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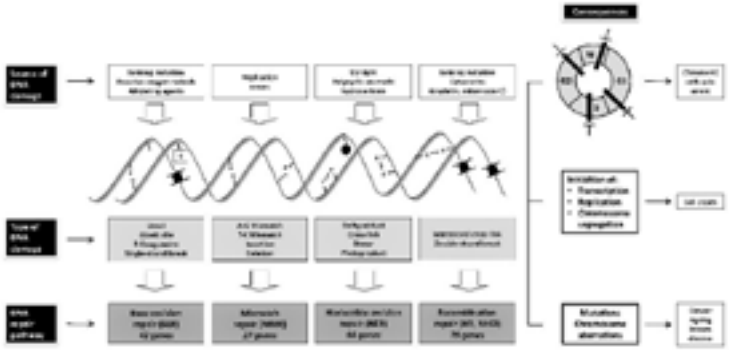
The role of DNA repair in response to treatment, disease progression and survival of sporadic colorectal cancer patients

Statement of the Problem: DNA repair and DNA damage response maintain universal genomic stability and preserve cellular functions in healthy cells, whereas the suppression of DNA repair capacity (DRC) in malignant cells would enhance the effectiveness of chemotherapy through DNA damage accumulation and consequent apoptosis. Alternatively, the patients with tumor cells with high DRC may contend with poor response, resistance to treatment and decreased survival. We investigated DRC of excision repair in target tissue as a predictive marker for a treatment strategy and long-term survival in patients with newly diagnosed colon cancer. Additionally, we explored links between functional genetic polymorphisms (SNPs) in DNA repair genes covering the main DNA repair pathways, the risk of colorectal cancer (CRC) and clinical outcomes.

Methodology: Our set of patients (with data on microsatellite stability and 5-FU treatment) was followed-up at least for 30 months. Tumor tissue and adjacent mucosa samples were obtained at surgical resection. Protein extracts from tissues were isolated both for protein expression (western blot) analysis and for measurement of DRC. Functional DRC was performed by comet assay-based *in vitro* DNA repair assay. Functional and genomic databases enabled identification of DNA repair gene variants affecting protein coding.

Findings: DNA repair gene variants were proven to modulate clinical outcome of colorectal cancer. In CRC patients, interestingly, the DNA repair capacity, significantly lower at the time of diagnosis, increased to the levels observed in healthy control subjects following the completion of chemotherapy. There are interesting associations between DRC measured in tumor tissue, adjacent mucosa and peripheral blood lymphocytes.

Conclusion: Present results identify plausible candidate DNA repair gene variants affecting survival of CRC patients and clinical outcome of the disease. DRC may constitute predictive biomarker in colorectal cancer therapy and targeting DNA repair processes may pose clinical benefit in cancer treatment.



Recent Publications

1. Slyskova et al. (2012) Functional, genetic and epigenetic aspects of base and nucleotide excision repair in colorectal carcinomas. Clin Cancer Res. 18(21):5878-87
2. Slyskova et al. (2015) Post-treatment recovery of suboptimal DNA repair capacity and gene expression levels in colorectal cancer patients. Mol. Carcinog. 54(9):769-778.
3. Pardini et al. (2013) Variation within 3' UTRs of base excision repair genes and response to therapy in colorectal cancer patients: a potential modulation of microRNAs binding. Clin. Cancer Res. 19: 6044-6056.
4. Naccarati et al. (2015) Double-strand breaks repair and colorectal cancer: gene variants within 3´UTR and microRNAs binding as modulators of cancer risk and clinical outcome. Oncotarget 7(17):23156-23169.

Biography

Vodicka P is the Head of the Department of Molecular Biology of Cancer at the Institute of Experimental Medicine in Prague. He has published more than 175 scientific articles in peer-reviewed journals. He acted as a Principal Investigator on numerous national and international grants. He was a member of international scientific committee for several international conferences and acts in the Editorial Board of international peer-reviewed journals. In 2004 and 2005, he acted as an Expert for evaluating carcinogenic risks of chemicals within the programmed of US State Department of Health and NIES, Research Triangle Park, NC, USA. He is involved in the evaluation of reports within 6th and 7th EU FP, in evaluation of grant applications within ESC and Horizon 2020, EU Commission, Brussels, Belgium and collaborates with UICC, Geneve, Switzerland. He has been working from 2002-2008 and from 2012-2016 for the National Science Foundation of the Czech Republic and was reviewing submissions to numerous international journals.

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