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Molecular and functional characteristics of sporadic colorectal cancer

Pavel Vodicka
Institute of Experimental Medicine, Czech Republic

Background: Sporadic colorectal cancer (CRC) is hallmarked by a complex interplay between the genetic and environmental factors with important involvement of genetic variants in low penetrance genes. Accumulation of DNA damage ultimately results in genomic instability and uncontrolled proliferation. Both events point to the DNA repair and DNA damage response as to the key players. Differences in DNA repair efficiency pose an important issue in etiology and progression of sporadic CRC. In the present study, we overview several gene variants determining risk of CRC, its prognosis and, finally, therapeutical efficacy. Genetic and epigenetic features of sporadic CRC as well as DNA repair phenotypic reflection will be also addressed.

Materials and methods: Candidate gene variants were analyzed on highthroughput platforms by RT-PCR instruments, by High Resolution Melting and NGS. Mutations in candidate genes were assayed for by HRM (LightCycler®480, Roche), denaturating capillary-electrophoresis (ABI PRISM 310 System, Applied Biosystems) and NGS (GS Junior, Roche). The cDNA and cRNA arrays for determination of mRNA, miRNA and lncRNA transcripts were carried out by qRT-PCR (Applied Biosystems). Methylation levels in promoter sequences of both microRNA- and protein-coding genes were determined by HRM following bisulfite conversion. Functional aspects of DNA repair have recently been published.

Results: Gene variants in several important pathways (DNA repair, cell cycle control, folate metabolism and methylation, insulin resistance and obesity, ABC transporters, selenoproteins, inflammatory/immune response) have shown various degree of association with CRC risk. Data on mutations in CRC high risk genes are presented along with gene expressions in relevant pathways and epigenetic regulators of transcription by methylation. The post-transcriptional regulation via miRNA or lncRNA was investigated in relation to the CRC risk and the efficacy of chemotherapy: SNPs in miRNA binding sites of *SMUG1* gene affected significantly survival in 5-fluorouracil-treated CRC patients. We assayed for the expression of the specific proteins in important pathways (mismatch repair, base excision repair). DNA repair tests have been implemented as functional markers of CRC susceptibility and prognosis.

Conclusions: Various molecular, epigenetic and functional tests to define genetic and phenotypic landscape of CRC were applied. Functional DNA repair assays reflect the capacity to cope with a chronic exposure to environmental and dietary genotoxicants and may be used as predictive markers in cancer therapy.

pvodicka@biomed.cas.cz