

TELOMERE DYSFUNCTION MEDIATES ANTI-TUMOR IMMUNITY IN SMALL CELL LUNG CANCER

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Background Small cell lung cancer (SCLC) is a pulmonary neuroendocrine cancer with very poor prognosis and limited effective therapeutic options. Chemotherapy is used as first-line treatment for this highly proliferative cancer. High telomerase activity was observed in SCLC which may contribute to active proliferation. 6-thio-2-deoxyguanine(6T-dG) is a novel telomere-specific nucleoside precursor recognized by telomerase. It is incorporated into *de novo* synthesized telomeres and lead to telomere dysfunction. It specifically affects cells with high telomerase activity such as cancer cells. Here we induced telomere dysfunction in SCLC by 6T-dG to investigate the effects on tumor growth and the tumor microenvironment.

Methods We first evaluated the anti-tumor effect of 6T-dG on SCLC by cell viability assay and colony formation *in vitro*. Then the effect was examined *in vivo* by mouse allografts or xenografts. Post-treatment tumor microenvironment was characterized by flow cytometry and *in vitro* co-culture assay was performed to set up mechanistic study on drug-evoked immunity. For therapeutic studies 6T-dG was combined with other current treatments for SCLC to assess its therapeutic potential.

Results 6T-dG induces DNA damage in SCLC and inhibited tumor progression both *in vitro* and *in vivo*. Cancer cells with higher telomerase activity were more vulnerable to the inhibition. Flow cytometry analysis of 6T-dG treated mouse tumors revealed changes in the tumor microenvironment such as infiltration and activation of cytotoxic lymphocytes while reducing infiltration of immune-suppressive myeloid cells and T regulatory cells. 6T-dG also works synergistically with common clinical treatment of SCLC such as immune checkpoint blockade (ICB) in mouse allograft model.

Conclusions Inducing telomere dysfunction impairs tumor progression by eliminating cancer cells with high telomerase activity and triggers anti-tumor immunity in SCLC. Inhibiting telomerase activity is a promising therapeutic strategy as single agent or synergistically with immunotherapy in SCLC.

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