

Genetic polymorphism of xenobiotic metabolizing enzymes: role in cancer susceptibility and risk assessment

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Xenobiotic metabolizing enzymes (XMEs) have been found to undergo numerous polymorphisms (PM) on genetic and phenotypic levels. Variable combinations of XME polymorphic variants in different individuals can lead to 30-40-fold differences in activation and degradation of xenobiotics (XB) and as result to great individual differences in risk of toxicity, cancer and other pathologies.

In this study the phenotypic interline differences in activities of liver XMEs in 8 mouse lines have been investigated. For the determination of XMEs activities the standart methods have been used. The ROS production in microsomes was detected by ESR-Spin Trapping technique.

The results have allowed to substantiate the conception of Provisional Criterion of Protective Metabolic Status (PCPMS) of organisms. PCPMS is ratio of total activities of veritable protective enzymes (EH, GST, UDP-GT etc.) to total activities of enzymes, which produce reactive intermediates (CYP isoforms). Taking into account the physiological and biochemical meaning of PCPMS, one could suggest, that organisms with PCPMS < 1 must be unstable, with high susceptibility to various diseases. On the other hand, the organisms with PCPMS > 1 have to be more resistant to toxicity and to risk of diseases. Indeed, PCPMS for CBA mice equal 0.25 and these animals in accordance with Jackson's Laboratory Database have very high per cent of spontaneous tumors of differ localization. On the contrary, for C57BL/6J mice PCPMS equal 1.85 and these animals almost have not spontaneous tumors.