Abstract

Loss of telomere function and unrepaired DNA damage contribute to chromosome integrity disruption and genomic instability development, which can initiate malignant transformation of the cells. This dissertation focused on telomeres and their maintenance and regulation mechanisms in sporadic colorectal, breast, and ovarian tumors. In colorectal cancer (CRC), a place was also dedicated to research on base excision repair glycosylases.

The findings of the Thesis are elaborated in detail in seven attached Manuscripts. The main results of each of the articles are as follows: I) Mitochondrial DNA copy number changes and telomere length (TL) shortening already occur in precancerous lesions of CRC, but in early carcinomas, the association between their mitochondrial DNA content and TL diminishes; II) TL of leukocytes in peripheral blood of patients with CRC can be affected by postoperative cytostatic treatment based on 5-fluorouracil; III) CRC liver metastases maintain the same TL as primary tumors. In addition, neoadjuvant treatment with (chemo)radiotherapy applied to patients with rectal cancer probably causes telomere shortening in the primary tumor and the surrounding rectal cells in addition to DNA damage; IV) TL of ovarian cancer cells can be influenced by epigenetic regulations and expressions of genes encoding shelterin or telomerase subunits. In peripheral blood, shorter leukocytes of ovarian cancer patients may indicate a more favorable long-term response to platinum-based chemotherapy; V) Breast cancer patients have longer telomeres in peripheral blood lymphocytes than healthy women. A gene variant of the telomerase RNA component *TERC* was associated with longer telomeres in these patients; VI) Colorectal carcinomas have lower levels of DNA glycosylases MUTYH and OGG1, which cooperate in removing 8-oxoguanine caused by reactive oxygen species, and frequent mutations due to oxidative damage compared to the adjacent mucosa; VII) Standard DNA repair pathways are at telomeres partially suppressed or adjusted. Proteins associated with telomeres ensure correct telomere folding and, under physiological conditions, block at their ends mechanisms repairing DNA double-strand breaks. Their loss leads to severe disturbances in telomere homeostasis.

The outcomes regarding the dysregulation of TL and DNA repair may contribute to a better understanding of the initiation and progression of neoplastic diseases. TL has potential as a biomarker in clinical oncology in terms of patient prognosis or treatment effect.

Key Words: telomeres, telomerase, shelterin, DNA repair pathways