Telomere maintenance mechanism

Cancer cells acquire replicative immortality by activating a telomere maintenance mechanism (TMM), either the telomerase or the Alternative Lengthening of Telomeres (ALT) mechanism. ALT is frequently activated in tumors derived from Mesenchymal stem cells, which are more frequent in childhood cancers. Studies showed that, occasionally, cancer cells can arise without any TMM activation. [1)]

Tumour cells can adopt telomere maintenance mechanisms (TMMs) to avoid telomere shortening, an inevitable process due to successive cell divisions. In most tumour cells, telomere length (TL) is maintained by reactivation of telomerase, while a small part acquires immortality through the telomerase-independent alternative lengthening of telomeres (ALT) mechanism. A great amount of data was generated, and different TMMs were reported and explained in detail, benefiting from genome-scale studies of major importance. Gaspar et al. addressed seven different TMMs in tumour cells: mutations of the TERT promoter (TERTp), amplification of the genes TERT and TERC, polymorphic variants of the TERT gene and of its promoter, rearrangements of the TERT gene, epigenetic changes, ALT, and non-defined TMM (NDTMM). We gathered information from over fifty thousand patients reported in 288 papers in the last years. This wide data collection enabled us to portray, by organ/system and histotypes, the prevalence of TERTp mutations, TERT and TERC amplifications, and ALT in human tumours. Based on this information, we discuss the putative future clinical impact of the aforementioned mechanisms on the malignant transformation process in different setups, and provide insights for screening, prognosis, and patient management stratification [2)]

In gliomas, TERT expression and TERT promoter mutation are considered to reliably indicate telomerase activation, while ATRX mutation and/or loss indicates an alternative lengthening of telomeres (ALT). However, these relationships have not been extensively validated in tumor tissues.

Telomeric repeat amplification protocol (TRAP) and C-circle assays were used to profile and characterize the telomere maintenance mechanism (TMM) cross-sectionally (n = 412) and temporally (n = 133) across glioma samples. WES, RNA-seq, and NanoString analyses were performed to identify and validate the genetic characteristics of the TMM groups.

Kim et al. showed through the direct measurement of telomerase activity and Alternative lengthening of telomeres (ALT) in a large set of glioma samples that the TMM in glioma cannot be defined solely by the combination of telomerase activity and ALT, regardless of TERT expression, TERT promoter mutation, and ATRX loss. Moreover, they observed that a considerable proportion of gliomas lacked both telomerase activity and ALT. This telomerase activation-negative and ALT negative group exhibited evidence of slow growth potential. By analyzing a set of longitudinal samples from a separate cohort of glioma patients, they discovered that the telomere maintenance mechanism is not fixed and can change with glioma progression.

This study suggests that the telomere maintenance mechanism is dynamic and reflects the plasticity and oncogenicity of tumor cells. Direct measurement of telomerase enzyme activity and evidence of alternative lengthening of telomeres should be considered when defining telomere maintenance mechanism. An accurate understanding of the telomere maintenance mechanism in glioma is

expected to provide important information for establishing cancer management strategies [3]

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