TRF1

Telomere-binding proteins (also known as TERF, TRBF, TRF) function to bind telomeric DNA in various species. In particular, telomere-binding protein refers to TTAGGG repeat binding factor-1 (TRF1) and TTAGGG repeat binding factor-2 (TRF2).

The telomere binding protein TRF1 is essential for telomere protection, and for adult and pluripotent stem cells.

Bejarano et al., finded TRF1 upregulation in mouse and human GBM. Brain-specific Trf1 genetic deletion in GBM mouse models inhibited GBM initiation and progression, increasing survival. Trf1 deletion increased telomeric DNA damage and reduced proliferation and stemness. TRF1 chemical inhibitors mimicked these effects in human GBM cells and also blocked tumor sphere formation and tumor growth in xenografts from patient-derived primary GSCs. Thus, targeting telomeres throughout TRF1 inhibition is an effective therapeutic strategy for GBM [1].

Despite a standard of care combining surgery, radiotherapy (RT), and temozolomide chemotherapy, the average overall survival (OS) of glioblastoma patients is only 15 months, and even far lower when the patient cannot benefit from this combination. Therefore, there is a strong need for new treatments, such as new irradiation techniques. Against this background, carbon ion hadrontherapy, a new kind of irradiation, leads to a greater biological response of the tumor, while minimizing adverse effects on healthy tissues in comparison with RT. As carbon ion hadrontherapy is restricted to RT-resistant patients, photon irradiation resistance biomarkers are needed. Long telomeres and high telomerase activity have been widely associated with photon radioresistance in other cancers. Moreover, telomere protection, telomere function, and telomere length (TL) also depend on the shelterin protein complex (TRF1, TRF2, TPP1, POT1, TIN2, and hRAP1). We thus decided to evaluate an enlarged telomeric status (TL, telomerase catalytic subunit, and the shelterin component expression level) as a potential radioresistance biomarker in vitro using cellular models and ex vivo using patient tumor biopsies. In addition, nothing was known about the role of telomeres in carbon ion response. We thus evaluated telomeric status after both types of irradiation. We report here a significant correlation between TL and the basal POT1 expression level and photon radioresistance, in vitro, and a significant increase in the OS of patients with long telomeres or a high POT1 level, in vivo. POT1 expression was predictive of patient response irrespective of the TL. Strikingly, these correlations were lost, in vitro, when considering carbon irradiation. We thus propose (1) a model of the implications of telomeric damage in the cell response to both types of irradiation and (2) assessment of the POT1 expression level and TL using patient tumor biopsies to identify radioresistant patients who could benefit from carbon hadrontherapy [2].

1)
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2)
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