

Genomic instability, microenvironment and telomere homeostasis in solid malignancies

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Abstract

Both impaired DNA repair mechanisms and disrupted telomere length homeostasis represent key culprits in cancer initiation, progression and prognosis. 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. 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. We undertook a comparison of telomere homeostasis genetics (based on GWAS study) with telomere length (TL) in 7,000 patients with sporadic CRC. We also studied TL as a biomarker for cancer risk, patient therapy response and/or survival.

The mitochondrial dysfunction is linked with DNA repair capacity and compensate for damage by increasing the mitochondrial DNA copy number (mtDNA-CN). We investigated mtDNA-CN in CRC tissues and adjacent mucosa in relation with TL. Moreover, gene expressions within DNA repair pathways were related to the damage of mtDNA. The association of mtDNA damage and gene expressions has been found among 48 genes representing all putative repair pathways in mitochondria. In comparison with adjacent mucosa CRC tumors exhibited *lower* extent of mtDNA damage ($P=0.047$), but there was *higher* expression of the majority of DNA repair genes. Out of 48 DNA repair genes 14 with the strongest correlation between the expression and mtDNA damage (*LIG3*, *MUTYH*, *RAD50*, *BRCA2*, *BRCA1*, *LIG1*, *PARG*, *NEIL3*, *RFC3*, *POLD3*, *POLD4*, *MRE11*, *NEIL1*, *UNG*) are validated on a larger cohort of patients.

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