TELOMERASE-DRIVEN TELOMERIC DNA MODIFICATION IN CANCER CELLS LEADS TO EFFICIENT INDUCTION OF CGAS-MEDIATED INNATE AND ADOPTIVE IMMUNE RESPONSES

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Background Telomeres and telomerase in cancer cells are highly attractive targets for specific anti-tumor therapy, since telomerase is almost universally expressed in cancer cells, but not in the majority of normal counterparts.

Methods In this presentation we summarize an unexpected, yet promising functional property of a modified nucleoside - 6-thio-2'-deoxyguanosine (6-thio-dG; THIO), as a potential anticancer agent with a unique mechanism of action. In vitro and in vivo, THIO is readily converted into the corresponding 5'-triphosphate, which is a substrate for mammalian telomerase. Incorporation of THIO into de novo synthesized cancer cell telomeres by telomerase leads to a fast induction of DNA damage responses and cancer cell senescence and apoptosis. Importantly, cancer cell death occurs in a telomere length-independent manner. THIO treatment leads to the generation of chromosomal bridges and, eventually, to the formation of cytosolic micronuclei structures, containing de novo modified telomeric DNA fragments. In addition to activation of innate immunity (i.e., cGAS pathway and NK cells), these in situ produced neo-adjuvants are exported extracellularly and then sensed by host-derived naïve dendritic cells, resulting in an enhanced cross-priming and tumor-specific T- cell (both CD4+ and CD8+) activation.

Results Treatment with THIO overcomes resistance to checkpoint blockade (by aPD-1 or aPD-L1 agents) in advanced in vivo cancer models, leading to profound and persistent tumor regression with induction of cancer type specific long-term immune memory. Thus, in vivo cancer curative activity was observed in murine syngeneic models of colorectal (MC-38) and lung (LLC) cancers, when THIO administration was followed sequentially by atezolizumab. Combinations with other immune checkpoint inhibitors (cemiplimab; pembrolizumab) were also highly effective

Conclusions In summary, our findings demonstrate the importance of cancer cell telomeric DNA structural and functional integrity, as well as a therapeutically attractive opportunity to induce telomerase-mediated telomere replication stress. THIO modified telomeres increase innate sensing and adaptive antitumor immunity via “cancer cell self-produced” chemical modification of telomeres.

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