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Alterations of methionine metabolism in hepatocarcinogenesis: the emergent role of glycine Nmethyltransferase in liver injury

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Abstract

S-Adenosylmethionine (SAM) plays a central role in liver physiology. It is used for polyamine synthesis, methylation reactions and phosphatidylcholine synthesis, while its derivative, Sadenosylhomocysteine (SAH) is used for GSH and methionine synthesis. Several mechanisms regulate methionine cycle. Methionine adenosyl transferases I and III (MATI/III) and MATII synthesize SAM. At physiological liver level SAM slowly inhibits MATI and stimulates MATIII, while inhibits MatIIA and MATIIB. A decrease in MATI/III and an increase in MATII with consequent decrease in SAM level occurs in hepatocellular carcinoma (HCC). The experimental reproduction of this situation in MATI/III knockout mice (MAT-0 mice) induces liver tumors. In contrast, the administration of SAM to rats and mice subjected to HCC inducing protocols, inhibits the development of preneoplastic and neoplastic liver lesions. The study of SAM antitumor effect showed that exogenous SAM antagonizes liver damage induced by galactosamine or acetaminophen and prevents steatosis in ethanol-intoxicated rats and mice, an effect associated with SAM ability to maintain adequate GSH liver content and prevention of lipid peroxidation and fibrogenesis induced by CCl4 intoxication. Furthermore, treatment of rats with SAM during hepatocarcinogenesis inhibits polyamine synthesis in preneoplastic liver lesions. SAM also inhibits NO• production by iNOS and eNOS, activated during chronic hepatitis and hepatocarcinogenesis, inhibits c-myc, H-ras, and K-ras expression in preneoplastic liver lesions and induces overexpression of oncosuppressor PP2A gene, activates ERK1/2 Inhibitor Dusp1, prevents the inhibition of C/EBPα and UCA1 expression and blocks LKB1/AMPK activation. However, the trials of SAM therapy in different preneoplastic conditions did not demonstrate a clear therapeutic effect. Recent attempts of manipulation of MAT1A/MAT2A switch by inhibition of Mat2A by miR-203 have shown inhibition of MAT2A and MAT2B mRNAs and MATα2 and MATβ2 proteins (MATTIIA and B enzymes) and viability, growth, migration, and invasiveness and HCC cell lines.

Biography

Rosa M Pascale has graduated in Medicine, University of Sassari (Italy) in 19; Specialist in Clinical Pathology, University of Sassari (Italy), 1986; PhD Experimental and Molecular Pathology, University of Turin (Italy), 1988. Currently, she is the director of the Residency in Clinical Pathology and Clinical Biochemistry, University of Sassari (Italy).

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