Alternative lengthening of telomeres

Alternative lengthening of telomeres (ALT) is a telomerase-independent mechanism used by a broad range of neoplasms to maintain telomere length, permitting uncontrolled replication during their progression.

About 10% of all tumors, including most low-grade astrocytoma, rely on the alternative lengthening of telomere (ALT) mechanism to resolve telomeric shortening and avoid limitations on their growth. Here, we found that dependence on the ALT mechanism made cells hypersensitive to a subset of poly(ADP-ribose) polymerase inhibitors (PARPi). Mukherjee et al. found that this hypersensitivity was not associated with PARPi-created genomic DNA damage as in most PARPi-sensitive populations but rather with PARPi-induced telomere fusion. Mechanistically, we determined that PARP1 was recruited to the telomeres of ALT-dependent cells as part of a DNA damage response. By recruiting MRE11 and BRCC3 to stabilize TRF2 at the ends of telomeres, PARP1 blocked chromosomal fusion. Exposure of ALT-dependent tumor cells to a subset of PARPi induced a conformational change in PARP1 that limited binding to MRE11 and BRCC3 and delayed release of the TRF2-mediated block on lethal telomeric fusion. These results therefore provide a basis for PARPi treatment of ALT-dependent tumors, as well as establish chromosome fusion as a biomarker of their activity [1)]

According to the World Health Organization Classification of Tumors of the Central Nervous System 2016 diffuse astrocytic tumor and oligodendroglial tumors are differentiated by the presence of isocitrate dehydrogenase 1 or 2 (IDH1/2) mutation and the combined loss of the short arm of chromosome 1 and the long arm of chromosome 19 (1p/19q co-deletion). Diffuse astrocytoma IDH mutant often has p53 and alpha-thalassemia/mental retardation syndrome X-linked (ATRX) mutation, showing the alternative lengthening of telomeres (ALT) phenotype, while Oligodendroglioma, IDH-mutant & 1p/19q-codeleted often have wild-type p53 and telomerase reverse transcriptase (TERT) promoter mutation, showing telomerase activation. Ohba et al. analyzed IDH, ATRX, and TERT promoter mutations, and the correlation between them. Immortalized cells overcome the telomere-related crisis by activating telomerase or ALT. In glioma, telomerase is mainly activated by TERT promoter mutation, while ALT is usually associated with ATRX mutation. Although the mechanism of how ATRX mutation induces ALT remains unclear, ATRX loss alone is believed to be insufficient to induce ALT. Treatments targeting telomere maintenance are promising [2)].

1)
Mukherjee J, Pandita A, Kamalakar C, Johannessen TC, Ohba S, Tang Y, Dalle-Ore CL, Bjerkvig R, Pieper RO. A subset of PARP inhibitors induces lethal telomere fusion in ALT-dependent tumor cells. Sci Transl Med. 2021 May 5;13(592):eabc7211. doi: 10.1126/scitranslmed.abc7211. PMID: 33952676.
2)
Ohba S, Kuwahara K, Yamada S, Abe M, Hirose Y. Correlation between IDH, ATRX, and TERT promoter mutations in glioma. Brain Tumor Pathol. 2020 Mar 29. doi: 10.1007/s10014-020-00360-4. [Epub ahead of print] Review. PubMed PMID: 32227259.