CHARACTERIZATION OF ALTERED IMMUNITY IN ANAPLASTIC THYROID CANCER

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Background

- Anaplastic thyroid cancer (ATC) occurs in less than 2% of all thyroid cancer cases, and it is almost uniformly lethal with an average median survival of 6 months (Manikas et al; JAMA Oncol, 2020)

- ATC is very aggressive and spreads rapidly within the neck and metastasizes to distant parts of the body, which makes it resistant to standard therapy (surgery, radioactive iodine therapy and chemotherapy) (Zhang et al; EJMC, 2022)

- The mutational landscape of ATC is very complex compared to other forms of thyroid cancer, including Papillary (PTC) and Follicular (FTC), due to multiple mutations in oncogenes and tumor suppressors (Cancer Genome Atlas Research N; Cell, 2014; Landa et al; JCI, 2016)

- Thyroid cancers are rich in immune cells, making them a reasonable candidate for immunotherapies (Varrichi et al; IJMS 2019)

- To develop new therapeutic strategies, further studies determining the immune cell composition of ATC that favors tumor progression are required

Hypothetical scheme of immune contexture of thyroid cancer (Varrichi et al; IJMS 2019)
**Results**

**Experimental design**
- Control mice (WT 6-8-week-old mice) → Healthy control → Thyroid gland
- Experimental design
  - TP53CreER;Brca1flox/flox
  - TP53CreER;Brca1flox/flox;TP53flox/flox
- Flow cytometry analysis
- Single cell suspension
- Thyroid tumors
- Tamoxifen treatment (75 mg/kg daily for 5 consecutive days)

**Cellular composition of ATC tumors**
- Hematopoietic cell distribution in ATC and PTC tumors compared to thyroid gland
  - Higher infiltration of lymphoid immune cells in ATC and PTC compared to normal thyroid gland

**Immune microenvironment in ATC**

**Lymphocyte subsets**
- Higher infiltration of follicular CD8+ T cells (PD1+ CXCR5+) in ATC compared to PTC and normal glands
- Exhaustion markers (PD1+, LAG3+ and CTLA4+) expression is increased in CD4+ T cells in ATC
- Treg cells produce higher levels of IL17 in ATC
- Mature NK cells levels are decreased in ATC

**Myeloid subsets**
- Myeloid cells express decreased levels of T-cell activation molecules and increased levels of the suppressor factor PDL1
- ATC enriched in suppressor myeloid cells (cDC2 and M2)

**Immune cell composition in thyroid tumors**
- Percentage of immune cells among hematopoietic cells (CD45+)

[Graphs and data visualizations showing cellular composition and immune microenvironment in ATC are present in the image.]
Summary

• ATC tumor microenvironment is highly enriched with exhausted CD4+ T cells expressing PD-1, LAG3 and CTLA-4
• ATC tumors are infiltrated with immunosuppressive myeloid cells, cDC2 and M2 macrophages, expressing high levels of PDL1
• Treg cells changed phenotype towards inflammatory Th17 cells in ATC

Future directions

• Assess the contribution of immune cells to ATC pathogenesis
• Evaluate the efficacy of cell-targeted and immune checkpoint blockade therapy in ATC model
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