Review Article

MAT gene deregulation and liver cancer

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ABSTRACT

Rodent models with low heterogeneity premalignant and malignant lesions provide a valuable contribution to hepatocellular carcinoma (HCC) pathogenesis in the field of research. Studies have been performed in transgenic mice, and rodent strains on signaling pathways deregulation in hepatocarcinogenesis with varying susceptibilities, and human HCC subtypes. Because ethionine, an antagonist of methionine, causes cancer and methyl-deficient diets cause steatohepatitis, followed by the development of HCC, researchers began to look into mechanisms regulating availability of S-adenosylmethionine (SAM) and its role in liver injury, including HCC development. Cirrhotic livers have decreased methionine adenosyltransferase (MATI/III) levels due to oxidation of cysteine residues in the ATP-binding site. MATII upregulation is inhibited by its reaction product, leading to MATI/III downregulation. Decreased MATI/III: MATII activity ratio, along with increased SAM decarboxylation for polyamine synthesis, results in decreased SAM. Some of the molecular pathways associated with specific cancer phenotypes are evolutionarily conserved, according to previous comparative functional genomics research. Cell cycle regulators (WNT/FZD, PI3K/AKT, and MAPK) and key genes (MAPK, IKK/NF-kB) are upregulated in human and rodent HCC progression. Pseudoprognostic markers for HCC include MAT1A/MAT2A switch. Changes in MAT1A expression and SAM levels occur during hepatocarcinogenesis. No evidence of SAM's therapeutic effect on HCC has been found. The effects of stable MAT1A overexpression or MAT2A/MAT2B inhibition *in vivo* should be studied first. MAT2A or MAT2B-silenced HepG2 cells proliferate less in leptin. However, intracellular viral vector transduction *in vivo* has many limitations. This review interprets recent advances in SAM metabolism deregulation in liver injury predisposing to HCC and determining HCC prognosis.

Key words: *Hepatocarcinogenesis, Hepatocellular carcinoma, Liver cirrhosis, Methionine adenosyltransferase, S-adenosylmethionine*

Approximately 0.25–1 million new cases of hepatocellular carcinoma (HCC) are diagnosed each year [1]. Chronic hepatitis B virus (HBV) and hepatitis C virus infections, alcoholic steatohepatitis (ASH), aflatoxin B1, and inherited metabolic disorders are major risk factors for HCC [2-4]. Human population exposed to risk factors differs in incidence of HCC [5], indicating a pathogenetic role for environmental and/or genetic factors [6-8]. Human HCC has genotypic and phenotypic heterogeneity due to complex genetic, etiologic, and environmental risk factors [9]. As a result, determining pathogenetic mechanisms and prognostic subtypes of HCC is difficult. Rodent models with low heterogeneity premalignant and malignant lesions provide a valuable contribution to HCC pathogenesis research [10,11]. Studies on signaling pathways deregulation in hepatocarcinogenesis have been performed in transgenic mice, rodent strains with varying hepatocarcinogenesis susceptibilities, and human HCC subtypes [12]. Because ethionine, an antagonist of methionine, causes cancer and methyl-deficient diets cause steatohepatitis, followed by HCC development even in the absence of carcinogens, researchers began looking into mechanisms regulating availability of S-adenosylmethionine (SAM) and its role in liver injury, including HCC development.

This review interprets recent advances in SAM metabolism deregulation in liver injury predisposing to HCC and determining HCC prognosis. We investigated the molecular mechanisms associated with antitumor effect of SAM to discover new prognostic markers and potential targeted therapies.

SAM is produced in the liver from methionine and ATP by methionine adenosyltransferases (MATs) [13]. SAM can be decarboxylated and used in polyamine synthesis, or it can be transmethylated to S-adenosylhomocysteine (SAH). SAHH catalyses a reaction that turns SAH into homocysteine and adenosine. Homocysteine can enter the transsulfuration pathway to make cystathionine and glutathione (GSH). Alternatively, betaine homocysteine (BHMT) converts homocysteine to methionine and dimethylglicine. When homocysteine and 5-methyltetrahydrofolate are combined,

methyltetrahydrofolate-histone methyltransferases (MTHF-HMT) produces methionine and tetrahydrofolate. SAH and Methylthioadenosine (MTA), polyamine biosynthesis products, may inhibit transmethylation. High SAM levels activate cystathionine beta synthase (CBS). The isozymes MATI and MATIII, tetramer and dimer of subunit a1, are encoded by MAT1A [3]. The widely distributed enzyme MATII isoform is encoded by MAT2A. In foetal and adult liver, MAT2A predominates over MAT1A [4,14]. MATI and MATIII isozymes have Michaelis constant (Km) for methionine of 23 lM–1 mM and 215 lM–7 mM, respectively. Physiological liver SAM (60 lM) inhibits MATI but stimulates MATIII [7,15,16]. Inhibition of MATII by the reaction product (Km 4–10 lM) MAT2B encodes a non-catalytic b-subunit that regulates MATII by lowering its Km for methionine and Ki for SAM [16]. As a result, b-subunit association makes MATII more susceptible to SAM inhibition [16]. It has recently been discovered that the main enzyme involved in SAM catabolism in the liver is Glycine N-methyltransferase (GNMT), which is correlated with MAT1A and GNMT/BHMT liver proteins [17].

Variations in the SAM: SAH ratio: The lack of choline causes a decrease in phosphatidycholine synthesis and a decrease in phosphatidylethanolamine transmethylation in rats. Steatohepatitis results from impaired lipoprotein assembly and membrane synthesis [18,19]. Lipid peroxidation and SAM depletion affect mitochondrial function, which is required for fatty acid oxidation. SAM helps to maintain normal mitochondrial function by stabilising PHB1 [20]. SAM treatment of methyl deficient dies-fed rat hepatocytes induces phosphatidycholine synthesis, very low density lipoprotein (LDL) and LDL secretion, and reduction in cytoplasmic triacylglycerol [21]. SAM changes play an important role in ASH pathogenesis. Pre-fibrotic alcoholic rat liver injury is associated with increased MATII activity, decreased SAM/SAH ratio, global DNA hypomethylation, c-Myc upregulation, and DNA strand break [21]. SAM protects against ASH. Human studies on ASH were inconclusive, but SAM treatment improves survival or delays liver transplantation in alcoholic liver cirrhosis patients [10]. In chronic hepatitis C, adding SAM with/without betaine to Peg IFNa and ribavirin improves treatment efficacy. In addition, HBV X Protein upregulates MAT2A and MAT2b while decreasing MAT1A expression and SAM production in hepatoma cells *in-vitro*. SAM also protects rodents from D-galactosamine, acetaminophen [4], and CCl_4 toxicity. The SAM/SAH ratio was low and c-Myc expression was high 0.5 h after partial hepatectomy in rats fed on normal diet. The changes peaked at 5–12 h, and then gradually returned to pre-pH levels. This corresponded to the peak of DNA synthesis 24–30 h post-pH [7]. Also, in rats fed on sufficient diet, SAM levels and SAM/SAH ratios decrease significantly during hepatocarcinogenesis induced by various carcinogens and experimental models, and persist for weeks after stopping carcinogen administration [5]. During hepatocarcinogenesis, highly purified SAM can restore normal SAM levels and SAM/SAH ratios. This treatment reduces preneoplastic liver lesions and prevents HCC development, while increasing preneoplastic cell apoptosis [18].

SAM inhibits thiobenzamide-induced preneoplastic lesions in"diethylnitrosamine-induced rats [20]. Human HCC cell lines transfected with MAT1A or cultured with SAM also show strong proliferation inhibition [7,16]. Lu *et al*. [17] recently confirmed these findings by injecting human HCC cell line, H4IIE, into rat liver parenchyma. After tumour cell injection, SAM infusion inhibited HCC formation. The 24-day SAM infusion had no effect on the size of existing tumours. This was explained by a compensatory induction of hepatic GNMT. Stable MAT1A transfectants had higher SAM levels and lower DNA synthesis than control cells [18]. MAT1A-transfected HCCs had slower growth, microvessel density, CD31 and Ki-67 staining, and higher apoptosis than control tumours [11].

The MAT1A: MAT2A ratio (called the MAT1A/MAT2A switch) decreases in liver cirrhosis, and human HCC [4]. Cirrhotic livers have decreased MATI/III levels due to oxidation of cysteine residues in the ATP binding site [4]. It restores GSH levels, protects MATI/III, and reduces liver fibrosis in both rats and humans [21]. MATII upregulation is inhibited by its reaction product, MATI/III downregulation [14]. Decreased MATI/III: MATII activity ratio, along with increased SAM decarboxylation for polyamine synthesis, result in decreased SAM. All in all, these findings point to a role for MAT1A/MAT2A switch and SAM level drop in hepatocarcinogenesis. Consequently, the MAT1A-Ko mouse model exhibited hepatomegaly without histologic abnormalities at 3 months and macrovesicular steatosis involving 25–50% of hepatocytes and mononuclear cell infiltration in periportal areas at 8 months. Many of these mice developed HCC by 18 months [15].

Recent research revealed oxidative stress, steatosis, and fibrosis in GNMT-Ko mice, followed by HCC development [7] and increased susceptibility to aflatoxin B1-related HCC [16]. They have DNA hypomethylation, aberrant expression of DNA methyltransferases 1 and 3b [17], hypermethylation of Ras and JAK/STAT pathway inhibitors, and upregulation of Beta-catenin, cyclin D1, and Myc [18]. Furthermore, Ras-mediated LKB1 overactivation promotes GNMT-deficient hepatoma cell proliferation. In GNMT-Ko mice, impaired liver regeneration stimulates dormant stem/progenitor cells to replicate, possibly promoting HCC formation [19]. Children with GNMT mutation have high liver transaminases, liver injury, fibrosis, and HCC development. Upregulation of MAT2A may also promote HCC cell growth. HCC H35 cells require MAPK and PI3K/AKT pathways for cell proliferation and MAT2A upregulation [20].

Molecular mechanisms of MAT gene deregulation and numerous CpG MAT1A and MAT2A promoters inspired the study of epigenetic regulation of HCC expression [6]. MAT1A is downregulated in CCl4-cirrhotic liver and human HepG2 cell line CCGG methylation in MAT1A promoter. This was found in HuH7 cells. CCGG methylation at +10 and +80. MAT2A upregulation in HCC is linked to CCGG DNA hypomethylation. CpG methylation in rat slow-growing HCC and histone H4 acetylation in human poor prognosis HCC was highest in

promoter hypermethylation of MAT1A and hypomethylation of MAT2A [8]. Sp1, c-Mybl2, NF-kB, AP-1 and MAT2A transcriptional upregulation of HCC 18 MAT2B expression is regulated by unknown Sp1 promotes MAT2B [16]. Two dominant splicing variants of MAT2B, V1 and V2 are involved in HCC. TNFa induces only MAT2B V1 via AP-1 and NF-kB [7], while MAT2B Leptin stimulates V1 promoter expression.

Post-transcriptional regulation is thought to be mediated by a class of mRNA-binding proteins (RBPs). Genes in cancer cells mutated RBPs: ARE/poly(U)-binding/degradation factor 1 (AUF1) promotes mRNA decay while HuR binds to AU-rich elements that stabilise mRNA. A recent study found MAT1A mRNA decrease in the foetal rat liver, associated with an increased MAT2A mRNA and AUF1 interaction. It was found that Human HuR and AUF1 protein levels were elevated by immunofluorescence. Post-transcriptional regulation of AUF1 MAT proteins was done in HCC using these findings. A recent study found there was increase in AUF1 and HuR in F344 and human HCC linked to an increase in AUF1 and HuR ribonucleoproteins in HCC. These changes were either minimal or absent in BN rats' HCC. Recent evidence links reduced MAT1A expression to miRNAs in HCC [19]. MiR-664 knockdown individually in Hep3B and HepG2 cells, inhales MAT1A Nude Hep3B cell tumorigenesis stable overexpression reduces mice and increases miRNA-664/485-3p/495. These miRNAs promote hepatocarcinogenesis by suppressing MAT1A expression. These findings show that transcriptional and MAT1A/MAT2A post-transcriptional mechanisms in HCC reduces SAM and switch. MAT1A/MAT2A switch and SAM reduction may be used to predict hepatocarcinogenesis. SAM's anti-tumor effect and DNA interaction with carcinogens and reactive""oxygen and nitrogen species, generated during early hepatocarcinogenesis, carcinogen metabolism, and/or inflammation results in genomic copy number instability (GI), somatic point mutations gene mutations, and chromosomal gain/loss arms. The accumulation of genomic alterations leads to signaling pathways deregulation, DN and HCC.

The antioxidative action of SAM may have a chemopreventive role in CCl_4-intoxicated rats. Inhibiting oxidative DNA damage prevents tumor growth in many organs, including the liver [6]. Polyamine synthesis may favor preneoplastic and neoplastic liver cell growth. Progressive ODC gene and activity upregulation and hepatocarcinogenesis in rats produce polyamines. Polyamine synthesis-related genes are also upregulated in HCC [21] and SAM inhibiting oDC activity, preventing polyamine synthesis [17].

CONCLUSION

DNA hypomethylation, production of oxygen reactive and nitroactive species, and activation of LKB1/AMPK axis, may induce G1 cell cycle activation followed by upregulation of c-MYC and genes involved in polyamine synthesis, and NFkB signaling upregulation, leading to G1. They were discovered in rodent models. Some of the molecular pathways associated with specific cancer phenotypes are evolutionarily conserved, according to previous comparative functional genomics research. Cell cycle regulators (WNT/FZD, PI3K/AKT, and MAPK) and key genes (MAPK, IKK/NF-kB) are upregulated in human and rodent HCC progression. Pseudo prognostic markers for HCC include MAT1A/MAT2A switch. No evidence of SAM's therapeutic effect on HCC has been found so far. The effects of stable MAT1A overexpression or MAT2A/MAT2B inhibition *in vivo* should be studied first. HepG2 cells with MAT2A or silenced MAT2B proliferate less in leptin. However, intracellular viral vector transduction *in vivo* has many limitations.

In this context, the therapeutic effect of a family of fluorinated N, N-dialkylaminostilbene agents on HCC cells should be texted. These molecules bind to MATIIa and stop SAM synthesis. WNT/b-catenin signaling inhibition may be particularly useful against b-catenin mutant HCC. Recent evidence suggests that specific anti-miRNA oligonucleotides can reduce the expression of miRNAs-664/485-3p/495 in HCC. Antisense oligonucleotides that inhibit or decoy miRNAs can enter the liver vessels.

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