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Differences in DNA damage and DNA repair capacities as transient biomarkers of colorectal carcinogenesis

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Abstract

DNA repair is crucial in maintaining universal genomic stability and preserving cellular functions. Defects in the DNA repair increase vulnerability to endogenous and exogenous DNA-damaging agents, consequent accumulation of mutations in the genome leading to development of several disorders. Individuals with defective DNA repair are at severely increased risk of developing cancer and other diseases. A number of factors are hypothesized to influence individual DNA repair capacity. Measurement of DNA repair capacity, through functional assays, therefore, represents an integrated marker that incorporates the effects of epigenetic factors, genetic polymorphisms, gene expression, stability of gene product, effect of inhibitors/stimulators, environmental factors and lifestyle factors. Functional DNA repair assays reflect the capacity of an organism to cope with a chronic exposure to numerous environmental and dietary genotoxicants and may be used as predictive markers in cancer therapy.

We, recently, developed functional assays to to measure nucleotide excision (NER) and base excision (BER) repair capacities in human tissues. Our initial data showed that in healthy subjects, occupationally exposed to potential chemical carcinogens, BER capacity inversely correlated with the levels of DNA damage and showed an increase with increased exposure. In contrast, both BER and NER capacities were significantly lower and DNA damage higher in incident colorectal cancer patients than in matched healthy control subjects. In colorectal cancer patients, interestingly, the DNA repair capacity increased to the levels observed in healthy control subjects following the completion of chemotherapy. In our another study, BER and NER capacities were measured in blood cells, healthy mucosa and tumor tissues from 70 patients with sporadic CRC. Lymphocytes in contrast to tumor tissues exhibited lowest levels of BER and NER capacities. The definition of genetic and phenotypic landscape of the disease is, thus, further extended by DNA repair functional characteristics, both on the surrogate (systemic) and target tumor (topical level) tissues. The role of DNA excision repair in the response to chemotherapy has also been recently addressed on the patients sampled prior to and after the chemotherapy. Additional studies on DNA repair efficiency to determine influence on onset of the disease and in the context of gene-environment interactions are warranted.