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Role of methionine adenosyltransferase and *S*-adenosylmethionine in alcohol-associated liver cancer

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Abstract

Two genes (*MAT1A* and *MAT2A*) encode for the essential enzyme methionine adenosyltransferase (MAT), which catalyzes the biosynthesis of *S*-adenosylmethionine (SAMe), the principal methyl donor and, in the liver, a precursor of glutathione. *MAT1A* is expressed mostly in the liver, whereas *MAT2A* is widely distributed. *MAT2A* is induced in the liver during periods of rapid growth and dedifferentiation. In human hepatocellular carcinoma (HCC) *MAT1A* is replaced by *MAT2A*. This is important pathogenetically because *MAT2A* expression is associated with lower SAMe levels and faster growth, whereas exogenous SAMe treatment inhibits growth. Rats fed ethanol intragastrically for 9 weeks also exhibit a relative switch in hepatic MAT expression, decreased SAMe levels, hypomethylation of c-*myc*, increased c-*myc* expression, and increased DNA strand break accumulation. Patients with alcoholic liver disease have decreased hepatic MAT activity owing to both decreased *MAT1A* expression and inactivation of the *MAT1A*-encoded isoenzymes, culminating in decreased SAMe biosynthesis. Consequences of chronic hepatic SAMe depletion have been examined in the *MAT1A* knockout mouse model. In this model, the liver is more susceptible to injury. In addition, spontaneous steatohepatitis develops by 8 months, and HCC develops by 18 months. Accumulating evidence shows that, in addition to being a methyl donor, SAMe controls hepatocyte growth response and death response. Whereas transient SAMe depletion is necessary for the liver to regenerate, chronic hepatic SAMe depletion may lead to malignant transformation. It is interesting that SAMe is antiapoptotic in normal hepatocytes, but proapoptotic in liver cancer cells. This should make SAMe an attractive agent for both chemoprevention and treatment of HCC.

Keywords: *S*-adenosylmethionine; Methionine adenosyltransferase; Hepatocellular carcinoma; Alcoholic liver injury

1. Introduction

Individuals who abuse alcohol on a chronic basis are predisposed to the development of hepatocellular carcinoma (HCC), but the molecular mechanisms are unknown. Although ethanol is not considered to be carcinogenic to the liver, it is thought to enhance the tumorigenic process. This review focuses on the possible role of two changes that occur in alcoholic liver disease, namely decreased methionine adenosyltransferase 1A (*MAT1A*) expression and *S*-adenosylmethionine (SAMe) levels, in the development of liver cancer.

2. *S*-adenosylmethionine biosynthesis and hepatic methionine metabolism

The liver is the main source of SAMe biosynthesis and consumption, turning over nearly 8 g per day in a healthy adult (Mudd et al., 1980). *S*-adenosylmethionine biosynthesis is the first step in methionine metabolism in a reaction catalyzed by methionine adenosyltransferase (MAT) (Mato et al., 2002). In mammals, this reaction in the liver catabolizes nearly half the daily intake of methionine (Fig. 1). *S*-adenosylmethionine is the principal biologic methyl donor, the precursor for polyamine biosynthesis, and, in liver, a precursor of glutathione (GSH) by means of the transsulfuration pathway (Mato et al., 2002). Under normal conditions, most of the 6 to 8 g of SAMe generated per day is used in transmethylation reactions, and SAMe is converted to *S*-adenosylhomocysteine (SAH) (Finkelstein, 1990). *S*-adenosylhomocysteine is a potent competitive inhibitor of transmethylation reactions. Both an increase in

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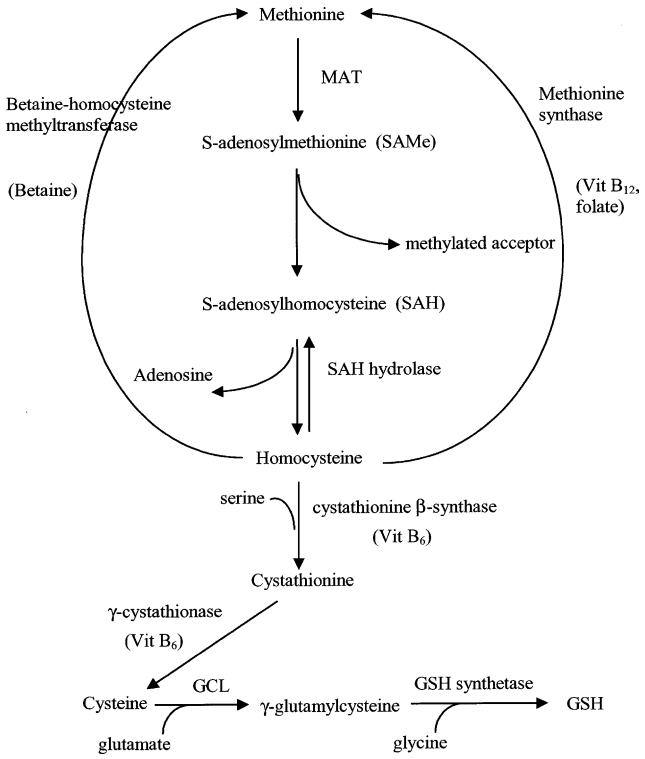

Fig. 1. Hepatic methionine metabolism. The first step in methionine metabolism is catalyzed by methionine adenosyltransferase (MAT), generating *S*-adenosylmethionine (SAMe). *S*-adenosylmethionine is converted to *S*-adenosylhomocysteine (SAH) during transmethylation reactions. Next, SAH hydrolase catalyzes the reversible hydrolysis of SAH to yield homocysteine and adenosine. In the liver, homocysteine can undergo three metabolic pathways. One is the transsulfuration pathway, which converts homocysteine to cysteine. In this pathway, homocysteine condenses with serine to form cystathionine in a reaction catalyzed by cystathionine β-synthase, which requires vitamin B_6 as a co-factor. Cleavage of cystathionine, catalyzed by another vitamin B_6–dependent enzyme, γ-cystathionase, subsequently releases free cysteine, the rate-limiting precursor for glutathione (GSH) synthesis. The GSH is synthesized in all mammalian cells through a two-step process. The first step is rate limiting, and GSH is catalyzed by glutamate-cysteine ligase (GCL). The second step is catalyzed by GSH synthetase. The other two pathways that metabolize homocysteine resynthesize methionine from homocysteine. One is catalyzed by methionine synthase, which requires normal levels of folate and vitamin B_{12}. The other is catalyzed by betaine homocysteine methyltransferase, which requires betaine, a metabolite of choline.

SAH level and a decrease in the SAMe:SAH ratio are known to inhibit transmethylation reactions (Hoffman et al., 1980; Mato et al., 2002). For this reason, the removal of SAH is essential. The reaction that converts SAH to homocysteine and adenosine is reversible and catalyzed by SAH hydrolase (Finkelstein, 1990). In fact, the thermodynamics favor synthesis of SAH (Finkelstein, 1990). In vivo, the reaction proceeds in the direction of hydrolysis only if the products, adenosine and homocysteine, are rapidly removed (Hoffman et al., 1980). In liver, there are three pathways that metabolize homocysteine. One is the transsulfuration pathway, which converts homocysteine to cysteine. This is a pathway that is very active in the liver, allowing methionine to serve as a precursor for cysteine and GSH (Lu, 1999). In the transsulfuration pathway, homocysteine condenses with serine to form cystathionine in a reaction catalyzed by cystathionine β-synthase, which requires vitamin B_6 as a co-factor. Cleavage of cystathionine, which is catalyzed by another vitamin B_6–dependent enzyme, γ-cystathionase, subsequently releases free cysteine, the rate-limiting precursor for GSH synthesis (Lu, 1999). The other two pathways that metabolize homocysteine resynthesize methionine from homocysteine. One pathway is catalyzed by methionine synthase, which requires normal levels of folate and vitamin B_{12}. The other pathway is catalyzed by betaine homocysteine methyltransferase, which requires betaine, a metabolite of choline (Lu, 1999; Mato et al., 2002).

3. Methionine adenosyltransferase genes and enzyme isoforms

Methionine adenosyltransferase is a critical cellular enzyme because it catalyzes the only reaction that generates SAMe (Mato el al., 2002). In mammals, two different genes, *MAT1A* and *MAT2A*, encode for two homologous MAT catalytic subunits, α_1 and α_2 (Kotb et al., 1997). *MAT1A* is expressed mostly in the liver, and it encodes the α_1 subunit found in two native MAT isozymes, which are either a dimer (MAT III) or tetramer (MAT I) of this single subunit (Kotb et al., 1997). *MAT2A* encodes for a catalytic subunit (α_2) found in a native MAT isozyme (MAT II), which is widely distributed (Horikawa & Tsukada, 1992; Kotb et al., 1997). *MAT2A* and its gene product also predominate in the fetal liver and are progressively replaced by *MAT1A* during development (Gil et al., 1996; Horikawa et al., 1993). The composition of MAT II varies, depending on the tissue (Horikawa et al., 1990; Kotb & Kredich, 1985; Mitsui et al., 1988). A regulatory β subunit encoded by another gene controls the activity of MAT II in lymphocytes (Halim et al., 1999; Kotb & Kredich, 1985; LeGros et al., 2000). The β subunit lowers the Michaelis–Menten constant (K_m) of MAT II for methionine and renders the enzyme more susceptible to feedback inhibition by SAMe (Halim et al., 1999). The β subunit also plays a similar role in liver cancer cells and, along with the relative expression of MAT isozymes, can influence the rate of liver growth (Martínez-Chantar et al., 2003a).

The two genes that encode for the two catalytic subunits of MAT share a great deal of similarity, both coding for a 3.4-kb mRNA product, and they may have originated from a common ancestral gene. Despite the similarities, different isoforms of MAT differ in kinetic and regulatory properties and sensitivities to inhibitors of MAT (Mato et al., 2002). MAT II has the lowest K_m (~4–10 μM), MAT I has intermediate K_m (23 μM–1 mM), and MAT III has the highest K_m (215 μM–7 mM) for methionine (Cabrero et al., 1987; Liau et al., 1979; Okada et al., 1981; Pajares et al., 1992; Sullivan & Hoffman, 1983). The activity of MAT is