

## Abstract

Impaired chromosome segregation during mitosis, inaccurate DNA damage response and excessive telomere shortening may all modulate the frequency of chromosomal aberrations (CAs) in peripheral blood lymphocytes (PBL). There is evidence that increased frequency of structural CAs in PBL may be considered as a marker of enhanced cancer risk. In the present Thesis, an effect of variants in genes involved in mitotic checkpoint and DNA damage response on the inter-individual differences in CAs frequency in PBL was investigated. Considering the importance of disrupted telomere structure and its function in cancer biology, a link between telomere length and clinicopathological and molecular features of cancer patients was analysed. Furthermore, the relevance of telomere length and CAs frequency as markers of patients' survival was examined.

The major outcomes of the Thesis, fully reported in detail in seven attached Manuscripts, are: I) Increased frequency of structural CAs and/or disrupted telomere length in PBL may be considered as risk factors for the different types of solid cancer; II) Telomere shortening in PBL of healthy subjects increased the frequency of structural CAs; III) Binary interactions of gene variants in mitotic checkpoint and DNA repair pathways may modulate the frequency of structural CAs in PBL of healthy subjects; IV) The application of genome-wide association study revealed novel loci associated with genes important for mitosis and linked to the frequency of CAs in PBL; V) Telomere shortening in PBL of breast and colorectal cancer (CRC) patients was associated with decreased capacity to repair mutagen-induced DNA double-strand breaks; VI) Telomere length in tumor tissue was modulated by clinicopathological features (e.g. tumor-site origin, stage of tumor development, microsatellite instability) of CRC patients and finally, it was demonstrated that VII) CRC patients with more pronounced telomere shortening in tumor tissue compared to the adjacent mucosa evinced prolonged survival.

The results may be utilized in the future, when inter-individual differences in terms of identified gene variants and disrupted telomere length maintenance may provide a prediction tool for cancer risk assessment. Furthermore, as telomerase inhibitors are currently being applied in clinical practice, it is important to understand tumor telomere length variability and its link to clinicopathological and molecular features of cancer patients.