GENETIC POLYMORPHISM OF BLEOMYCIN HYDROLASE: A NEW BIOMARKER FOR HUMAN MUTAGEN SENSITIVITY

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Mutagen sensitivity assay, measuring chromosome damage induced by an in vitro treatment of peripheral lymphocytes with the antitumor drug bleomycin, has been proposed as a biomarker for assessing cancer susceptibility. Some case-control studies have demonstrated that in vitro sensitivity of peripheral lymphocytes to bleomycin, is associated with the risk for development of different tumours such as those of upper aerodigestive tract, head-neck, lung. It has been also suggested that this assay can function as a biomarker to predict responses and outcomes in patients under chemotherapy and radiotherapy. Recently, genetic polymorphism of bleomycin hydrolase (BLHX), a specific neutral cysteine protease able to metabolise bleomycin, was put forward as a plausible candidate to variation in mutagen sensitivity. To shed more light on the effect of BLHX genotype on the expression of chromosome damage induced in vitro by bleomycin, we determined mutagen sensitivity for 50 young no smoker healthy volunteers (30 women and 20 men; mean age: 25.3 ± 10.6). The level of bleomycin-induced chromosome damage was assessed as frequencies of micronuclei (MN) in cytokinesis-blocked lymphocytes. The subjects were genotyped for the BLHX gene, to determine the possible effect of this polymorphism on mutagen sensitivity.

No difference in the spontaneous value of MN was detected between the homozygotes wild-type (A/A) and the carriers of variant alleles A/G heterozygotes or G/G homozygites (MN/1000 binucleated (BN) cells: 6.69±2.53 and 6.37±4.87, respectively). On the other hand a substantial effect of BLHX polymorphism in predetermining individual mutagen sensitivity status was observed: subjects with the BLHX A/A genotype displayed significantly lower mean levels of bleomycin-induced MN frequency than the carriers of A/G or G/G variant alleles combined (12.00±3.76 vs 16.37±8.86, respectively; P=0.029). The multiple regression analysis, including BLHX genotype, age and gender, confirmed the significant effect of BLHX variant alleles (A/G, G/G) on the chromosome damage induced by bleomycin (P=0.01), whereas no influence was found for age or gender.

Although it can not be excluded the possibility that the mutagen sensitivity could also depend on other genetic polymorphisms of DNA repair, our results indicate that BLXH polymorphism influences bleomycin sensitivity. These findings are suggestive and warrant further studies on the relationship between BLXH genotype and bleomycin sensitivity for validating this biomarker as a predictor of cancer susceptibility.