Compensation of glutathione *S*-transferase (GST) M1-null by a high identical GST superfamily member GSTM5 through DNA demethylation

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Abstract

Glutathione *S*-transferase (GST) is a superfamily of drug metabolism phase 2 enzymes. There are 7 families in the cytosolic form of GST including Mu family. In the GST Mu, 5 subfamily members named GSTM1-M5 locate on human chromosome 1. It is known that people of about fifty percent have the gene type of homozygous GSTM1-null. Besides, one study showed that function of GSTM1-null could be compensated by GSTM2. In our previous study, we found that GSTM1 RNA and protein expression of bladder were down-regulated by the intake of carcinogen *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine (BBN) in mice. It is known that GSTM5 is the most identity protein to GSTM1. In order to study whether the expression of GSTM5 compensated GSTM1-null or not, we analyzed the expression and activity of GSTM1 and GSTM5 in human cells. In seven human bladder cancer cell lines, GSTM1 only presents in T24 cells, the other six cell lines are GSTM1-null genotype. In T24 study, it showed that GSTM1 and GSTM5 gene expression were not affected under the treatment of DNA demethylation drug 5-aza-2'-deoxycytidine (5Aza-dC). In this condition, the DNA CpG methylation level of GSTM1 and GSTM5 genes also were not changed by 5Aza-dC treatment. In contrast, the GSTM5 gene expression was up-regulated in 5637 and J82 cells by 5Aza-dC treatment, simultaneously, the DNA CpG methylation level of GSTM5 genes was also decreased. In GST activity assay, 5Aza-dC induced the metabolism of 1-Chloro-2,4-dinitrobenzene (CDNB) in T24 and J82 cells. It suggests that DNA CpG demethylation and/or gene activation of GSTM5 might compensate GST activity in T24 and J82 cells. In clinical study, people of about fifty percent have the genotype of homozygous GSTM1-null. Besides, it showed that the DNA CpG methylation level of GSTM5 gene were higher in bladder cancer tissue than in normal urine pellets. In summary, gene expression activation of GSTM5 by DNA demethylation provides compensatory effect in GSTM1-null people, which might increase their defensive ability in xenobiotics-induced cell damage.