SHELTERING TELOMERES FROM OXIDATIVE DAMAGE IN THERAPEUTIC T CELLS PROTECTS AGAINST TUMOR-INDUCED IMMUNE DYSFUNCTION

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Background Failure of adoptive cell therapies (ACTs) is associated with insufficient persistence within the patient, inability to infiltrate tumor sites, and cell-intrinsic loss of functionality. One of the key factors responsible for T cell dysfunction are metabolic barriers such as nutrient competition, low oxygen tension and damaging byproducts in the tumor microenvironment. This leads to a T cell metabolic deregulation affecting their ability to find and kill cancer cell targets effectively. Therefore, elucidating the metabolic pressures experienced in the TME could provide new therapeutic targets to improve ACTs. Reactive Oxidative Species (ROS) accumulation in the TME have detrimental effects on T cell function and anti-tumor response, although the precise targets of ROS are unclear. There are accumulating data showing that mitochondrial ROS can have profound effects on the telomere status of cells. However, there is little evidence describing the role or oxidative stress on telomere health, or the importance of telomere function in immune cells. Our current study demonstrates that tumor infiltrating lymphocytes (TIL) accumulate DNA damage at telomeres. Furthermore, inducing ROS accumulation at telomeres alone drives T cell dysfunction. Importantly we discovered that alleviating ROS specifically at telomeres improves the response to adoptive cell therapies in a mouse tumor model.

Methods We perform telomeric and centromeric FISH assays to analyze TIL for DNA damage accumulation. We used a chemo-optogenetic FAPS-TAPS to generate oxidative lesions specifically at telomeres. 1 We tethered the antioxidant protein GPX1 to the telomere shelterin TRF1 to generate a telomere-guided ROS scavenger.

Results Telo-FISH analysis demonstrates an accumulation of telomeric DNA damage in TIL from B16 mouse tumors shown by the presence of 53BP1 and γH2AX at telomeres (figure 1A). Our data show that mitochondrial and telomeric ROS cause the accumulation of DNA damage at telomeres, as well as the development of telomere fragility (figure 1B). These cells ultimately become dysfunctional showing a diminished capability for cytokine production. Importantly, localizing the ROS scavenger GPX1 directly to telomeres reduced telomere fragility and improved the function of therapeutic T cells in the B16 melanoma (figure 1C).

Conclusions Our data suggest that dysfunctional T cells in cancer are not classically senescent, bearing short telomeres, but rather harbor damaged telomeres due to exposure to oxidative stress. Telomeric damage is sufficient to drive a dysfunctional state in newly activated T cells. Protecting telomeres through expression of a telomere-targeted antioxidant protein may preserve T cell function in the tumor microenvironment and drive superior responses to adoptive cell therapies.

REFERENCE