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S-Adenosylmethionine in cell growth, apoptosis and liver cancer

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Abstract

S-Adenosylmethionine (SAME), the principal biological methyl donor, is synthesized from methionine and ATP in a reaction catalyzed by methionine adenosyltransferase (MAT). In mammals, two genes (*MAT1A* and *MAT2A*), encode for two homologous MAT catalytic subunits, while a third gene *MAT2B*, encodes for the β -subunit that regulates *MAT2A*-encoded isoenzyme. Normal liver expresses *MAT1A*, whereas extrahepatic tissues express *MAT2A*. *MAT2A* and *MAT2B* are induced in human hepatocellular carcinoma (HCC), which facilitate cancer cell growth. Patients with cirrhosis of various etiologies, including alcohol, have decreased hepatic MAT activity and SAME biosynthesis. Consequences of hepatic SAME deficiency as illustrated by the *Mat1a* knock-out mouse model include increased susceptibility to steatosis and oxidative liver injury, spontaneous development of steatohepatitis and HCC. Predisposition to HCC can be partly explained by the effect of SAME on growth. Thus, SAME inhibits the mitogenic effect of growth factors such as hepatocyte growth factor and, following partial hepatectomy, a fall in SAME level is required for the liver to regenerate. During liver regeneration, the fall in hepatic SAME is transient. If the fall were to persist, it would favor a proliferative phenotype and, ultimately, development of HCC. Not only does SAME control liver growth, it also regulates apoptosis. Interestingly, SAME is anti-apoptotic in normal hepatocytes but pro-apoptotic in liver cancer cells. In liver cancer cells but not in normal human hepatocytes, SAME can selectively induce Bcl-x_S, an alternatively spliced isoform of Bcl-x_L that promotes apoptosis. This should make SAME an attractive agent for both chemoprevention and treatment of HCC.

Keywords

apoptosis; cell proliferation; hepatocellular carcinoma; methionine adenosyltransferase; S-adenosylmethionine

Introduction

S-Adenosylmethionine (SAME, also abbreviated as SAM and AdoMet), widely available in the USA as a nutritional supplement for liver, joint and mental health, is being increasingly recognized for its role in hepatocyte growth, death and malignant degeneration. Although SAME biosynthesis occurs in all mammalian cells in a reaction catalyzed by the essential enzyme methionine adenosyltransferase (MAT), the liver is the major site of its synthesis and utilization. Patients with chronic liver disease have impaired SAME biosynthesis, which may contribute to the pathogenesis of liver disease and predisposition to malignant degeneration.

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The present review summarizes hepatic SAdenosylmethionine metabolism, regulation of *MAT* genes, and recent development in the understanding of how SAdenosylmethionine regulates hepatocyte growth and apoptosis. How SAdenosylmethionine deficiency can predispose to hepatocellular carcinoma is also proposed.

Hepatic SAdenosylmethionine metabolism

S-Adenosylmethionine is the principal biological methyl donor made in the cytosol of every cell, but the liver plays a central role in the homeostasis of SAdenosylmethionine as the major site of its synthesis and degradation (Fig. 1).¹ In the liver, up to half of the daily intake of methionine is converted to SAdenosylmethionine and up to 85% of all methylation reactions takes place.² MAT is the enzyme responsible for the formation of SAdenosylmethionine from methionine and ATP.¹ SAdenosylmethionine is the link to three key metabolic pathways, polyamine synthesis, transmethylation and transsulfuration. In polyamine synthesis, SAdenosylmethionine is decarboxylated and the remaining propylamino moiety is donated to putrescine to form spermidine and methylthioadenosine (MTA) and to spermidine to form spermine and a second molecule of MTA. In transmethylation, SAdenosylmethionine donates its methyl group to a large variety of acceptor molecules in reactions catalyzed by methyltransferase (MTs). S-Adenosylhomocysteine (SAH) is generated as a product of transmethylation and is hydrolyzed to form homocysteine (Hcy) and adenosine through a reversible reaction catalyzed by SAH hydrolase. SAH is a potent competitive inhibitor of methylation reactions and prompt removal of adenosine and Hcy is required to prevent accumulation of SAH. Hcy can be remethylated to form methionine by two enzymes: methionine synthase (MS), which requires normal levels of folate and vitamin B₁₂; and betaine homocysteine methyltransferase (BHMT), which requires betaine, a metabolite of choline. Remethylation of homocysteine via MS requires 5-methyltetrahydrofolate (5-MTHF), which is derived from 5,10-methylenetetrahydrofolate (5,10-MTHF) in a reaction catalyzed by methylenetetrahydrofolate reductase (MTHFR). 5-MTHF is then converted to tetrahydrofolate (THF) as it donates its methyl group and THF is converted to 5,10-MTHF to complete the folate cycle. Hcy can also undergo the *trans*-sulfuration pathway to form cysteine (the rate-limiting precursor for glutathione [GSH]) via a two-step enzymatic process catalyzed by cystathionine β -synthase (CBS) and cystathionase, both requiring vitamin B₆. The *trans*-sulfuration pathway is particularly active in the liver, making SAdenosylmethionine an important precursor of GSH.³ All mammalian tissues express MAT and MS, whereas BHMT is limited to the liver and kidney. In the liver, SAdenosylmethionine inhibits MTHFR and MS and activates CBS.^{4,5} Thus, when SAdenosylmethionine is depleted, homocysteine is channeled to remethylation to regenerate SAdenosylmethionine, whereas when the SAdenosylmethionine level is high, homocysteine is channeled to the *trans*-sulfuration pathway.

MAT genes and isoenzymes

The *MAT* gene is one of 482 genes required for survival of an organism because MAT is the only enzyme that can catalyze the biosynthesis of SAdenosylmethionine.⁴ In mammals, two different genes, *MAT1A* and *MAT2A*, encode for two homologous MAT catalytic subunits, $\alpha 1$ and $\alpha 2$.⁶ *MAT1A* is expressed mostly in the liver and it encodes the $\alpha 1$ subunit found in two native MAT isoenzymes, MAT III (dimer) and MAT I (tetramer).⁶ *MAT2A* encodes for a catalytic subunit ($\alpha 2$) found in a native MAT isoenzyme (MAT II), which is widely distributed.^{6,7} *MAT2A* and its gene product also predominate in the fetal liver and are progressively replaced by *MAT1A* during development.^{8,9} There is a regulatory subunit (β) that is associated only with MAT II.^{6,10} The β -subunit is encoded by the gene *MAT2B* that is expressed in extrahepatic tissues but not in normal liver.^{10,11}

Although MAT isoenzymes catalyze the same reaction, they differ in kinetic and regulatory properties and sensitivities to inhibitors of MAT.¹ MAT II has the lowest (~ 4 – 10 μ M), while MAT I has intermediate (23 μ M– 1 mM) and MAT III has the highest (215 μ M– 7 mM) K_m for methionine. SAdenosylmethionine strongly inhibits MAT II ($IC_{50} = 60$ μ M), close to intracellular [SAdenosylmethionine],

¹² whereas it minimally inhibits MAT I ($IC_{50} = 400 \mu M$) and stimulates MAT III (up to eight-fold at $500 \mu M$ SAME).¹³ Thus, the SAME level in cells that express only MAT II should be relatively unaffected by fluctuations in methionine availability because of negative feedback inhibition. One caveat is the β -regulatory subunit, which lowers the K_m of MAT II for methionine and the K_i for SAME, thereby rendering MAT II more efficient but also more susceptible to feedback inhibition by SAME.¹⁴

MAT1A is a marker of differentiated liver phenotype.¹ *MAT1A* gene transcription is turned off in hepatocellular carcinoma (HCC),¹⁵ and its expression is decreased in patients with liver disease.^{16,17} In contrast, *MAT2A* is induced transcriptionally in human HCC,¹⁵ and in rodents during rapid liver growth and dedifferentiation.¹⁸⁻²⁰ This switch in MAT expression from *MAT1A* to *MAT2A* in liver cancer is important as it facilitated liver cancer cell growth.²¹ Similar to *MAT2A*, *MAT2 β* expression is also increased in HCC.¹¹ Increased expression of the β -subunit reduced SAME content and stimulated DNA synthesis.¹¹ Thus, both increased *MAT2A* and *MAT2 β* expression offer the liver cancer cell a growth advantage.

While the type of MAT expressed by the cell can influence the steady-state SAME level,²¹ SAME level can influence MAT expression in return. *MAT1A* expression falls whereas *MAT2A* is induced in primary cultures of hepatocytes, due to de-differentiation.²² This change is prevented by the addition of SAME. A similar regulation occurs in human *MAT2A* as well. *MAT2A* gene expression is rapidly induced when SAME falls (by restricting L-methionine in medium) and downregulated when SAME is added.^{23,24} Thus, a fall in hepatic SAME level can feed into a vicious cycle that favors a switch in MAT expression and liver de-differentiation. Table 1 summarizes properties of mammalian MAT.

MAT and SAME in liver disease

It has long been recognized that patients with cirrhosis often have hypermethioninemia and delayed plasma clearance of methionine after an intravenous methionine injection.^{25,26} Subsequent studies showed that this could be attributed to a 50–60% decrease in the activity of MAT I/III,²⁷ which may contribute to decreased hepatic GSH level in these patients, as SAME administration normalized GSH levels.²⁸ The decrease in MAT activity occurs by two mechanisms: pretranslational and post-translational.²⁷ *MAT1A* expression is diminished in end-stage cirrhotic patients independent of the etiology.¹⁶ MAT I/III (but not MAT II) can also be inactivated via covalent modification of a critical cysteine residue at position 121 by nitric oxide and hydroxyl radical.²⁷ Decreased *MAT1A* expression and reduced hepatic SAME levels were also reported in patients hospitalized for alcoholic hepatitis, where some only had liver fibrosis.¹⁷

The *Mat1a* knock-out (KO) mouse model has provided important insights regarding the consequences of chronic hepatic SAME deficiency. *Mat1a* KO mice have markedly increased serum methionine levels, reduced hepatic SAME and GSH levels.²⁹ *Mat1a* KO mice are more prone to develop choline-deficient diet-induced fatty liver and develop spontaneous non-alcoholic steatohepatitis (NASH).²⁹ Mechanisms for these changes include increased expression of cytochrome P450 2E1 (CYP2E1) and impaired mitochondrial function.^{30,31} By 18 months, the majority of the KO mice develop HCC on a normal diet.³⁰ Taken together, the fall in MAT activity observed in human liver cirrhosis may contribute to the pathogenesis and progression of the disease as well as predisposition to HCC.

SAME regulates hepatocyte growth

In hepatocytes, SAME levels are related to the differentiation status, being high in quiescent and low in proliferating hepatocytes.²¹ In rat liver after partial hepatectomy (PH), SAME levels are dramatically reduced shortly afterwards, coinciding with the onset of DNA synthesis and

the induction of early response genes.¹⁸ Preventing this fall in SAME after PH by giving exogenous SAME inhibited hepatocyte DNA synthesis.³² Additionally, exogenous SAME inhibits the growth of hepatoma cells,²¹ prevents development of HCC in rats treated with hepatocarcinogen,^{33,34} and chronic SAME depletion results in spontaneous HCC development.³⁰ One of the molecular mechanisms of the growth inhibitory response of SAME is inhibition of hepatocyte growth factor (HGF).³⁵ Thus, following PH, the fall in hepatic SAME level releases the inhibitory effect it exerts on HGF and allows the liver to respond to growth factors. SAME's inhibition of the mitogenic effect of HGF in hepatocytes involves blocking HGF-mediated activation of AMP kinase (AMPK) and Hu protein R (HuR) nuclear to cytoplasmic translocation.³⁶ HuR is a mRNA-binding protein that increases the half-life of target mRNAs such as cyclin A2 and cyclin D.³⁶ It should be noted that the AMPK signaling pathway does not affect HuR translocation or cell growth in HepG2 cells,³⁶ which illustrates the inherent difference between normal and cancerous hepatocytes in their growth response. Thus, how SAME inhibits the growth of liver cancer cells remains unclear.

SAME regulates hepatocyte apoptosis

S-Adenosylmethionine regulates not only the growth response, it also regulates the apoptotic response. Cell death by apoptosis contributes to the development of many liver injuries that are palliated by SAME treatment. This prompted us to examine the effect of SAME on apoptosis. Whereas SAME protected against okadaic acid-induced apoptosis in normal hepatocytes, it induced apoptosis in liver cancer cell lines HepG2 and HuH-7 via the mitochondrial death pathway.³⁷ The same effects were observed with MTA. MTA can be derived from SAME enzymatically and non-enzymatically. MTA is a product of SAME metabolism in the polyamine pathway (Fig. 1). Exogenous SAME can also undergo non-enzymatic hydrolysis into MTA.¹ In contrast to SAME, MTA does not contribute to GSH synthesis, is not a methyl donor and inhibits methyltransferases.³⁸ Thus, the death regulatory effects of SAME are GSH-independent and may be mediated in part through its conversion to MTA. These results are consistent with the chemopreventive action of SAME and MTA in an *in vivo* model of chemical hepatocarcinogenesis in rats, which was accompanied by an increase of apoptotic bodies in atypical nodules and HCC foci in SAME-treated animals.^{34,39}

One mechanism of SAME and MTA's differential effect on apoptosis in normal versus cancerous liver cells involves Bcl-x.⁴⁰ Bcl-x is alternatively spliced to produce two distinct mRNAs and proteins, Bcl-x_L and Bcl-x_S. Bcl-x_L is anti-apoptotic while Bcl-x_S is pro-apoptotic. SAME and MTA induced selectively Bcl-x_S in HepG2 cells by increasing alternative splicing. Alternative splicing is known to be modulated by protein phosphatase 1 (PP1) and inhibitors of PP1 blocked SAME and MTA's ability to induce Bcl-x_S. SAME and MTA increased PP1 catalytic subunit mRNA and protein levels in HepG2 cells but not in normal human hepatocytes. Consistently, the effects of SAME and MTA on Bcl-x_S and apoptosis were not seen in primary hepatocytes. Another mechanism of SAME and MTA's differential effect on apoptosis in liver cancer cells involves the ability of these agents to inhibit the transcription of BHMT.⁴¹ Lower BHMT expression impairs homocysteine metabolism (Fig. 1) leading to endoplasmic reticulum (ER) stress.⁴² Indeed, MTA treatment increased ER stress markers. Interestingly, SAME and MTA have no influence on BHMT expression in primary human hepatocytes (SC Lu, unpubl. obs, 2007). The difference in response of normal versus cancerous hepatocytes to SAME and MTA in these different pathways remains unclear.

Summary

S-Adenosylmethionine has rapidly moved from being a methyl donor to a key metabolite that regulates hepatocyte growth, death and differentiation. There is increasing evidence that many of its actions are independent of its role as a methyl donor. SAME inhibits the growth of both

normal and cancerous hepatocytes, but the mechanisms appear to be quite different. In contrast, SAME is anti-apoptotic in normal hepatocytes but pro-apoptotic in cancerous hepatocytes. While the molecular mechanisms are still being elucidated, there is increasing evidence and support for the use of this agent in the chemoprevention and possibly treatment of HCC.

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Biography

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Figure 1.

Hepatic S-adenosylmethionine (SAME) metabolism. SAME biosynthesis, catalyzed by methionine adenosyltransferase (MAT), is the first step in methionine catabolism. SAME is the link to three key metabolic pathways – polyamine synthesis, transmethylation and transsulfuration. In polyamine synthesis, SAME is decarboxylated and the remaining propylamino moiety attached to its sulfonium ion is donated to putrescine and spermidine. Methylthioadenosine (MTA) is a by-product in this pathway. In transmethylation, SAME donates its methyl group to a large variety of acceptor molecules in reactions catalyzed by methyltransferases (MT). SAME is converted to S-adenosylhomocysteine (SAH) during transmethylation and SAH is a potent inhibitor of all transmethylation reactions. SAH is hydrolyzed to form homocysteine (Hcy) and adenosine through a reversible reaction catalyzed by SAH hydrolase, whose thermodynamics favors biosynthesis rather than hydrolysis. *In vivo*, this reaction proceeds as hydrolysis because the products Hcy and adenosine are promptly removed. Hcy can be remethylated to form methionine via methionine synthase (MS), which requires folate and vitamin B₁₂ and betaine homocysteine methyltransferase, which requires betaine. Remethylation of homocysteine via MS requires 5-methyltetrahydrofolate (5-MTHF), which is derived from 5,10-methylenetetrahydrofolate (5,10-MTHF) in a reaction catalyzed by methylenetetrahydrofolate reductase (MTHFR). 5-MTHF is then converted to tetrahydrofolate (THF) as it donates its methyl group and THF is converted to 5,10-MTHF, which is important for thymidylate and purine synthesis. Hcy can also become converted to cysteine, the rate-limiting precursor for glutathione (GSH), via the *trans*-sulfuration pathway via a two-step enzymatic process catalyzed by cystathionine β-synthase (CBS) and cystathionase, both requiring vitamin B₆.

Table 1

Properties of mammalian methionine adenosyltransferases

MAT isoform	Gene	Catalytic subunit	Regulatory subunit	Structure	$K_m^{\dagger}$ (methionine)	Tissue localization	Inhibition by SAMe
MAT I	<i>MAT1A</i>	$\alpha 1$	No	$(\alpha 1)_4$	23 μ M–1 mM	Liver, pancreas	No
MAT III	<i>MAT1A</i>	$\alpha 1$	No	$(\alpha 1)_2$	215 μ M–7 mM	Liver, pancreas	No
MAT II	<i>MAT2A</i>	$\alpha 2$	β	Varies	4–10 μ M	Extrahepatic tissues Fetal liver, HCC	Yes
	<i>MAT2β</i>					Same as MAT2A	Unknown

[†] K_m s differ depending on purity of the enzyme.

HCC, hepatocellular carcinoma; MAT, methionine adenosyltransferase; SAMe, S-adenosylmethionine.