxidant function (4), regulates energy metabolism (5), and improves reproductive performance (6). Over the past several decades, research has focused on the beneficial effects of methionine supplementation (dietary dosage of methionine exceeding the animal requirements) in various species (**Table 1**). However, there is evidence that excess methionine intake (2 times higher compared with a basal diet) results in growth retardation and atherosclerosis in *Apoe*-deficient mice, which is referred to as "methionine toxicity" (7). Methionine restriction (MR), a partial depletion of methionine from dietary nutrition, is proposed to improve health by increasing energy expenditure, regulating protein homeostasis, and improving antioxidant functions and gut microbiota functions (Table 1) (8–10). Notably, MR as an approach to prolonging lifespan has been validated extensively in various animal models, such as *Caenorhabditis elegans*, *Drosophila*, yeast, and mice (11–14). Mechanisms by which MR extends lifespan may include growth hormone signaling, nutritional factors, and mitochondrial function (15).

Considering that the intestinal microflora regulates various crucial metabolic and immune responses of the host

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Abbreviations used: AHL, acyl-homoserine lactone; AI, autoinducer; AI-2, autoinducer-2; CAI-1, cholerae autoinducer-1; CBS, cystathionine β-synthase catalysis; CGL, cystathionine γ-lyase; ETEC, enterotoxigenic *Escherichia coli*; GHRKO, growth hormone knockout; IGF-I, insulin-like growth factor I; MR, methionine restriction; QS, quorum sensing; ROS, reactive oxygen species; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine.

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TABLE 1 Influence of methionine supplementation or restriction on physiologic function in different animals[1]

Animal models	Methionine dosage compare with control	Main findings	Reference
Met supplementation			
IUGR piglets	30% supplementation	Improves intestinal integrity and oxidative status in weaning piglets	(16)
Pregnant sows	33% supplementation	Increases antioxidant capacity and alters intestinal microbiota of offspring	(17)
Broilers	71% supplementation	Improves growth performance and breast muscle yield	(18)
Infected seabass[2]	100% supplementation	Fosters plasma cortisol levels and promotes immune cells proliferation during inflammatory insult	(19)
SD hypertensive rats	120% supplementation	Enhances aortic constriction but decreases responsiveness to acetylcholine, bradykinin, and sodium nitroprusside	(20)
Mice	133% supplementation	Induces atherosclerosis and increases the aortic lesion area	(7)
CSE-deficient mice	400% supplementation	Induces acute lethal hepatitis and splenic atrophy	(21)
Met restriction			
Rats	40% reduction	Decreases mitochondrial oxygen radical production and lowers oxidative damage to proteins and mitochondrial DNA	(22)
Rats	80% reduction	Improves epithelial barrier function by inducing altered tight junctional protein composition	(23)
Mice	80% reduction	Increases energy expenditure by 31% and reduces adiposity by 25%	(24)
Mice	80% reduction	Produces therapeutic responses in colorectal cancer by changing one-carbon metabolism	(25)
Mice	80% reduction	Enhances suppression of hepatic glucose production by insulin; enhances insulin-dependent Akt phosphorylation in the liver; increases hepatic expression and circulating FGF-21	(26)
Mice	86% reduction	Induces bone marrow fat accretion through the body; decreases cortical bone tissue density; decreases bone tissue density, bone surface, trabecula, bone volume, and trabecular thickness	(27)
Mice	86% reduction	Modulates renal response and attenuates kidney injury	(28)

[1] Methionine supplementation or restriction is compared with the basal dietary in different animals. CSE, cystathionine γ-lyase; FGF, fibroblast growth factor; IUGR, intrauterine growth retardation; SD, Sprague-Dawley.
[2] *Photobacterium damselae* subsp. *Piscicida* infection.

(29–31), the gut microbiota also affects the lifespan. For example, polysaccharide colanic acid (a polysaccharide metabolite secreted by multiple enterobacteria species) increases the lifespan of the host by regulating mitochondrial dynamics and unfolded protein responses (32). Although *Lactobacillus plantarum* promotes lifespan, the overgrowth of *L. plantarum* shortens lifespan in flies through a complex mechanism involving lactic acid secretion and production of reactive oxygen species (ROS) (33). Therefore, the preservation of commensal microbiota homeostasis is pivotal for preventing age-associated pathologies and even expanding the lifespan of the host. Bacterial infection is one of the threats to intestinal microbiota homeostasis and is also the pathogeny of some age-associated diseases, such as diarrheal diseases, lower respiratory infections, and pneumococcal meningitis (34). Bacterial quorum sensing (QS) is necessary for the expression of virulence genes during infection, and QS inhibition has been considered as a potential antivirulence strategy. *S*-adenosylmethionine (SAM), a methionine metabolite, is the essential precursor of several QS signaling molecules, such as acyl-homoserine lactones (AHLs), autoinducer-2 (AI-2), and cholerae autoinducer-1 (CAI-1) (35). Thus, MR may extend lifespan by inhibiting the bacterial QS system. In this perspective, we try to summarize the mechanism of MR-induced lifespan extension, with special emphasis on antioxidative capacity and insulin/insulin-like growth factor I (IGF-I) signaling. More importantly, we propose a mechanism involving the inhibition of the bacterial QS system for MR-induced lifespan extension.

Widely Accepted Mechanisms of MR-Induced Lifespan Extension

As early as the last century, investigations on aging reversal and lifespan prolongation received a great deal of attention. In fact, a recent report indicated that the heritability of longevity (h^2) is only 16%, which is considerably lower than expected (36). Apart from genetic factors, dietary and environmental factors seem to play important roles in lifespan control. In particular, dietary MR prolongs lifespan, possibly through promoting proteostasis balance, reducing oxidative damage, and modulating mitochondrial activity (37–39), but there still exist some challenges to be elucidated in these theories. Therefore, the exact mechanism by which MR modulates lifespan remains to be well studied, and in this paper, we examine the information on the recent progress in MR-induced lifespan prolongation.

MR Postpones Senility by Reducing Oxidative Stress

Free radicals accumulate in mitochondria as a function of time, resulting in the irreversible damage of various cellular biomolecules (e.g., unsaturated fatty acids, proteins, and nucleic acids), cellular senescence, and age-related diseases

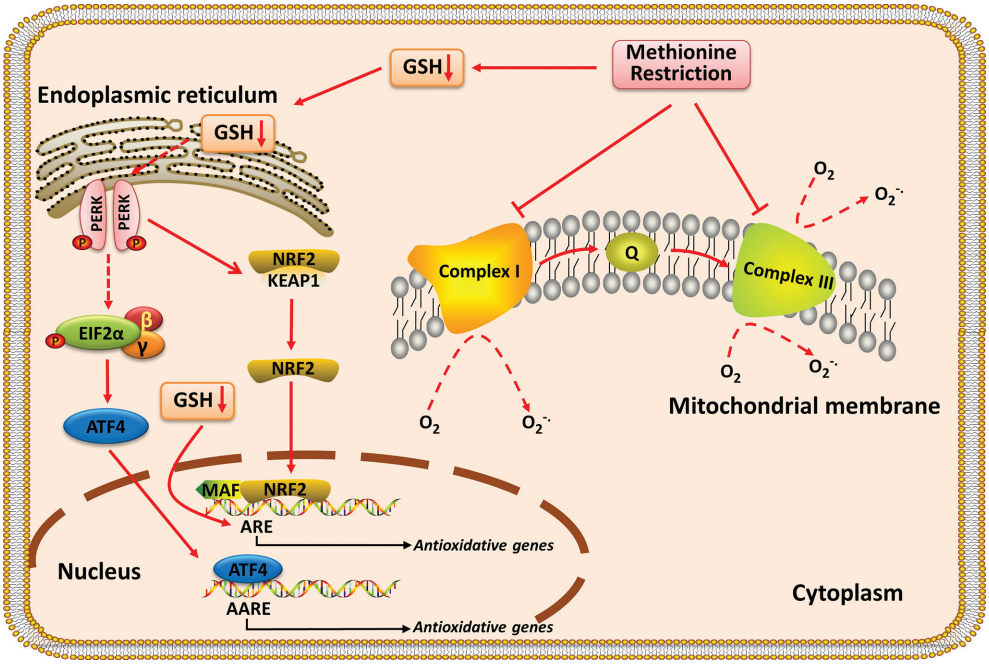

FIGURE 1 Diagrams of MR-induced oxidation resistance. Reduced intake of methionine in the diet reduces glutathione biosynthesis, and GSH deprivation promotes the phosphorylation of PERK. Activated PERK represses the reassociation of NRF2/KEAP1 complexes to induce transport of the NRF2 protein into the nucleus, where NRF2 preferentially combines with the small MAF protein to bind to the ARE and activate the expression of genes for multiple antioxidant enzymes, like NQO1, CAT, HO-1, GSTs, and GCL. GSH deprivation also induces ARE activity to enhance the NRF2 transcriptional response. In addition to activating the expression of NRF2, phosphorylated PERK triggers the α-subunit of EIF2, which further activates ATF4 and the downstream antioxidative genes. Moreover, MR treatment lowers mitochondrial ROS production by affecting complexes I and III, which are principal sites of mitochondrial ROS production on the mitochondrial membrane, converting O_2 to the strong oxidizing superoxide ($O_2^{-\bullet}$). The lines show the interactions between the players, with arrows indicating activation and hammerheads indicating repression. AARE, amino acid–responsive element; ARE, antioxidant response element; ATF4, activating transcription factor 4; CAT, catalase; EIF2-α, α-subunit of eukaryotic initiation factor 2; GCL, glutamate-cysteine ligase; GSH, glutathione; GST, glutathione S transferase; HO-1, heme oxygenase-1; KEAP1, Kelch-like ECH-associated protein 1; MAF, small Maf protein; MR, methionine restriction; NQO1, NAD(P)H quinone oxidoreductase 1; NRF2, nuclear respiratory factor 2; PERK, protein kinase R–like endoplasmic reticulum kinase; Q, ubiquinone; ROS, reactive oxygen species.

(e.g., hypertension, atherosclerosis, and Alzheimer disease) (40, 41). Therefore, strategies to neutralize or scavenge mitochondrial free radicals may postpone senility and extend lifespan. It has been hypothesized that MR-induced lifespan prolongation is due to attenuated oxidative stress. MR is one of the robust nutritional interventions to mitigate oxidative stress in mammals and birds through promoting the expression of antioxidative genes and inhibiting the production of mitochondrial ROS (**Figure 1**) (42–54). In the MR condition, although higher resistance to oxidative stress is observed in long-lived mammals, there is a lack of direct evidence to demonstrate that resistance to oxidative stress accounts for lifespan prolongation. In addition, the contribution of mitochondrial ROS production to lifespan control needs further clarification. Elevated mitochondrial ROS seems to be beneficial to lifespan prolongation due to the elevated ROS responsible for intrinsic apoptosis, which is crucial for lifespan prolongation in *C. elegans* (55). The site of mitochondrial ROS production also determines its effects on the lifespan of *Drosophila* based on the discovery that ROS produced through complex I, rather than complex II or III, rescues oxidative stress–induced pathogenesis, and extends the lifespan of *Drosophila* (56). As most evidence about MR-induced lifespan prolongation through attenuation of oxidative stress is from invertebrates, more investigations should be conducted to test this hypothesis in mammals and other long-lived animals. If the attenuation of oxidative stress accounts for MR-induced lifespan prolongation, other antioxidative measures (such as antioxidant supplementation) should also be beneficial for longevity. However, dietary supplementation of multiple antioxidants, such as vitamin C and vitamin E, has little effect on lifespan extension (57). Collectively, it is challenging for us to conclude that MR-induced longevity is mediated through the attenuation of oxidative stress. Thus, it remains to be determined through well-designed investigations if MR extends lifespan through attenuating oxidative stress.

MR Extends Lifespan by Regulating Insulin/IGF-I Cell Signaling

Inhibition of IGF-I signaling plays a positive role in lifespan extension in *C. elegans*, *Drosophila*, mice, and humans (58, 59). The possible mechanism involves increased resistance to organismic stressors and tumors (60). Inhibition of insulin/IGF-I signaling, such as mutations in insulin/IGF-I signaling and lowering circulating concentrations of insulin and IGF-I, can extend both the maximum and average lifespan in mammals and invertebrates, despite there being differences in insulin/IGF-I signaling between them (61–65). MR-treated mice have lower concentrations of insulin and IGF-I in plasma, as well as extended maximum and average lifespans (66–68). Similarly, mice with dysfunctional IGF-I synthesis [growth hormone knockout (GHRKO) and Ames dwarf mice] were found to exhibit a longer median lifespan (24% and 69%, respectively) than normal mice with adequate methionine intake (150% of methionine requirements) (69). However, there was no difference in median and maximal lifespan between the Ames dwarf or GHRKO mice and their wild-type counterparts when fed a severely methionine-deficient diet (20% of normal requirements) (69). Although these compelling results suggest that severe MR is highly correlated with insulin/IGF-I signaling in lifespan prolongation, a limitation of the study is that the author failed to explore the lifespan of GHRKO and Ames dwarf mice with a basal diet (100% of methionine requirements). In addition, the mechanism through which MR modulates insulin/IGF-I signaling needs to be elucidated in further investigations. In fact, dysfunctional IGF-I synthesis in mice enhances the methionine metabolism and modulates the related enzyme activity (70, 71); thus, MR regulates insulin/IGF-I signaling, possibly via the alteration of methionine metabolism.

MR may inhibit insulin/IGF-I signaling through the generation of hydrogen sulfide (H_2S), which decreases insulin and IGF-I production (72). Endogenous H_2S is synthesized by the catalysis of cystathionine γ-lyase (CGL) and cystathionine β-synthase catalysis (CBS) in the liver (**Figure 2**A). MR increases the enzymatic activities of CGL and CBS via the amino acid deprivation/integrated stress response pathway, leading to the production of hepatic H_2S (73, 74). In pancreatic β cells, endogenous H_2S inhibits insulin secretion by suppressing intracellular glucose metabolism and ATP production (75). H_2S also decreases the concentrations of IGF-I and thyroxine (T_4) in the blood (76). Therefore, H_2S likely mediates the inhibitory effect of MR on insulin/IGF-I cell signaling (**Figure 3**). However, MR extends the chronological lifespan of wild-type yeast, but it has little effect on the sulfate assimilation-related gene mutant (H_2S production deficiency) (77). Although this finding by Choi et al. queries the favorable effects of MR on longevity via H_2S production, it is noteworthy that such results arose from a yeast model–based study without endogenous H_2S able to regulate the insulin/IGF-I signaling while considering mammals with an endogenous H_2S effect. This suggests that MR induces lifespan extension in yeast through a signaling-independent mechanism different from H_2S or H_2S-related insulin/IGF-I. Studies and analyses of insulin/IGF-I signaling in the sulfate assimilation-related gene mutant without H_2S production are needed to determine the correlations between H_2S production and insulin/IGF-I signaling in yeast-based experiments.

Inhibition of insulin/IGF-I signaling is another potential mechanism of MR-induced lifespan extension in mammals; however, some research challenges this hypothesis. For instance, mutation of insulin receptors in peripheral tissues fails to prolong the murine lifespan (78). A possible explanation is that insulin signaling affects lifespan in a tissue-specific manner, such as a neuron-specific manner.

Perspective: MR May Prolong Lifespan by Modulating Intestinal Bacterial QS

There is increasing evidence for additional mechanisms whereby the intestinal microbiota manages the host lifespan. Modulation of the intestinal microbiota by caloric restriction reduces the antigen load to the host and is positively correlated with lifespan in animals (79). Although there have been few investigations on MR and the intestinal microbiota, MR may have a favorable regulatory effect on the profile of the intestinal microbiota (80). MR contributes to intestinal microbiota homeostasis, possibly by modulating the bacterial QS system by reducing the concentrations of methionine and SAM.

Methionine is transformed into SAM by the methionine adenosyltransferase (MAT) with ATP, and SAM is subsequently processed into *S*-adenosylhomocysteine (SAH) and decarboxylated SAM (dcSAM) to participate in cysteine and polyamine synthesis, respectively (Figure 2A). Methionine is the only synthetic precursor for SAM, and >80% of methionine in the liver is used to synthesize SAM (81). Dietary MR reduces the levels of SAM as well as the SAM to SAH ratio in the liver of mice, especially in young mice (72, 82, 83), which contributes to maintaining the free methionine concentration for protein synthesis. These observations demonstrate that, apart from limiting systemic SAM levels, MR also changes the metabolic pathway of SAM, which tends to favor the transmethylation pathway (84).

MR has a major influence on intestinal health, such as improving epithelial barrier function and suppressing the development of intestinal tumors (23, 85), whereas the influence of MR on the intestinal microbiota is not well known. SAM is the essential synthetic precursor in the biosynthesis of QS signal molecules, AHLs, AI-2, and CAI-1 (86) (Figure 2B), which coordinates bacterial activities in high-cell-density environments. QS regulates the expression of multiple genes and thereby controls bacterial behaviors, such as bioluminescence, motility, biofilm formation, virulence, and antibiotic production (**Table 2**). To achieve these behaviors, bacteria sense the signaling molecules autoinducers (AIs) released by other bacteria through membrane and cytoplasmic receptors.

The intestines of mammals harbor an extremely high density of intestinal bacteria, and the concentration and

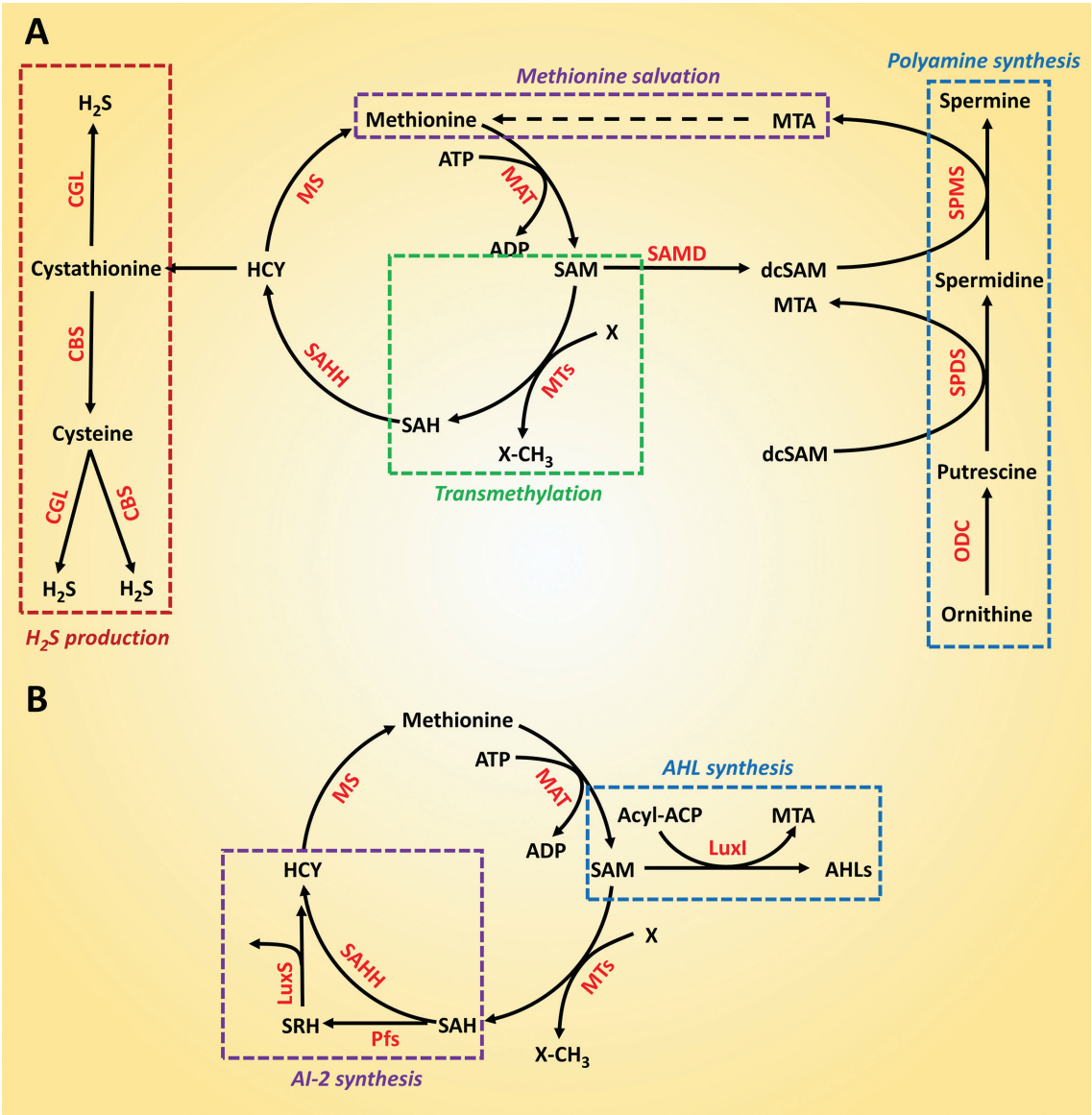

FIGURE 2 SAM metabolism and the synthesis of AI-2 and AHL. (A) Pathways of SAM metabolism through participation in the synthesis of cysteine and polyamines. (B) Methionine cycle and synthesis of AI-2 and AHL. In gram-negative bacteria, LuxI-type synthase catalyzes the biosynthesis of AHLs through bonding the lactone moiety with a particular acyl chain, which is derived from SAM and acyl-ACP, respectively. In this process, acyl-ACP is not the specific acyl chain donor because AHLs can also be synthesized from isovaleryl-CoA and SAM in the catalysis of BjaI (the LuxI homolog). Notably, no other lactone moiety sources, except SAM, are known to participate in the synthesis of AHLs. Similarly, AI-2 biosynthesis involves a series of enzymatic reactions in both gram-positive and gram-negative bacteria. SAM first generates the toxic intermediate SAH via the transmethylation pathway, and then SAH is hydrolyzed into SRH in the presence of Pfs; finally, SRH is converted into homocysteine and AI-2 in the catalysis of LuxS. The red letters represent the required enzymes in the pathway. acyl-ACP, acyl-acyl carrier protein; AHL, acyl-homoserine lactone; AI-2, autoinducer-2; CBS, cystathionine β-synthase catalysis; CGL, cystathionine γ-lyase; dcSAM, decarboxylated *S*-adenosylmethionine; HCY, homocysteine; H_2S, hydrogen sulfide; LuxI, acyl homoserine lactone synthase; LuxS, *S*-ribosylhomocysteine lyase; MAT, methionine adenosyltransferase; MS, methionine synthase; MTA, 5′-methylthioadenosine; MT, methyl transferase; ODC, ornithine decarboxylase; Pfs, *S*-adenosylhomocysteine nucleosidase; SAH, *S*-adenosylhomocysteine; SAHH, *S*-adenosylhomocysteine hydrolase; SAM, *S*-adenosylmethionine; SAMD, *S*-adenosylmethionine decarboxylase; SPDS, spermidine synthase; SPMS, spermine synthase; SRH, *S*-ribosylhomocysteine; X-CH_3, methylated products.

diversity of the QS signal molecules could be much higher than in any other ecosystem. Quorum sensing controls nearly 10% of gene expression in certain pathogens (87). For instance, the AHL and AI-2 signal molecules control bacterial bioluminescence and virulence factor secretion (e.g., extracellular toxins and metalloproteases) in *Vibrio harveyi* by activating the target gene *luxCDABE* (88, 89). In enterohemorrhagic *Escherichia coli*, AHLs and AI-2 also

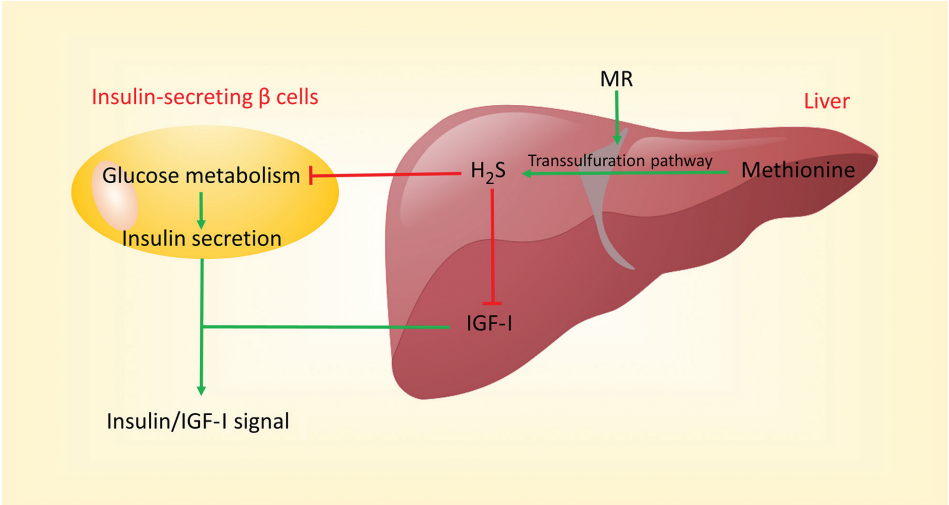

FIGURE 3 MR inhibits insulin/IGF-I cell signaling via the production of H_2S. In the liver, MR increases the endogenous production of H_2S by increasing cystathionine γ-lyase and cystathionine β-synthase catalysis activities. Subsequently, H_2S reduces the hepatic production of IGF-I, which may be partly responsible for the reduced circulating concentrations of T_4. H_2S also decreases the secretion of IGF-I by suppressing glucose metabolism in insulin-secreting β cells. The lines show the interactions among the players, with green arrows indicating activation and red hammerheads indicating repression. H_2S, hydrogen sulfide; IGF-I, insulin-like growth factor I; MR, methionine restriction; T_4, thyroxine.

affect the acid resistance of bacteria and the formation of attaching and effacing (A/E) lesions (90). Hence, disruption of bacterial QS signaling (also called quorum quenching) by inhibiting the synthesis of the QS signal, degrading QS signals, inhibiting QS signal diffusion, and blocking the binding of QS signals and receptor proteins is an effective therapeutic approach for combating bacterial infections (91, 92).

The strategies that suppress the production of AIs include inhibition of AI synthase and restrictions on levels of synthetic substrates, although most studies have focused on inactivation of AI synthase. Sinefungin, a methyltransferase

TABLE 2 The role of QS in the virulence expression of pathogenic bacteria[1]

Bacteria	Gram stain	QS signal molecule	Function	Reference
Staphylococcus aureus	G^+	AIP	Expression of hemolysins, enterotoxins, exfoliating toxins, enzymes, and surface proteins	(93, 94)
Streptococcus pneumoniae	G^+	CSP, BlpC	Uptake and recombination of exogenous DNA, formation of biofilms, and lysis of competitive bacteria	(95)
Pseudomonas aeruginosa	G^-	AHLs (OC12-HSL, C4-HSL)	Expression of genes involved in the production of rhamnolipids and components of the type III secretion system	(96, 97)
Agrobacterium tumefaciens	G^-	AHL (OC8-HSL)	Dissemination of the Ti plasmid by horizontal transfer	(98)
Chromobacterium violaceum	G^-	AHL (C6-HSL)	Bacterial aggregation, biofilm formation, swarming, production of pigment violacein, and alkaline exoprotease activity	(99)
Burkholderia glumae	G^-	AHL (C8-HSL)	Expression of flagellar biosynthesis genes and control of virulence, motility, and protein secretion	(100)
Escherichia coli	G^-	AHL, AI-2, AI-3, NE, Epi	Control of acid resistance and formation of A/E lesions	(90)
Vibrio harveyi	G^-	CAI-1, AHL, AI-2	Expression of virulence factors involved in biofilm formation, type III secretion, and production of chitinase A	(101, 102)
Yersinia pseudotuberculosis	G^-	AHLs (C6-HSL, C8-HSL)	Control cellular aggregation/flocculation and swimming motility	(103, 104)
Salmonella typhimurium	G^-	AI-2, AI-3, NE, Epi	Control of SPI-1 (*invF*, *sicA*, *sopB*, *sopE*) and flagellar (*fliC*, *fliD*) gene transcription	(105)

[1] A/E, attaching and effacing; AHL, acyl-homoserine lactone; AIP, autoinducing peptide; AI-2, autoinducer 2; AI-3, autoinducer 3; BlpC, bacteriocin-like peptide QS signals; CAI-1, cholerae autoinducer-1; CSP, competence-stimulating peptide; C4-HSL, N-butyryl homoserine lactone; C6-HSL, N-hexanoyl-L-homoserine lactone; C8-HSL, N–octanoyl–l–homoserine lactone; Epi, epinephrine; G^-, gram-negative bacteria; G^+, gram-positive bacteria; NE, norepinephrine; OC8-HSL, N-3-oxo-octanoyl-homoserine lactone; OC12-HSL, N-3-oxo-dodecanoyl-L-homoserine lactone; QS, quorum sensing; SPI-1, *Salmonella* pathogenicity island 1.

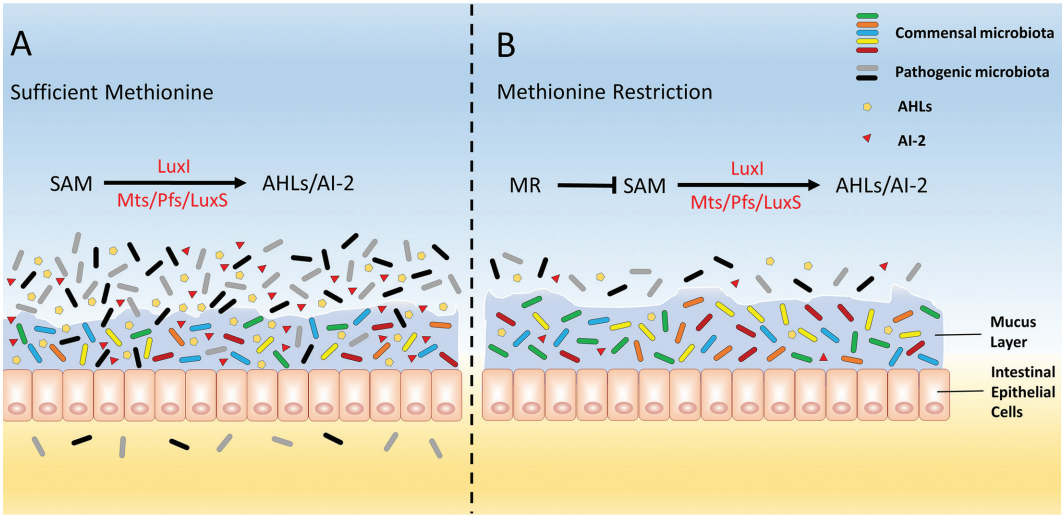

FIGURE 4 MR protection of the intestine from invasion by pathogenic bacteria. (A) When methionine is limited, the intestinal commensal microbiota and pathogenic microbiota utilize SAM to synthetize AHLs and AI-2 signaling molecules. Once the amounts of AHLs and AI-2 reach the threshold concentrations, they trigger the expression of a series of genes involved in bacterial bioluminescence, motility, biofilm formation, virulence, and antibiotic production via a complex regulatory cascade, eventually resulting in colonization of the intestine by pathogenic bacteria. (B) In the MR condition, the synthesis of AHLs and AI-2 is limited due to the deficiency in dietary methionine. Thus, the low abundances of AHLs and AI-2 fail to activate the expression of the bacterial behavior-related genes, which suppresses colonization of the intestine by pathogenic bacteria. AHL, acyl-homoserine lactone; AI-2, autoinducer 2; LuxI, acyl homoserine lactone synthase; LuxS, *S*-ribosylhomocysteine lyase; MR, methionine restriction; Mts, methyl transferases; Pfs, *S*-adenosylhomocysteine nucleosidase; SAM, *S*-adenosylmethionine.

inhibitor that suppresses transmethylation, decreases AI-2 production and downregulates the expression of *luxS*, *pfs*, and *speE* in *Streptococcus pneumoniae*, thereby inhibiting biofilm growth and colonization in vivo (106). Sinefungin also inhibits the methionine cycle of *S. pneumoniae*, which may alter the bacterial metabolites, biofilm formation, acid tolerance, and lactic acid production (107). Whether sinefungin treatment inhibits the biofilm growth and colonization by inhibiting AI-2 production or by inhibiting methionine metabolism remains to be determined. Several analogs of SAM, such as butyryl-SAM and sinefungin, inhibit LuxI-type synthase activity and decrease AHL production (108). Mechanistically, SAM serves as the essential precursor for the synthesis of AHLs and AI-2; therefore, SAM concentrations may directly influence the production of AHLs and AI-2. However, the quorum-quenching approach through targeting the SAM concentration has not been well investigated; we could consider that SAM is the crucial metabolic intermediate involved in transmethylation in mammals and pan-inhibition with a nonspecific approach, likely resulting in uncontrollable manifestations in the experimental animals. As MR is the available dietary intervention that decreases hepatic SAM production without adverse effects, MR is a potential quorum-quenching strategy to prevent pathogenic bacterial invasion.

Enteric bacterial infections trigger intestinal microbiota dysbiosis, intestinal inflammation, and cancer. For example, enterotoxigenic *Escherichia coli* (ETEC) infections increase the abundance of γ-aminobutyric acid (GABA)–producing bacteria to promote the expression of IL-17 and evoke intestinal chronic inflammatory disease through mechanistic target of rapamycin complex 1 (mTORC1) signaling (109, 110). In addition, various enteric bacterial infections (e.g., ETEC, *Salmonella enteritidis*, and *Shigella flexneri*) disrupt the intestinal barrier to increase intestinal permeability, thereby enabling the bacterial products (antigens) to enter the bloodstream to induce systemic inflammation. Long-term exposure to inflammation is adverse to health maintenance and lifespan prolongation because the chronic inflammatory status leads to macrophage dysfunction, oxidative stress, and inexorable tissue injury, which accelerates cellular senescence and metabolic syndrome (111). Consequently, the prevention of enteric bacterial invasion and maintenance of homeostasis of the intestinal microbiota are crucial for lifespan extension.

Based on the above analysis, we propose that dietary MR could protect the host intestine and even the whole body from pathogenic bacteria invasion because MR is an effective strategy for QS inhibition (**Figure 4**) that maintains the homeostasis of the intestinal microbiota and attenuates systemic inflammation. Hence, it is conceivable that MR-induced intestinal protection is also a possible mechanism of lifespan extension.

Conclusions

Despite MR having been shown to extend the lifespan of multiple species, the precise mechanism involved in this process has not been elucidated because the lifespan is controlled by numerous factors. Currently, the attenuation of

oxidative stress and inhibition of insulin/IGF-I signaling are the widely accepted mechanisms responsible for MR-induced lifespan extension. In addition, we propose that dietary MR is beneficial for preventing enteric pathogen invasion and maintaining homeostasis of the intestinal microbiota by inhibiting pathogenic QS, thereby preventing chronic inflammation and postponing senility.

QS also serves as a communication system for stabilizing commensal bacterial populations. For example, to overcome ammonia-mediated alkaline toxicity, *Burkholderia* bacteria produce oxalate in a QS-dependent manner to neutralize the alkaline metabolites (112). Additionally, manipulation of AI-2 contributes to the alleviation of antibiotic-induced intestinal microbiota dysbiosis, which is accomplished by favoring the expansion of *Firmicutes* bacteria and reducing *Bacteroidetes* bacteria (113). Therefore, another specific question is whether MR-induced quorum quenching affects the composition of intestinal commensal microbes. Unfortunately, due to the presence of multiple QS signals in the mammalian intestine, current knowledge about the influences of quorum quenching on the intestinal microbiota is restricted. Hence, the open questions include the following: *1*) whether MR affects the concentrations of QS signal molecules (AHLs and AI-2), *2*) whether MR affects the intestinal microbiota through quorum quenching, and *3*) whether QS plays critical roles in MR-induced lifespan extension.

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