

GENETIC C677T POLYMORPHISMS OF METHYLENETETRAHYDROFOLATE REDUCTASE IN COMBINATION WITH FOLATE STATUS AND MITOCHONDRIAL DNA DELETIONS MODULATE RISKS OF TUMOUR PROGRESSION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Previous studies have revealed that low folate status increased risks of tumour progression in patients with hepatocellular carcinoma (HCC). Genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) modulate folate-mediated one carbon metabolism and possibly affect DNA integrity, all of which may mechanistically impact on tumour progression in HCC patients. The hypothesis was tested in 147 HCC patients and 152 healthy controls without liver disease, any HCC and other cancers detected. Demographic, life style and clinical data of all subjects were collected. Blood samples were assayed for folate and homocysteine (Hcy) concentrations. DNAs of peripheral blood mononucleocytes (PBMC) were extracted for genotyping of MTHFR C677T polymorphisms. Mitochondrial DNA (mtDNA) large deletions of PBMC were analyzed using real time PCR method. The data revealed that the distributions of CT/TT genotypes significantly differ between HCC patients and controls (38 vs. 53%, $P < 0.05$). As compared to HCC patients with CC genotype, CT/TT variants had significantly lower rate of having tumor size greater than 3 cm and reduced mitochondrial large deletion of PBMCs. 90 % of HCC patients with low mitochondrial large deletion are CT and TT variants, whereas 90% of HCC patients with high mtDNA deleted lesions were CC variants ($P < 0.05$). High levels of PBMCs' DNA lesions, low folate status and elevated homocysteine (Hcy) levels were all associated with advanced tumour stages of HCC patients. After adjustment for age, sex, lifestyle, general nutritional status, Hcy levels and liver dysfunction, CT/TT variants with adequate folate status (serum folate > 14 nmol/L) had reduced risks for advanced tumour progression in large tumours (OR = 0.1 ; 95% CI: 0.02-0.4), tumour multiplicity (OR = 0.2; 95% CI: 0.1-0.95) and metastasis (OR = 0.1; 95% CI: 0.01-0.5) relative to CC variants with folate deficiency (serum folate < 14 nmol/l). The protected effects of folate and CT/TT genotype against multiple tumour and metastasis were negated by further adjustment by mtDNA deletions. Taken together, our data suggest that CT/TT genotype in combination with adequate folate status reduced risks of tumour progression in HCC patients, which is partially, if not all, mediated by the protection against mtDNA deleted lesions. (This study was supported by the grants :DOH95, 96-TD-F-113-008 from the Department of Health, Taiwan, ROC, to R.F.S. Huang)

Key words:

folate status, methylenetetrahydrofolate reductase polymorphism, mitochondrial DNA deletions, hepatocellular carcinoma, tumour progression