

## **Genomic instability, microenvironment and telomere homeostasis in solid malignancies**

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### ***Abstract***

Solid tumors belong to the leading malignancies and causes of deaths worldwide. Both impaired DNA repair mechanisms and disrupted telomere length homeostasis represent key culprits in cancer initiation, progression and prognosis. Altered DNA repair results through accumulation of mutations into the genomic instability. DNA repair determines the response to chemotherapeutics in cancer treatment. Telomere attrition resulting in replicative senescence, simultaneously by-passing cell cycle checkpoints, is a hallmark of cellular malignant transformation. Telomerase is ubiquitous in advanced solid cancers and its expression is fundamental to cell immortalisation. Large-scale sequencing of human cancer samples has revealed genetic heterogeneity within individual tumors, since they are composed of diverse subpopulations/subclones variable in space and time. Aneuploidy is present in ~80% of human solid neoplasms, the majority of which often exhibit chromosomal instability (CIN), both structural and numerical. CIN generates either abnormal aneuploid karyotypes, or continually expands phenotypic heterogeneity as tumor cell populations undergo consecutive cell divisions. Here we searched for the CIN markers in the adenoma-adenocarcinoma transition and in colorectal cancer progression, in breast and ovary cancers. Understanding the mechanisms and dynamics of tumor genomic diversification, where DNA damage response and telomere homeostasis are important players, is critical to understand carcinogenesis and overcome the drug resistance. A part of the above search is the comparison of telomere homeostasis genetics (based on GWAS study) with TL in 7,000 patients with sporadic CRC.

The mitochondrial dysfunction, another cancer hallmark, is linked with DNA repair capacity and compensate for damage by increasing the mitochondrial DNA copy number (mtDNA-CN). Current studies on the mtDNA-CN reported ambiguous and inconsistent results for various cancer types. Telomere shortening has a dual role in tumorigenesis. It promotes cancer initiation by inducing CIN, while TL maintenance characterized by telomerase expression is required for cancer cell proliferation and tumour growth. The reports on TL as a biomarker for cancer risk, patient therapy response and/or survival are contradictory as well. Our investigations were also focused on mtDNA\_CN in CRC tissues and adjacent mucosa.

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