S6. Genetic Risk Profiles for Cancer Susceptibility and Therapy Response

H. Bartsch, H. Dally, O. Popanda, A. Risch, P. Schmezer

German Cancer Research Center (DKFZ), Division of Toxicology and Cancer Risk Factors, Heidelberg, Germany (h.bartsch@dkfz.de)

Cells in the body are permanently attacked by DNA-reactive species, both from intracellular and environmental sources. Inherited and acquired deficiencies in host-defense mechanisms against DNA-damage (metabolic and DNA repair enzymes) can modify cancer susceptibility as well as therapy response. Genetic profiles should help to identify high risk individuals who subsequently can be enrolled in preventive measures or treated by tailored therapy regimens. Some of our attempts to define such risk profiles are presented. Cancer susceptibility: Polymorphisms in metabolic and repair genes were investigated in a hospital-based lung cancer case-control study. When evaluating the risk associated with different genotypes for N-acetyltransferases (Wikman et al., Pharmacogenetics, 2001) and glutathione-S-transferases (Risch et al., Pharmacogenetics, 2001), it is important to distinguish between the different histological subtypes of lung tumors. A promoter polymorphism of the myeloperoxidase gene MPO was shown to affect lung cancer susceptibility mainly in SCLC (Dally et al., Int J. Cancer, 2002). The CYP3A4*1B allele was also linked to an increased SCLC risk especially in smoking women, where the risk was 8-fold increased (Dally et al., Pharmacogenetics 2003). Polymorphisms in DNA repair genes were shown to modulate lung cancer risk in smokers, and reduced DNA repair capacity elevated the disease risk (Rajaee-Behbahani et al., Int J Cancer, 2001). Investigations of several DNA repair gene variants revealed that lung cancer risk was only moderately affected by a single variant but was enhanced up to 3-fold by specific variant allele combinations (Popanda et al., Carcinogenesis, 2004). Therapy response: Interindividual differences in therapy response are consistently observed with cancer chemotherapeutic agents. Initial results from ongoing studies showed that certain polymorphisms differentially affect response outcome in histological subgroups of lung cancer: Stronger effects were seen in NSCLC- and SCLC-patients following gemcitabine and etoposide-based treatment, resp. Several DNA repair parameters (polymorphisms, RNA expression and DNA repair capacity) were measured in vitro in lymphocytes of patients before radiotherapy and correlated with the occurrence of acute side effects (radio-hypersensitivity). Our analysis of several repair gene variants in breast cancer patients (n = 446) who received radiotherapy revealed no association of single polymorphisms and the development of side effects (moist desquamation of the irradiated normal skin). The risk for this side effect was however strongly reduced in normal weight women carrying a combination of XRCC1 399Gln and APE1 148Glu alleles indicating that these variants afford some protection against radio-hypersensitivity (Chang-Claude et al., Clin Cancer Res, 2005). Based on these data we conclude that specific metabolic and DNA repair gene variants can affect cancer risk and therapy outcome. Translation of these findings into the clinic and application for public health measures will require large population-based studies and validation of the results.

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