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Chromosomal damage as markers of genotoxic effect and carcinogenesis

Human cancers arise from cells unable to maintain genomic and chromosomal stability, mainly due to altered DNA repair mechanisms. Chromosomal instability (CIN) is consistently observed in virtually all cancers. Non-specific chromosomal aberrations (CAs) may arise as a result of direct DNA damage by ionizing radiation (chromosome-breaks; CSAs) or replication on a damaged DNA template (CSAs and chromatide-breaks; CTAs). CAs have been used in monitoring of radiation exposure and exposure to genotoxic compounds and they represent a sequential consequence of altered DNA repair mechanisms (base and nucleotide excision, mismatch, non-homologous DNA end joining and nonconservative homologous recombination repair). In this study, we describe a search for intermediary cancer biomarker among healthy subjects with or without the exposure to potentially carcinogenic compounds. We disclosed associations of CAs with polymorphisms in genes encoding DNA repair, xenobiotic metabolizing and mitotic apparatus regulating enzymes. Recently we have described significant effect of occupational exposure (OR 1.68) and CCND1 AA genotype (OR 1.85) on the total CAs, and on CSAs (OR 1.99). The G870A genotype differentially influences the splicing of CCND1 mRNA. The G870 allele creates an optimal splice donor site at the exon 4/intron 4 boundary, whereas the A870 allele partially hinders splicing and allows read-through into intron 4 resulting in the cyclin D1b transcript. Cyclin D1 participates in DNA DSB repair via recombinase RAD51. The induction of the DNA damage response is mediated by the cyclin D1a, whereas cyclin D1b lacks this activity. The shortening of telomeres in each cell division may lead to telomere crisis and complex CAs. Relative telomere length (RTL) was determined in 187 individuals based on their CA count in peripheral lymphocytes. The median RTL in subjects with no CAs was 1.28, while subjects with a total of more than 2 CAs had the median 1.19. Further shortening was observed in individuals with CSAs. The present results provide strong novel evidence that telomere biology contributes to CA formation. Furher support for the link between CAs and cancer risk was provided by the analyzes of CAs in peripheral lymphocytes of incident solid cancers (breast, colorectum and lungs). The association between clinicopathological characteristics, prognostic factors and the frequency of CAs is also reported. Since CIN hallmarks nearly 65-70% of colorectal tumors, we assayed for the CIN by aCGH in colon tumor tissues and healthy mucosa. Striking diference in CIN was observed between the right and left colon. Additionally, we analysed long deletions in CRC tumor suppresor gene *MLH1*.

Biography

Pavel Vodicka graduated at the Medical Faculty, Charles University, Prague and in 1986 obtained PhD in biochemistry. He worked as visiting Scientist at the Finnish Inst. Occupat. Health, Helsinki, Finland (1987-1990) and at Karolinska Institute, Huddinge, Sweden (1990-1993). Since 2002 he is the Head of the Dept. Molec. Biol. Cancer, Inst. Exper. Medicine, Acad. Sci., Prague, Czech Republic. He has published more than 120 (2670 citations, HI 31) articles. His main research topics were carcinogenic effects of industrial monomers, DNA and chromosomal damage and DNA repair functional tests in humans and dissection of transient biomarkers in the onset of gastrointestinal cancers. He edited the Special Issue (2012) in Mutagenesis *entitled Colorectal Cancer-Current Insights into Susceptibility.*

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