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PRE-CONDITIONING OF THE IMMUNE SYSTEM MODULATES THE RESPONSE OF PAPILLARY THYROID CANCER TO IMMUNE CHECKPOINT INHIBITORS

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Background

The response of solid tumors such as papillary thyroid cancer (PTC) to Immune Checkpoint Inhibitors (ICIs) is highly variable. The biological basis of this variability remains unknown.

Methods

To test the hypothesis that pre-conditioning of the immune system modulates the therapeutic effect of ICIs, we used a murine model where PTC and iodine exacerbated thyroiditis (IET) can be induced in a temporally predictable fashion. A total of 122 mice were divided into 3 experimental groups. In the first one, named concomitant IET and PTC (No. = 40), IET and PTC were induced at the same time; in the second one, named pre-existing IET (No. = 44), IET was induced prior to the induction of PTC; in the third one, named no IET (No. = 38), only PTC was induced. Following disease induction, mice of each group were treated with anti-PD-1 antibody, anti-LAG-3 antibody, anti-TIM-3 antibody, or IgG control. Ten weeks after the initial ICI injection, mice were sacrificed to collect the thyroid gland for histological analysis, to quantify the incidence and burden of PTC, and to perform. High-throughput single-cell RNA sequencing of infiltrating $CD45^+$ cells.

Results

In the concomitant IET and PTC group, ICI treatment reduced PTC incidence ($p=0.002$ comparing treatment with any ICI vs. control), while it had no effect in the pre-existing IET and no IET groups. Single-cell sequencing of thyroidal $CD45^+$ cells showed that the different ICIs tested had both specific and shared effects on all the components of the thyroidal immune cell infiltrate. The shared effect of the tested ICIs was dependent on the presence of pre-existing vs. concomitant IET. In the context of concomitant IET, ICI treatment resulted in the modulation of a greater number of pathways related to both innate and adaptive immunity.

Conclusions

Response to ICIs is modulated by the inflammatory status of the treated individual. Modulation of the inflammatory state should be explored as a tool to improve response to ICIs in patients with PTC or other forms of cancer.